

## Perioperative Treatment of the Patient Taking Anticoagulation Medication

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Prolonged intraoperative and postoperative bleeding is a concern for oral and maxillofacial surgeons who treat patients taking anticoagulation medication. In the United States alone, nearly 2.3 million patients have been found to have atrial fibrillation; of those, 40% receive anticoagulant medications [1]. Anticoagulation medications are often given prophylactically to patients who are at risk of thrombus formation and its sequelae as the result of acquired or hereditary medical disorders, most commonly coronary artery disease, atrial fibrillation, and deep venous thrombosis. Patients who have undergone heart valve replacement, particularly persons who have received mechanical valves, are treated with warfarin. Medical conditions such as cancer, ulcerative colitis, heparin-induced thrombocytopenia, antiphospholipid antibody syndrome, disseminated intravascular coagulation, and hyperhomocystinemia may predispose patients to a hypercoagulable state and the need for anticoagulation therapy. Oral and maxillofacial surgeons also may treat patients with hereditary conditions. Patients who have deficiencies of protein C, protein S, or antithrombin III, patients who have factor V Leiden thrombophilia, and patients who have abnormal plasminogen production may require anticoagulation to prevent thrombotic sequelae.

Patients in a hypercoagulable state who do not receive prophylactic anticoagulation medications are at risk of venous or arterial thrombotic events that may result in substantial morbidity or mortality rates.

These events include cerebrovascular accident, transient ischemic attack, peripheral venous or arterial thrombus or embolus, and clotted arteriovenous grafts. Of these complications, oral and maxillofacial surgeons are probably most familiar with deep venous thrombosis, which is a common occurrence among surgical patients. Its incidence in association with general and orthopedic surgery is 25% to 50% in the absence of any form of prophylaxis [2].

Various pharmacologic methods can be used to treat or prevent complications, such as deep venous thrombosis, or other sequelae related to a hypercoagulable state. Patients who take anticoagulation medications may be seen by oral and maxillofacial surgeons for evaluation and surgery in elective, urgent, and emergent situations. The purpose of this article is to familiarize readers with commonly encountered medications and recently published findings regarding their use by patients at risk of thromboembolic events.

### A review of hemostasis

Hemostasis is the cessation of bleeding. To achieve hemostasis, the body maintains a delicate balance between the risk of intravascular thrombus and the risk of hemorrhage. This balance depends on the normal functioning of the vascular endothelium, the coagulation cascade, blood flow, platelets, anti-clotting mechanisms, and the fibrinolytic system. It is important to understand the overall concept of hemostasis because multiple medications are used for anticoagulation, each with distinct characteristics and mechanisms by which they disrupt the coagu-

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lation cascade. A complete review of hemostasis is beyond the scope of this article, but the diagrams that cover the intrinsic and extrinsic schemes and the physiologic pathway provide an overview. The process includes primary hemostasis (platelet plug formation), secondary hemostasis (coagulation), and the formation of a stable fibrin clot (Fig. 1).

In general, the coagulation cascade can be described as having three parts: the intrinsic system, the extrinsic system, and the common pathway. Coagulation proteins circulate in the bloodstream in inactive forms. Unlike the subendothelium, the endothelium is devoid of thrombogenic tissue factor and collagen; activation of platelets and the coagulation cascade are prevented.

Maintaining normal, brisk flow through vessels ensures that any activated coagulation proteins are swept away quickly for disposal in the liver. When a vessel wall is injured, however, the coagulation apparatus is stimulated. The intrinsic system begins with the exposure of subendothelial collagen through the defect at the site of injury, which activates platelets and other coagulation proteins. One of the activated

proteins, factor XIIIa, cleaves and activates prekallikrein and factor XI into kallikrein and activated factor XIa. These proteins are anchored to the subendothelium by a high molecular weight kininogen. Kallikrein then amplifies the activity of the intrinsic system by activating neighboring molecules of factor XII. Once activated, factor XIa cleaves its anchoring cofactor, high molecular weight kininogen, and diffuses into solution, where it activates factor IX in the presence of calcium. Activated factor IXa forms a complex with activated factor VIIIa and calcium. This complex then binds to the surface of platelets that contain phospholipids, in which the activation of factor X occurs. This event marks the end of the intrinsic pathway and the initiation of the common pathway of the coagulation cascade (Fig. 2) [3].

