



ORAL SURGERY

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### Antithrombotic agents: Implications in dentistry

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Thrombosis and the complicating emboli that can result are important causes of illness and death. Thrombosis is of greater overall clinical importance in terms of morbidity and mortality than all of the hemorrhagic disorders combined. Agents such as heparin, low-molecular weight heparin, warfarin, aspirin, ticlopidine, clopidogrel, and tirofiban are used to prevent venous or arterial thrombosis. Patients taking these antithrombotic agents may be at risk for excessive bleeding after invasive dental procedures. The current antithrombotic agents used in medicine are reviewed, and the dental management of patients taking these agents is discussed. (*Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002;93:544-51)

The dentist today is seeing increased numbers of patients with chronic medical illnesses. Among these patients are those that are being treated with anticoagulant drugs or antiplatelet agents to prevent venous or arterial thrombosis. A major concern in the management of dental patients taking antithrombotic agents is the potential for excessive bleeding after invasive dental procedures. The purpose of this article is to review current antithrombotic agents and suggest how patients taking these agents may be managed when invasive dental procedures are performed.

#### THROMBOSIS

Thrombosis is the formation, from the components of blood, of an abnormal mass within the vascular system. It involves the interaction of vascular, cellular, and humoral factors within a flowing stream of blood. Thrombosis and the complicating emboli that can result

are among the most important causes of sickness and death in developed countries. Thrombosis is of greater overall clinical importance in terms of morbidity and mortality than all of the hemorrhagic disorders combined. Excessive activation of coagulation or inhibition of anticoagulant mechanisms may result in hypercoagulability and thrombosis. Injury to the vessel wall, alterations in blood flow, and changes in the composition of blood are major factors leading to thrombosis.<sup>1</sup>

Thrombotic disorders can be caused by an inherited deficiency of antithrombin III, heparin cofactor II, protein C, protein S, thrombomodulin, plasminogen, or tissue plasminogen activator; an activated protein C resistance (factor V Leiden); dysfibrinogenemia; and homocysteinemia. Most of these disorders have also been reported as acquired conditions. Patients should be considered for laboratory evaluation for inherited thrombotic disorders if they are younger than 45 years of age with recurrent thrombosis. In addition, patients who have had a single thrombotic event and have a family history of thrombosis should be tested.<sup>1</sup>

The pathologic basis for arterial thrombosis involves atherosclerotic vascular disease associated with platelet thrombi. Thrombin is a major mediator in this type of thrombosis. Drug therapy for arterial thrombi involves agents with antithrombin and antiplatelet activity. Venous thrombi usually occur in the presence of a normal vessel wall, with stasis or hypercoagulability being the major predisposing factors. Drugs that prevent thrombin formation or lyse fibrin clots are the major agents used to treat venous thrombi.<sup>1</sup>

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**Table I.** Current antithrombotic agents