Unlike the intrinsic system, the extrinsic system initiates the coagulation cascade with components outside the blood. Disruption of the endothelial surface exposes the subendothelium, which expresses tissue factor on its cell surface. Once exposed to the blood, circulating factor VII binds to the tissue factor and forms a tissue factor-factor VII complex that

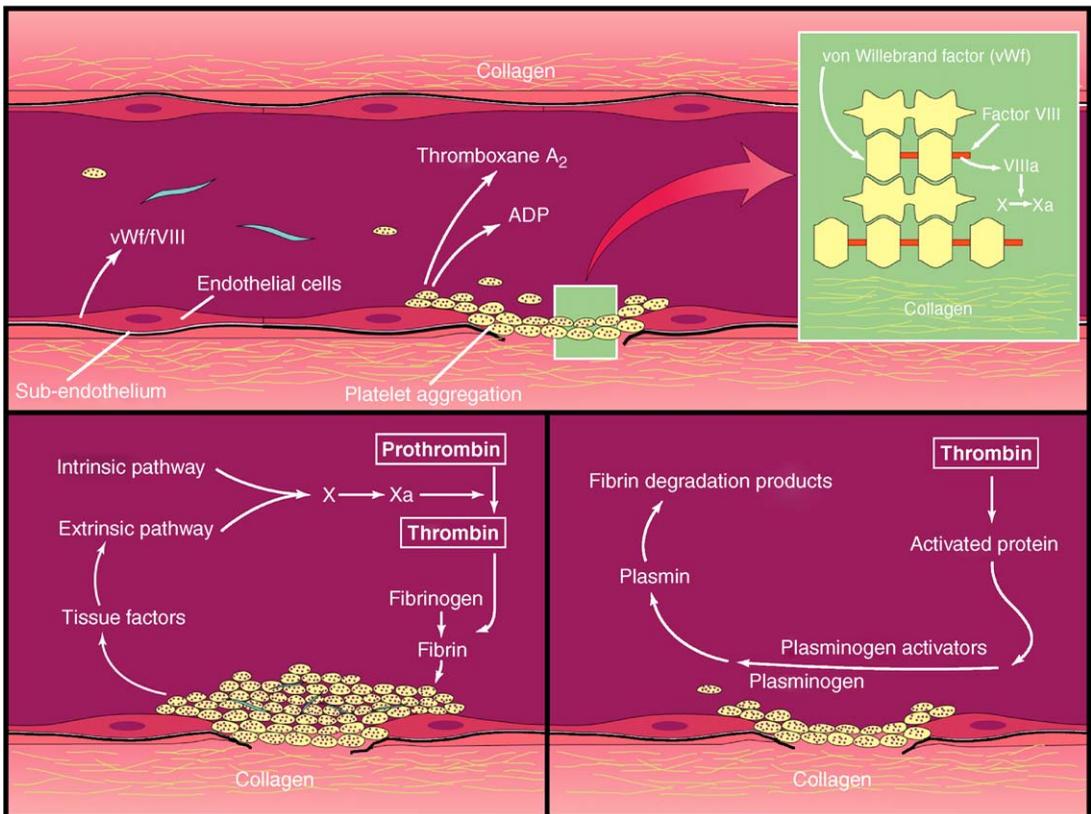


Fig. 1. Normal hemostatic process.

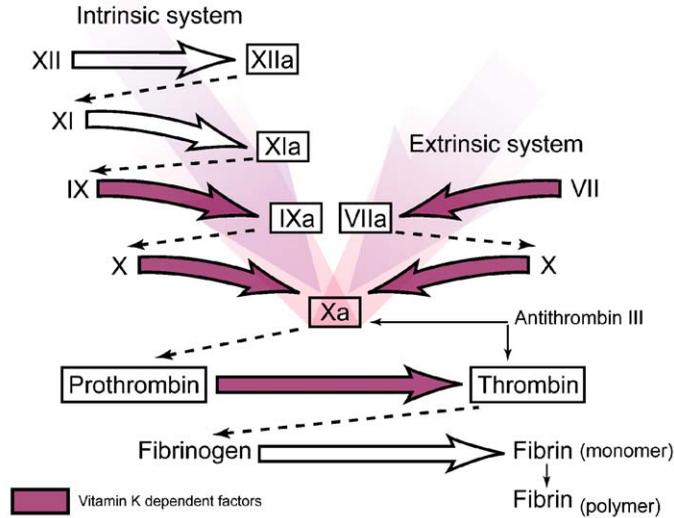


Fig. 2. The classic coagulation cascade.

promotes the autoactivation of factor VII to activated factor VIIa. In the presence of calcium and membrane phospholipids, this complex activates factor X.