Agent	Indications	Dosage	Monitoring	Complications
<i>Anticoagulants</i>				
Standard heparin: High-dose	Rx for DVT, PE Prevention of DVT	IV bolus 5-10,000 units, IV infusion at rate of 1,300 units per hour for 5-10 days	APTT 1.5 to 2.5 times the mean laboratory control value	Bleeding Thrombocytopenia
Standard heparin: Low-dose	Prevention of DVT	SC 5000 units 2 hours before surgery and every 8-12 hours until ambulatory	None	Bleeding Thrombocytopenia
Warfarin	Rx DVT, PE Prevention of DVT or thrombosis in AF, MPHV Prevention of recurrent MI	Oral, 5-7 mg/day for 3-6 months Oral, 7-10 mg/day long-term	INR: 2.0 to 3.0 INR: 2.5 to 3.5	Bleeding Intolerance: alopecia, GI dis- comfort, rash, skin necrosis
Low-molecular weight heparins Enoxaparin (Lovenox)*	Prevention DVT, PE Rx DVT	30 mg SC every 12 hours for up to 14 days (knee or hip) 40 mg SC once per day with first dose 2 hours prior to abdominal surg- ery 1 mg/kg SC every 12 hours up to 5 days	None Oral Warfarin started within 72 hours	Bleeding Thrombocytopenia Anemia Fever Peripheral edema
<i>Antiplatelet drugs</i>				
Aspirin	Prevention recurrent MI, stroke, coronary thrombosis	Oral, 75 to 325 mg once per day	Usually none, but bleeding time can be used	GI bleeding Tinnitus Urticaria Bronchospasm
Aspirin plus dipyridamole (Aggrenox)	Prevention stroke (history of TIA)	Oral, 200 mg dipyridamole and 50 mg aspirin twice per day	Usually none	GI bleeding GI ulceration Urticaria Bronchospasm
NSAIDs Ibuprofen (Advil, Motrin)	Prevention recurrent MI, Stroke, coronary thrombosis	Oral 400 mg once per day	Usually none	GI bleeding GI ulceration Rash, urticaria Tinnitus
Adenosine diphosphate inhibitors: Clopidogrel (Plavix), Ticlopidine (Ticlid)	Prevention TIA, stroke, and MI	Oral 75 mg once per day Oral 250 mg twice per day	Usually none Complete blood cell count every 2 weeks	GI bleeding Thrombocytopenia Diarrhea
Fibrinogen receptor inhibitors: Tirofiban (Aggrastat) <sup>†</sup>	Prevention recurrent MI, stroke, TIA	IV 4.0 µg/kg/min for 30 minutes, then 0.1 µg/kg/min until steady state	Usually none	GI bleeding GI ulceration Rash Neutropenia Thrombocytopenia

Rx, Prescription; DVT, deep venous thrombosis; PE, pulmonary embolus; IV, intravenous; SC, subcutaneous; MPHV, mechanical prosthetic heart valve; MI, myocardial infarction; INR, international normalized ratio; GI, gastrointestinal; AF, atrial fibrillation; TIA, transient ischemic attack; NSAIDs, nonsteroidal antiinflammatory drugs.

\*Other LMWHs: ardeparin (Normiflo), dalteparin (Fragmin), nadroparin (Fraxiparine), reviparin (Clivarin), and tinzaparin (Innohep).

<sup>†</sup>Other fibrinogen receptor (GP IIb-IIIa) inhibitors (FRIs): abciximab (ReoPro), eptifibatid (Integrilin).

## ANTICOAGULANT DRUGS

### Venous thrombosis

**Heparin.** Standard heparin is used in high-dose therapy to treat thromboembolism and in low-dose therapy as a prophylaxis for thromboembolism (Table I). Heparin itself is not an anticoagulant. Plasma antithrombin III (ATIII) is the actual anticoagulant, with heparin serving as a catalyst.<sup>1</sup> ATIII regulates coagulation by inactivating activated coagulation proteases such as thrombin and factor Xa. Heparin binds to ATIII to enhance the inactivation of these proteases.

It is now recommended that patients over the age of 40 who are going to have major surgery receive prophylaxis with graded compression elastic stockings, low-dose heparin therapy, or intermittent pneumatic compression.<sup>1</sup> If standard heparin prophylaxis is used, 5000 units are given subcutaneously (SC) 2 hours before surgery and every 8 to 12 hours until the patient is ambulatory.<sup>1</sup>

Standard heparin consists of an unfractionated heterogeneous mixture of polysaccharide chains with a mean molecular weight of 12,000 to 16,000 d. It inhibits factor Xa and thrombin equally. Treatment

with standard heparin usually consists of intravenous (IV) infusion in a hospital setting and requires monitoring with the activated partial thromboplastin time (aPTT). The aPTT is a laboratory test that uses a sample of the patient's blood to measure the ability of blood to clot. A control sample is always performed with the test. A contact activator, such as kaolin, is added to the patient's blood sample. Under normal circumstances, the blood should clot within 25 to 35 seconds. The effects of heparin are to prolong the aPTT. The goal for therapy with heparin is usually to give a dosage that will prolong the aPTT to 50 to 70 seconds. Standard heparin has a half-life of 1 to 2 hours. The only patients treated with standard high-dose heparin on an outpatient basis are those receiving hemodialysis. The heparin effect lasts only several hours after dialysis because of the short half-life of the drug.