The activation of factor X is the point at which the intrinsic and extrinsic pathways converge to form the common pathway of the coagulation cascade. Factor X is activated on the phospholipid-rich surface of activated platelets. Activated factor X forms a complex with its activated cofactor, factor Va, in the presence of calcium; it also converts prothrombin into thrombin [3].

Thrombin is referred to as the primary regulator of the coagulation cascade. Thrombin cleaves fibrinogen to form soluble fibrin monomers, which subsequently polymerize to form an insoluble fibrin clot at the site of injury. Thrombin also activates circulating factor XIII, which catalyzes the formation of cross-links between fibrin molecules. These cross-links provide the necessary structure for a stable fibrin clot. Thrombin also activates surrounding platelets that, in conjunction with the fibrin clot, seal the defect in the vessel wall. Finally, thrombin activates factor V and factor VIII in a positive feedback loop, which further amplifies the activation of the coagulation cascade [4].

Understanding thrombus formation—or the prevention thereof—requires a working knowledge of the three conditions associated with this pathophysiologic process that was first described by Virchow in 1856 [2]. Known as Virchow's triad, the three conditions necessary for thrombus formation are venous or arterial stasis, endothelial wall damage (ie, damage to the intima or inner layer of a vessel), and an

alteration in the blood's coagulability. These conditions produce a hypercoagulable state.

Stasis, the first condition of Virchow's triad, may occur in large and small blood vessels but occurs more commonly in larger vessels, such as the deep veins of the calf [3]. When blood flow is rapid, small quantities of thrombin and other procoagulants are mixed with large quantities of blood and are carried by the blood to the liver, where they are removed mainly by Kupffer cells. When blood flow is too slow, however, these procoagulants accumulate in local concentrations sufficient to initiate clotting [5].

The second condition of Virchow's triad refers to injury to a blood vessel wall. The injury causes disruption of the vessel's endothelial layer, which sets in motion the intrinsic pathway of coagulation. This disruption exposes the underlying collagen to platelets and other coagulation proteins, which are activated by this exposure. Once activated, the platelets spread in shape, and their procoagulant phospholipids become externalized. This change allows the coagulation proteins to assemble on the surfaces of the platelets and accelerates the coagulation reactions. Von Willebrand factor is synthesized and released by endothelial cells and is exposed during this endothelial disruption. During this second condition of Virchow's triad, von Willebrand's factor assists platelets in attaching to collagen; the adherent platelets spread out, and their cytoplasmic granules release substances such as adenosine 5'-diphosphate (ADP), serotonin, and thromboxane A<sub>2</sub>. These substances cause local vasoconstriction and platelet aggregation, which recruit

more platelets. This initial hemostatic plug is referred to as primary hemostasis; its proper function requires an adequate number of normally functioning platelets, collagen, and von Willebrand's factor, and products of the coagulation cascade, such as thrombin and fibrinogen [4].

Defects of primary hemostasis are recognized in the operating room when normal avascular planes continue to ooze as small capillaries continue to bleed despite the application of pressure and time. Coagulation continues through secondary hemostasis when the platelet plug is stabilized, and a mechanically strong clot composed of fibrin, platelets, and erythrocytes is formed.

Cross-linking of fibrin further strengthens the clot, which then contracts. Propagation of the clot is limited by three different mechanisms. First, tissue factor pathway inhibitor limits the initiation of coagulation. Second, the protein C pathway is activated by thrombomodulin, which binds excess thrombin. Along with the cofactor protein S, this pathway inactivates factors Va and VIIa of the coagulation cascade, which limits amplification of the clot. Finally, thrombin is inactivated by antithrombin III, which limits propagation of the clot [4]. Chemotactic factors then stimulate phagocytic leukocytes to clean up debris in the region of injury. Platelet-derived growth factor, released from degranulating platelets, stimulates vascular repair. When the continuity of the endothelium has been restored, the fibrinolytic system is activated and the occluding thrombus is lysed [4].

The final element of Virchow's triad, the hypercoagulable state, reflects an imbalance between procoagulant and anticoagulant tendencies. Patients who undergo oral or maxillofacial surgery may have medical conditions that cause hypercoagulable state, such as cancer, ulcerative colitis, heparin-induced thrombocytopenia, antiphospholipid antibody syndrome, disseminated intravascular coagulation, hyperhomocystinemia, Factor V Leiden thrombophilia, abnormal plasminogen production, and deficiencies in antithrombin, protein C, and protein S.

Because of the wide variety of diseases among surgical patients, it is important to understand where the coagulation factors are synthesized. Most of them are produced in the liver. In fact, hepatic synthesis has been confirmed for fibrinogen, factor V, and the group of factors that require vitamin K for synthesis, namely, factor II (prothrombin), factor VII, factor IX, factor X, protein C, and protein S [4]. Factor XIII is involved in fibrinogen cross-linkage and is synthesized partially in megakaryocytes and partially in the liver.

Factor VIII is believed to be produced at several sites. Although liver transplantation has corrected

factor VIII deficiency among patients with hemophilia A, for example, factor VIII concentrations actually may be increased rather than decreased among patients with severe liver disease. This increase is probably an acute phase response [4]. Fibrinogen is the precursor of fibrin, from which fibrin clots are built. Fibrinogen is produced by the liver and is an acute phase reactant. An inflammatory stimulus increases the hepatic output of fibrinogen to as much as eight times its normal level [4].

Platelets are the disk-shaped fragments of megakaryocyte cytoplasm that are initially found in bone marrow. These fragments adhere to the site of injury, become activated, and stimulate further aggregation. Once platelets have been activated, they change their shape, release the contents of their granules, and expose receptor sites that provide a surface for activation and assembly of the coagulation complexes. As mature cells, platelets circulate in the blood at a constant level, and approximately 33% of the platelet pool is sequestered in the spleen. These sequestered platelets are freely exchangeable with those in the blood and can be released in large numbers in response to epinephrine or exercise. It is important to remember that among patients who have hypersplenism, an increase in the sequestration of platelets may result in thrombocytopenia. Likewise, among patients who have undergone splenectomy, the entire platelet pool is contained within the circulation, and thrombocytopenia may persist to some degree after this procedure [4].

## Preoperative evaluation

Every preoperative evaluation begins with a comprehensive medical history, regardless of the type of surgery planned. Questioning should assess each patient's individual bleeding risk by emphasizing past and current usage and dosage of medications, including vitamins, herbal remedies, over-the-counter drugs, and prescription medications. Patients often forget to mention medications that they are currently taking. During the interview process, questions should focus on medical conditions that would warrant the use of anticoagulants or other medications that could cause prolonged bleeding after surgery, such as nonsteroidal anti-inflammatory drugs. Once the history has been obtained, bleeding risk should be assessed by a consideration of medical conditions, medications, previous surgical history or complications, and the type of surgery planned. Although individually these factors may not arouse suspicion before surgery, their combination in certain

situations may pose a serious preoperative risk of immediate or delayed hemorrhage.

For example, dentists and physicians view a simple extraction as minor surgery, after which prolonged bleeding would not be expected. When this "minor surgery" is combined with a history of poorly monitored anticoagulation use that results in inadvertent overmedication of a patient, a lack of preoperative laboratory assessment, and a preoperative diagnosis of advanced periodontal disease, the outcome can change drastically.

In any clinical situation, numerous steps can be taken preoperatively to reduce the risk of bleeding intraoperatively and postoperatively. In addition to a proper history that details medication usage and underlying medical conditions that may increase the effects of anticoagulant medication or contribute to prolonged bleeding, a detailed, focused physical examination should be performed. Certain anatomic considerations and disease processes can predispose a patient to bleeding complications. Surgery that requires a maxillary osteotomy or a neck dissection poses a greater risk than surgery that does not traverse such anatomic structures and does not increase the risk of severing a vessel that may or may not be amenable to ligation or cautery. Inflammation at the proposed surgical site may lead to fibrinolysis and prolonged bleeding. Excessive operative trauma also may predispose a patient to postoperative bleeding, especially from oral soft tissues.