*Low-molecular weight heparin.* The action of the low-molecular weight heparins (LMWH) is the same as for standard heparin, serving as a catalyst for ATIII. An LMWH can be used instead of standard heparin for patients having major surgery. LMWH is now the treatment of choice for patients undergoing total hip or knee replacement because of its superior efficacy compared with SC standard heparin in the prevention of thromboembolism (Table I).

LMWH is prepared by depolymerization of unfractionated heparin chains, yielding heparin fragments with a mean molecular weight of 4000 to 6000 d. LMWH preparations have greater activity against factor Xa than thrombin (factor II).<sup>2</sup> LMWHs exhibit less binding to plasma proteins, endothelial cells, and macrophages than standard heparin. Thus, they have better bioavailability when administered SC, longer half-lives, and more predictable anticoagulant effects. The LMWHs are administered SC in the abdomen. The dosage for each drug is based on body weight and no laboratory monitoring is needed. The half-life of the LMWHs is about 2 to 4 hours. Treatment with the LMWHs can occur on an outpatient basis.<sup>2-4</sup>

Enoxaparin (Lovenox) is the most widely used LMWH. There are 5 other LMWH preparations: ardeparin (Normiflo), dalteparin (Fragmin), nadroparin (Fraxiparine), reviparin (Clivarin), and tinzaparin (Innohep).\*

Unlike many drugs within the same class, it is difficult to compare the efficacy of one LMWH with another because of the difference in molecular weight and pharmacodynamic properties. As a result, each

LMWH must show efficacy in clinical trials for each indication before it can be considered effective for that indication. The mean molecular weight of these LMWHs range from 4200 d for enoxaparin to 6000 d for ardeparin and dalteparin. Their anti-Xa/thrombin ratio varies from 1.9 for ardeparin and tinzaparin to 3.8 for enoxaparin.<sup>3</sup>

*Warfarin.* Warfarin (Coumadin) is an oral anticoagulant that inhibits the biosynthesis of the vitamin K-dependent coagulation proteins (factors VII, IX, and X and prothrombin). This drug is bound to albumin, metabolized by hydroxylation in the liver, and excreted in the urine. The prothrombin time ratio (PTR, defined as the patient's prothrombin time divided by a laboratory control value) is used to monitor warfarin therapy because it measures three of the vitamin K-dependent coagulation proteins: factors VII and X and prothrombin. The PT is particularly sensitive to factor VII deficiency. Therapeutic anticoagulation with warfarin takes 4 to 5 days.<sup>1</sup>

The PT has been shown to be imprecise and variable. There may be little comparability of PT values taken in different laboratories. The variability of PT values is attributable to differences in the source of thromboplastin (human brain, rabbit brain), the brand of thromboplastin, and the type of instrumentation used. This variability has caused problems with bleeding in patients given high-dose anticoagulation based on an artificially low PT.<sup>5</sup>

In 1985, the International Committee on Thrombosis and Homeostasis requested that all lots of thromboplastin have their international sensitivity index (ISI) indicated.<sup>6</sup> The ISI establishes the reference standard of 1.0 based on human brain-derived thromboplastin. An ISI greater than 1.0 designates a less sensitive thromboplastin, whereas a value less than 1.0 indicates a more sensitive thromboplastin. This allows uniformity of the results from different laboratories by the introduction of the international normalized ratio (INR), which is calculated by the formula  $INR = (PTR)^{ISI}$ , where the PTR corresponds to the patient's prothrombin time divided by that of reference control plasma.<sup>5,6</sup>

The INR system has slowly been accepted and adapted over the last decade by clinicians and laboratories. Minor problems remain with use of thromboplastins with high ISI values, incorrect ISI values assigned by manufacturers, and laboratories using different reagent-instrument combinations than those used by the manufacturers.<sup>1,7-11</sup>

Warfarin therapy is given in lower dosage (low-intensity therapy) for conditions such as the treatment or prevention of venous thrombosis. It is given in higher dosage (high-intensity therapy) to patients with prosthetic heart valves or to prevent recurrent myocardial

\*Note that the US Food and Drug Administration approves all of these agents for prophylaxis or treatment of deep vein thrombi (DVT) and asymptomatic pulmonary embolism.