Once a patient's history has been obtained and the type of surgery and its potential operative complications have been considered fully, clinicians should assess each patient's risk of intraoperative or postoperative bleeding and determine whether preoperative laboratory assessment is indicated. This determination does not depend entirely on the type or dose of anticoagulant medication but also is influenced by the type of surgery to be performed and a patient's preoperative diagnosis. Laboratory assessment may include determining hemoglobin or hematocrit, platelet count, prothrombin time (PT), partial thromboplastin time (PTT), an Ivy bleeding time, platelet function analysis, International Normalized Ratio (INR), or some combination of these factors.

Surgeons must assess a patient's coagulation status preoperatively. Surgeons commonly use a few basic measures that deserve a brief explanation. For the purposes of this article we categorize these measures as tests of primary hemostasis or tests of secondary hemostasis. Tests of primary hemostasis include determination of the platelet count, bleeding time, and platelet function and screening for von Willebrand's disease. Tests of secondary hemostasis include

determination of the PTT, PT, and thrombin time and mixing studies and tests for inhibitors, disseminated intravascular coagulation, and factor XIII deficiency.

Testing for primary hemostasis begins with determination of the platelet count. For this test, the blood must be collected in citrated tubes without exposure to ethylenediaminetetra-acetic acid, which may cause platelet clumping and an inaccurate count.

In the absence of overt thrombocytopenia, determination of bleeding time is a means of assessing platelet dysfunction as a cause of symptoms. Traditionally this is known as an Ivy bleeding time. A blood pressure cuff is placed on the upper arm and inflated to 40 mm Hg. A small wound is made on the forearm, filter paper is applied to the site, and the blood is pulled away by capillary action while bleeding time is measured at 20-second intervals. A prolonged bleeding time indicates a problem with platelet function or perhaps with capillary integrity [6].

Although some hospitals and laboratories still use the Ivy bleeding time to assess platelet function, a more recently developed test is the platelet function analysis. This laboratory test simulates the process of platelet adhesion and aggregation after a vascular injury *in vitro*. Using separate test cartridges known as the collagen/epinephrine test and the collagen/ADP test, the platelet function analysis is reported as a closure time. A closure time above the normal range may indicate the need for further testing to determine any possible causes of platelet dysfunction, including acquired, inherited, or induced by platelet-inhibiting medications. The collagen/epinephrine test determines if the platelet dysfunction is induced by intrinsic platelet defects, von Willebrand's disease, or exposure to platelet-inhibiting agents. The collagen/ADP test is used to determine if an abnormal collagen/epinephrine test was caused by either the effect of acetyl salicylic acid or medications that contain acetyl salicylic acid.

Screening for von Willebrand's disease screen is appropriate for a patient with a history of bleeding, a normal platelet count, and prolonged bleeding time.

Finally, platelet function studies, such as secretion and aggregation in response to agonists, can implicate platelet dysfunction as a cause of bleeding. Such studies are not indicated for the initial evaluation of anticoagulation status, however.

Tests of secondary hemostasis include the determination of PT (often reported as INR). For this test, calcium and thromboplastin (a mixture of tissue factor and phospholipid membrane fragments) are added to citrated blood, and the time required for a clot to form is measured. This test measures the extrinsic pathway of the coagulation cascade. The PT

is prolonged by deficiencies in factors II (prothrombin), V, VII, and X and in fibrinogen. The PT is used to monitor the anticoagulation status of patients who are taking warfarin [4].

The determination of PTT measures the slower intrinsic pathway. In vitro, this pathway requires all of the clotting factors except factor VII. Likewise, in vitro, a reliable result can be obtained only when the concentrations of factor XII, prekallikrein, and high molecular weight kininogen are normal. These concentrations are not believed to be as important in vivo as they are in vitro, because patients who lack these factors do not bleed abnormally [4]. The PTT is used to monitor anticoagulation with heparin. When PT and PTT are used as tools for measuring anticoagulation, the results are generally not prolonged until factor levels fall to less than 30% of normal [4]. Thrombin time measures the time to clot formation after thrombin is added to anticoagulated blood. This test is a good measure of quantitative and qualitative deficiencies in fibrinogen.