**Table II.** Recommended therapeutic range for warfarin therapy

<i>Low-intensity (INR* goal 2.5 with a range of 2.0 to 3.0)</i>
Prophylaxis of venous thrombosis (high-risk surgery)
Treatment of venous thrombosis
Treatment of pulmonary embolism
Prevention of systemic embolism
Tissue heart valves
Acute MI
Atrial fibrillation
Valvular heart disease
<i>High-intensity (INR goal 3.0 with a range of 2.5 to 3.5)</i>
Mechanical prosthetic heart valves
Prevention of recurrent myocardial infarction
Treatment of thrombosis associated with antiphospholipid antibodies

*INR*, International normalized ratio.

From Hirsh J, Fuster V. AHA medical/scientific statement. Guide to anticoagulant therapy, part 2: oral anticoagulants. *Circulation* 1994;89:1469-80, and Rodgers GM. Thrombosis and antithrombotic therapy. In: Lee GR, Foerster J, Lukens J, Paraskevas F, Greer JP, Rodgers GM, eds. *Wintrobe's clinical hematology*. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 1781-821.

infarction. The recommended INR goal for a patient on low-intensity warfarin therapy is 2.5 with a range of 2.0 to 3.0. For a patient on high-intensity anticoagulation therapy, the INR goal is 3.0 with a range of 2.5 to 3.5.<sup>1,4,12</sup> Table II shows the conditions recommended for low-intensity and high-intensity warfarin therapy and the recommended INR level.

Scardi and Mazzone<sup>13</sup> reported on new strategies being developed for managing the care of patients taking warfarin for anticoagulation therapy. One promising modality has the patients performing their prothrombin time measurements at home. This model is possible through point-of-care instrumentation for prothrombin testing. One instrument now available is the CoaguChek (Roche Diagnostics).<sup>14</sup> These portable monitors can measure a prothrombin time from a finger-stick sample of whole blood and provide results within seconds. It is far too early to know if this may turn out to be a management strategy that will maximize the benefit/risk ratio of anticoagulant therapy.

Patients with deep vein thrombosis or symptomatic pulmonary embolism are usually treated with intravenous standard heparin in dosages sufficient to prolong the aPTT to a range corresponding to a heparin level of 0.2 to 0.4  $\mu\text{g}/\text{mL}$  (1.5 to 2.5 times control value). Some patients with DVT or asymptomatic pulmonary embolism are treated with a LMWH. The usual dosage of enoxaparin is 1 or 1.5 mg/kg SC every 12 hours for approximately 5 to 7 days. Therapy is continued for at least 5 days or longer to decrease thromboembolism recurrence. Oral anticoagulation with warfarin is started early and should overlap the heparin treatment for 4 to 5 days to minimize the

increased hypercoagulability of warfarin when first initiated. The heparin treatment is stopped after 5 to 10 days once the INR from warfarin dosing is at a therapeutic level. The warfarin treatment is continued for at least 3 months in uncomplicated nonrecurrent DVT. Complications with heparin treatment include thrombocytopenia or thrombosis. Because of the risk and negative sequelae of heparin-induced thrombocytopenia, the platelet counts of patients on unfractionated or fractionated heparin (LMWH) should be monitored at least every 2 to 3 days. Significant reductions in the platelet count below 100,000/ $\mu\text{L}$  may require discontinuation of heparin therapy. Overdosage of heparin can cause significant clinical bleeding.<sup>1</sup>

### Arterial thrombosis: Antiplatelet drugs

Platelets are an important contributor to arterial thrombi. Antiplatelet treatment has been reported to reduce overall mortality from vascular disease by 15% and reduce nonfatal vascular complications by 30%. Aspirin is the prototypical antiplatelet drug. Aspirin exerts its antithrombotic action by irreversibly inhibiting platelet cyclooxygenase, preventing synthesis of thromboxane  $A_2$ , and impairing platelet secretion and aggregation. Aspirin is the least expensive, most widely used, and most widely studied antiplatelet drug. Dipyridamole increases cyclic adenosine monophosphate and was once used by itself for anticoagulation therapy. It was found to be ineffective, however, and is now compounded with aspirin (Aggrenox) and used for stroke prevention.<sup>1</sup>

The majority of nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen and indomethacin, act as reversible inhibitors of cyclooxygenase and are used clinically in a limited extent. Salsalate and COX-2 inhibitors (Celecoxib and Rofecoxib) are examples of NSAIDs that do not appreciably affect platelet activity when used in therapeutic dosage.<sup>1</sup>

Ticlopidine (Ticlid) and clopidogrel (Plavix) inhibit platelet activity by disrupting platelet aggregation through inhibition of adenosine diphosphate.<sup>1,15-18</sup>

A newer class of antiplatelet drugs, fibrinogen receptor (platelet cell surface glycoprotein IIb and IIIa) inhibitors, is now available for clinical use. Tirofiban (Aggrastat) is the most commonly used drug from this group. Other fibrinogen receptor inhibitors include abciximab (ReoPro) and eptifibatid (Integrilin).<sup>1,19,20</sup>

## DENTAL MANAGEMENT

### Patients taking standard heparin

Most patients treated with standard heparin are hospitalized and will be placed on warfarin once discharged. Dental emergencies in these hospitalized patients should be treated as conservatively as possible,

**Table III.** Topical hemostatic agents used to control bleeding

<i>Product</i>	<i>Company/dealer</i>	<i>Description</i>	<i>Indications and features</i>
Gelfoam	Upjohn	Absorbable gelatin sponge made from purified gelatin solution. Absorbs in 3-5 days.	Useful for most patients taking an antithrombotic agent. Helpful to place topical Thrombin on Gelfoam. For extensive or invasive surgery, one should consider placing inside a splint.
Instat	Johnson & Johnson	Absorbable collagen made from purified and lyophilized bovine dermal collagen. Can be cut or shaped. Adheres to bleeding surfaces when wet, but does not stick to instruments, gloves, or gauze sponges.	Mild-to-moderate bleeding is usually controlled in 2-5 min. More expensive than Gelfoam.
Surgicel Oxycel	Johnson & Johnson Becton-Dickinson	Oxidized regenerated cellulose. Exerts physical effect rather than physiologic. Swells upon contact with blood, with resulting pressure adding to hemostasis. Thrombin ineffective with these agents because of inactivation as a result of pH factors.	After 24-48 h, it becomes gelatinous. Can be left in place or removed. Useful to control bleeding when other agents ineffective.
Avitene Helistat	MedChem Marion Merrell Dow	Microfibrillar collagen hemostat (MCH). Dry, sterile, fibrous, water insoluble, HCl acid salt purified bovine corium collagen. MCH attracts platelets and triggers aggregation in fibrous mass.	Thrombin ineffective with these agents due to inactivation as a result of pH factors. Moderate-to-severe bleeding.
Colla-Cote, Tape, Plug	Colla-tec, Inc Marion	Absorbable dressings from bovine collagen. Can be sutured into place, used under stents, dentures, or alone. Fully resorbed in 10-14 days.	Shaped according to intended use; Cote ¾ in × 1.5 in, Tape 1 in × 3 in, Plug 3/8 in × ¾ in. All are superior hemostats for moderate-to-severe bleeding.
Thrombostat Thrombinar Thrombogen	Parke-Davis Jones Medical Johnson & Johnson —Merck	Topical thrombin. Directly converts fibrinogen to fibrin. Derived from bovine sources.	One 5000-unit vial dissolved in 5 mL of saline solution can clot equal amount of blood in less than 1 sec. Useful in severe bleeding.
Cyklokapron	KabiVitrum	Tranexamic acid. Works as a competitive inhibitor of plasminogen activation. Used as a rinse.	Useful in short term (2-8 d) for preventing hemorrhage following dental extractions.
Berioplast	Behringwerke	Fibrin/tissue glue.	Not available in the United States at this time.