Mixing studies should be one of the initial tests of coagulation status. A prolonged PT or PTT may indicate either a factor deficiency or the presence of an inhibitor. If the test plasma is mixed with an equal amount of normal plasma, deficient factors are restored to at least 50% of normal levels. These levels are sufficient to normalize the clotting results, but an excess of inhibitors remains, and test results are not correct. In the event that mixing studies fail to correct a prolonged coagulation time, confirmatory testing for the specific inhibitors should be conducted.

Another test that may be clinically appropriate is screening for disseminated intravascular coagulation. This test is especially helpful in differentiating disseminated intravascular coagulation from liver failure.

Finally, specific tests can be used to determine which of several inherited thrombophilic conditions may be present, such as abnormalities in antithrombin III activity, protein C level and activity, or protein S level and activity. When patients have a history of venous thromboses and a positive family history of such events, depending on patient age it may be appropriate to evaluate for inherited causes of the hypercoagulable state [6].

The two most common types of chronic anticoagulation medications that may be used by patients seen by oral and maxillofacial surgeons are warfarin and antiplatelet therapy. Understanding the mechanism or pathophysiology of anticoagulation and the indications for which medicated patients are being treated greatly aids in decisions regarding the treatment of these patients.

## Warfarin therapy

Patients may require warfarin therapy for such diagnoses as atrial fibrillation, pulmonary embolism, myocardial infarction, stroke, and deep venous thrombosis or because they have prosthetic heart valves. Warfarin causes anticoagulation by inhibiting the vitamin K-dependent coagulation factors II, VII, IX, and X. Its duration of action is 2 to 5 days. Warfarin is 99% bound to plasma proteins. The addition of other medications that are also protein bound may result in decreased binding of warfarin, which increases the level of anticoagulation. PT or INR is checked regularly so that therapeutic levels of the drug can be maintained in the blood.

Several studies have evaluated dentoalveolar surgery among anticoagulated patients. Souto and colleagues [7] prospectively studied bleeding complications in 92 patients who were chronically treated with acenocoumarol for valvular heart disease or cardiac valve prosthesis and who were scheduled for dental extractions (one or two teeth). At the time of surgery, the INR of all patients was between 2 and 3. Patients were assigned to one of six groups. For three groups, the acenocoumarol dosage was decreased before surgery and one of three antifibrinolytic therapies was initiated: oral epsilon-amino-caproic acid (4 g orally) before surgery, tranexamic acid as a mouthwash, or oral epsilon-amino-caproic acid as a mouthwash. The other three groups used the same antifibrinolytic therapies but maintained the normal dosage of acenocoumarol. There was no statistically significant difference between groups on the basis of gender, age, gingival hypertrophy, surgical trauma, or number of extracted teeth. The authors concluded that the most desirable treatment was no change in the dose of anticoagulation medication and topical treatment with tranexamic acid for 2 days after surgery. They also determined that heparin administration was an additional uncontrollable risk factor for hemorrhagic complications.

Blinder and colleagues [8] studied three types of local hemostasis after extractions performed on patients who were maintained on coumarin therapy. Reasons reported for anticoagulation included valvular disease, atrial fibrillation, ischemic heart disease, and venous thromboembolism. Patients in group one were treated with a gelatin sponge in the extraction site and sutures; patients in group two were treated with a gelatin sponge, sutures, and tranexamic acid mouthwash for 4 days; patients in group three were treated with fibrin glue, gelatin sponges, and sutures. Reasons for extraction were severe periodontitis and deep caries. The patients' preoperative INRs ranged

from 1.5 to 4. There was no statistically significant difference in postoperative bleeding between groups. Postoperative bleeding was associated with advanced periodontal disease but was not associated with an elevated INR. All postoperative bleeding episodes (13/150 patients) were controlled with local measures.

Blinder and colleagues [9] studied the association of INR and bleeding complications after dental extractions. In a study of 249 patients who underwent 543 extractions, the authors separated the INR values into five ranges: 1.5 to 1.99, 2.0 to 2.49, 2.5 to 2.99, 3.0 to 3.49, and higher than 3.5. After the extractions, patients were treated with gelatin sponges and sutures at the extractions sites. Prolonged postoperative bleeding occurred among 12% of patients, but there was no statistically significant difference in bleeding time between the five groups.

The invasiveness of the procedure is important in the determination of treatment for anticoagulated patients. Simple extractions can be accomplished without cessation of anticoagulation therapy. The use of gelatin sponges and sutures after simple extractions has been shown to control postoperative bleeding in patients with INRs as high as 3.5 [8,9]. For more invasive procedures, conventional therapy has included hospitalization, heparinization, and daily monitoring of PT, PTT, and INR. Such procedures are typically required for 3 to 4 days before surgery so that a patient's INR can normalize. Heparin administration is discontinued 6 hours before surgery and resumed postoperatively. Warfarin administration is also resumed postoperatively, and heparin administration can be discontinued when the INR reaches the therapeutic level [10,11].

The condition for which a patient is treated is also important in the decision about the anticoagulation process. For example, the risk of stroke in a patient treated for atrial fibrillation is lower than the risk of thrombus in a patient treated for a mechanical heart valve. These patients might be treated differently with regard to discontinuation of anticoagulation therapy.

An interesting study by Pham and colleagues [12] examined the risks associated with discontinuing warfarin therapy for high-risk patients who were being treated for intracranial hemorrhage. Indications for anticoagulation were prosthetic heart valves (group 1), atrial fibrillation and cardioembolic stroke (group 2), and recurrent transient ischemic attack or and ischemic stroke (group 3). The probability of an ischemic stroke 30 days (Kaplan-Meier curve) after the discontinuation of warfarin was 2.9% for group 1, 2.6% for group 2, and 4.8% for group 3. The authors concluded that cessation of warfarin therapy for 1 to 2 weeks is

associated with a comparatively low probability of embolic events in patients at high risk for embolism.

A review of 28 patients by Ananthasubramaniam and co-workers [13] led to similar conclusions. All patients had mechanical heart valves and were receiving chronic anticoagulation therapy. This therapy was discontinued because of severe bleeding complications. The mean duration of warfarin cessation was 15 days. Four deaths occurred: two were thought to be related to the initial diagnosis, one was caused by intracerebral bleeding, and one was caused by massive hematemesis. Telephone follow-up at 6 months found that no clinically recognized thromboembolic events had occurred in 19 of 21 patients.

Another strategy that can be used to treat patients undergoing long-term anticoagulation is decreasing a patient's INR to 1.5 to 2.0 without discontinuing treatment entirely. No study has shown that the risk of bleeding is significantly increased when the INR is kept in this range. Larson and colleagues [14] reported the outcomes of 93 patients treated in this way. Most of the patients, all of whom were chronically treated with warfarin, were at high risk of thromboembolic events during the perioperative period. Of the surgical procedures for which the INRs were adjusted, 58% were considered to be substantially invasive (joint replacement, vascular surgery). For 35 patients, warfarin was supplemented with heparin (administered intravenously or subcutaneously) or with low molecular weight heparin (LMWH) (administered subcutaneously) because the INR fell below 1.5. The mean INR was 2.1 on the day before and 1.8 on the day of surgery (range, 1.2–4.9). Complications were four minor bleeding episodes, two major bleeding episodes (2% rate of major bleeding), two events of thromboembolism (one death), and the need for 34 transfusions. Most of the transfusions occurred in patients who received autogenous units of previously donated blood for joint replacement surgery. The theoretical advantage of continuing warfarin therapy and maintaining the INR between 1.5 and 2 is the rebound phenomenon and the hypercoagulable state that occurs when warfarin therapy is stopped and started [14].

### Antiplatelet therapy

Multiple medications are used as antiplatelet therapy. Patients may be treated with antiplatelet drugs for various reasons. Antiplatelet therapy has been shown to be effective in decreasing the risk of myocardial infarction and nonfatal stroke among patients who have peripheral vascular disease [15,16].