avoiding invasive procedures. Consultation with the patient's physician is recommended. In contrast, patients undergoing hemodialysis are administered heparin in an outpatient setting. Since the half-life of heparin is only 1 to 2 hours,<sup>1</sup> these patients can safely receive invasive dental treatment the day after dialysis. Alternatively, the attending physician may give permission for hemodialysis to be performed without heparin when major surgical procedures are required on the day of dialysis.

### Patients taking LMWH

Outpatients taking LMWH can have invasive dental procedures performed without altering their LMWH medication. Any excessive postoperative bleeding can be managed using local measures. These patients are not typically monitored with laboratory tests such as PT or aPTT. If significant bleeding is anticipated, based on the type of surgery planned or a high dosage of LMWH, the LMWH could be discontinued for one day by the patient's physician (half-life is 2 to 4 hours) and the surgery performed the next day. The LMWH therapy could then be restarted once hemostasis is achieved. Another option is to wait until the LMWH

therapy has been completed and then perform elective invasive procedures. Consultation with the patient's physician is recommended before selection of any of these options.

### Patients taking warfarin

A review by Wahl<sup>21</sup> found little to no risk of significant bleeding following dental surgical procedures in patients with a PT of 1.5 to 2 times normal. Wahl also reported evidence that there was little risk of bleeding complications even if the PT is up to 2.5 times normal, and a greater risk of adverse outcome is associated with stopping anticoagulation. A study by Benolie<sup>22</sup> also suggested that dental surgery could be performed without major bleeding complications in patients with greater than 2 times the normal PT while receiving anticoagulation therapy. Devani et al<sup>23</sup> reported no differences in clinical bleeding problems in patients whose anticoagulant was discontinued (mean INR 1.6) and those who remained on their medication (mean INR 2.7). The authors concluded that there was no justification to alter warfarin dosage if an INR of 4 or less is found. Giglio<sup>24</sup> has suggested the following guidelines: single tooth extraction or minimally inva-

sive procedures are indicated if the INR is less than 4; in cases where moderate bleeding is expected, reduce the INR, depending on the risk to the patient; adjust warfarin to achieve an INR less than 3 if significant bleeding is expected; and avoid any surgery if the INR is greater than 5. On the basis of information from these studies, our suggestion is to obtain medical consultation and reduce the level of anticoagulation before surgery on patients with a PT value higher than 2.5 or INR value higher than 3.5

If the physician reduces the dosage, instructions will be given to the patient with respect to how much drug should be taken. Current information does not support stopping the anticoagulant, which increases the risk for thrombotic events. It should be noted that it takes 3 to 5 days for the effect of the reduced dosage of warfarin to be reflected in a decrease in the PT or INR.<sup>25</sup>

If infection is present, surgery should be avoided until the infection has been treated. When the patient is free of acute infection and the PT is less than 2.5 times normal or the INR is less than 3.5, surgery can be performed. The procedure should be done with as little trauma as possible. If excessive postoperative bleeding occurs, Gelfoam with thrombin can be used to control it. In some patients, it may be helpful to construct a splint before surgery to cover the surgical area, which will protect the clot, and Gelfoam with thrombin can be packed beneath the splint. In addition, primary closure over the sockets is desirable.