Clopidogrel, a commonly administered antiplatelet drug, inhibits ADP-induced platelet fibrinogen binding. Clopidogrel has been identified as an independent risk factor for re-exploration after coronary artery bypass graft surgery [17]. In one study, the risk of surgical re-exploration because of postoperative bleeding was 6.1% for patients treated with clopidogrel but only 1% for patients not treated with the drug ( $P=0.058$ ) [17]. The rate of transfusions was also higher for patients treated with clopidogrel. The findings of this study were confirmed in 2005 by Kapetanakis and associates [15], who demonstrated that patients taking clopidogrel and undergoing coronary artery bypass graft surgery had a higher risk of intraoperative hemorrhage, the need for transfusions with various blood products (platelets, packed red blood cells, and fresh frozen plasma), and the need for re-operation to control bleeding.

In only a few instances would maxillofacial surgery be needed within 3 weeks of the insertion of a coronary artery stent. Should major maxillofacial surgery be indicated during this 3-week period, however, antiplatelet therapy should not be stopped. Sharma and colleagues [18] reviewed the records of patients who underwent major noncardiac surgery after coronary stenting. They found that the risk of cardiac complications and death was greatest during the 3 weeks after stent placement; six of seven deaths occurred among patients whose antiplatelet therapy had been discontinued.

Many patients may receive a combination of antiplatelet drugs (eg, aspirin and clopidogrel) [16,19]. This combination has been shown to cause a synergistic antiplatelet action; in other words, the risk of bleeding complications is much higher in association with combined therapy than in association with single-drug therapy. No large trials have been performed to evaluate the risk of bleeding complications in association with combined antiplatelet therapy. A recent survey of vascular surgeons showed that most did not stop the administration of antiplatelet drugs preoperatively [20]. One might assume that the risk of bleeding complications would be much higher in association with vascular procedures (carotid endarterectomy or infrainguinal bypass) than in association with routine exodontia. For more invasive maxillofacial procedures, a surgeon may consider continuing the administration of aspirin alone. The small studies that have been reported indicate that the risk of myocardial infarction and stroke is lower for patients who continue to receive antiplatelet therapy than for patients who stop such therapy. The results also suggest that the risk additional surgery for a bleeding

complication is higher when antiplatelet therapy is not discontinued, however [20].

Other platelet-inhibiting medications are aspirin and ticlopidine. Aspirin inhibits the activity of cyclooxygenase, and ticlopidine inhibits ADP-induced platelet fibrinogen binding. Platelets are affected for the life of the cell, and complete reversal of antiplatelet activity does not occur until after approximately 2 weeks. It has been recommended that the administration of antiplatelet drugs should be discontinued 7 to 9 days before surgery, if indicated, so that sufficient numbers of normal circulation platelets can be regenerated [11].

### Low molecular weight heparins

An alternative to heparin for anticoagulation during warfarin cessation is the administration of LMWH. LMWHs are administered subcutaneously, have a bioavailability of more than 90%, and offer a predictable and reproducible anticoagulant response [21]. There is no need to monitor the anticoagulation activity of the drugs [22]. LMWHs are not totally reversed by protamine, as is regular heparin [21]. The mechanism of action of this group of drugs is via binding to antithrombin III, which increases the ability of antithrombin III to inactivate factor Xa and factor II [22].

LMWHs have been used as bridging therapy for patients taking warfarin. The reported incidence of major bleeding episodes in patients treated with this therapy ranges from 0% to 10% [14,23,24]. An advantage of this bridging therapy is that it avoids the need for postoperative hospitalization while the INR returns to normal [24]. Although LMWHs are approved only for prophylaxis of venous thromboembolism, they may be considered as an alternative to intravenously administered heparin.

### Summary

Patients who are undergoing chronic anticoagulation therapy and require maxillofacial surgery present a challenge to oral and maxillofacial surgeons. Typical treatment previously required prolonged hospital stays, complicated medication adjustments, multiple laboratory tests, and a high level of anxiety. A thorough surgeon continues to elicit a detailed history, perform a thorough physical examination, and consult with a patient's internist or cardiologist. A growing body of literature indicates that routine dental extractions can be completed with only local measures for hemostasis, without cessation of anti-

coagulation medications and without the risk of thromboembolic events.

For patients who need more invasive surgery (eg, patients who have suffered trauma), options include discontinuation of warfarin with heparin bridging, LMWH bridging, and maintaining the INR between 1.5 and 2.0. Patients who receive antiplatelet therapy and require invasive maxillofacial surgery can be treated with single-drug therapy with the use of local measures for hemostasis or can be considered for aspirin therapy alone if on two-drug therapy.

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