Oxycel, Surgicel, or microfibrillar collagen may be used in place of Gelfoam. See Table III for a summary of these and other treatments. However, thrombin should not be used in combination with these agents. Because thrombin is inactivated as a result of pH factors,<sup>26</sup> its use would thus represent an additional cost with no real benefit. Application of an inhibitor of fibrinolysis, such as tranexamic acid, also can be used. Tranexamic acid can be provided soaked into gauze or as a rinse, oral tablets, or IV injection. The usual oral dosage is 25 mg/kg three to four times per day for 2 to 8 days.<sup>26</sup> Tranexamic acid (Cyklokapron, KabiVitrum) in an oral rinse is the most common use of the agent in dentistry.<sup>27</sup>

The dentist must be aware that certain drugs will affect the action of warfarin. Drugs the dentist may use that potentiate the anticoagulant action of warfarin are acetaminophen, metronidazole, salicylates, broad-spectrum antibiotics, erythromycin, and the new COX-2-specific inhibitors. Other potentiating drugs are cimetidine, chloral hydrate, phenytoin, propranolol, and thyroid drugs such as thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>). Drugs the dentist may use that will antagonize the anticoagulant action of warfarin are barbiturates, steroids, and nafcillin. Other drugs that can

antagonize warfarin are carbamazepine, cholestyramine, griseofulvin, rifampin, and trazodone.<sup>1,28</sup>

Postoperative pain control can be obtained by using minimal dosage of acetaminophen with or without codeine. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) must be avoided in the patient who takes warfarin. Although when used in the indicated dosage, the COX-2-specific inhibitors do not affect platelet count, PT, or PPT and do not inhibit platelet aggregation, they can increase the PT and INR in patients taking warfarin. If used, the dosage of COX-2-specific inhibitors should be reduced.<sup>1</sup>

### Patients taking antiplatelet agents

*Aspirin.* The best screening test for the effect of aspirin on coagulation is the platelet function analyzer (PFA-100).<sup>29-35</sup> If this is not available, then the Ivy bleeding time can be used. Although aspirin affects platelets and the coagulation process through its effect on platelet release, it does not usually lead to a significant bleeding problem unless the bleeding time is greater than 20 minutes.

If surgery must be performed under emergency conditions and the bleeding time is in excess of 20 minutes, 1-desamino-8-D-arginine vasopressin (DDAVP) can be used to shorten the bleeding time. The mechanism of action is not clear but may involve enhancement of von Willebrand's factor activity.<sup>36,37</sup> DDAVP can be given parenterally or by nasal spray one hour before surgery. Parenterally the dose of DDAVP is 0.3 µg/kg of body weight, with a maximum dose of 20 to 24 µg. The nasal spray, Stimate (desmopressin), contains 1.5 mg/mL of DDAVP and is given in a dose of 300 µg/kg. Usually, one dose will be sufficient. DDAVP should be used with caution in older patients with cardiovascular disease because of the potential risk of drug-induced thrombosis.<sup>25, 36-40</sup> This should be done in consultation with the patient's physician or hematologist. On a less urgent basis, with approval from the physician, the aspirin can be discontinued for 3 days, which ensures that a sufficient number of new platelets to are released into the circulation.

*Nonaspirin NSAIDs.* The nonaspirin NSAIDs can also inhibit platelet cyclooxygenase, thereby blocking the formation of thromboxane A<sub>2</sub>. These drugs produce a systemic bleeding tendency by impairing thromboxane-dependent platelet aggregation and thus prolonging the bleeding time. However, these drugs inhibit cyclooxygenase reversibly, and the duration of their action depends on the specific drug dose, serum level, and half-life. Generally, if the clinician waits 3 half-lives of the drug, levels will be sufficiently eliminated to allow normal platelet function to return. It should be remembered that the clinical risks of

bleeding with aspirin or nonaspirin NSAIDs are increased by the use of anticoagulants or alcohol and conditions such as advanced age, liver disease, and coexisting coagulopathies.<sup>41</sup>

**ADP and fibrinogen receptor inhibitors.** Patients taking clopidogrel (Plavix) or fibrinogen receptor inhibitors can have invasive dental procedures performed without altering the dosage. If excessive bleeding occurs, it should be controlled by local measures. If major oral surgery is planned and excessive bleeding is anticipated, clopidogrel should be discontinued 7 days prior to surgery.<sup>18</sup> Medical consultation should be sought. The physician should inform the patient when to stop the drug prior to surgery and inform the patient when it is safe to resume the medication.

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