

Cardiovascular Drugs: Implications for Dental Practice

Part 2—Antihyperlipidemics and Antithrombotics

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Appropriate preoperative assessment of the dental patient should always include an analysis of the patient's medications. Cardiovascular diseases are the most common group of medical disorders that dentists encounter, and the number of drugs prescribed for managing these conditions is staggering. This justifiably raises concern and probable confusion regarding side effects and possible drug interactions with medications the dentist may deem necessary for dental care. This continuing education article is the second in a series that will address essential pharmacology of medications commonly prescribed for chronic medical care. A reasonable understanding of these agents will allow the dentist to better appreciate the medical status of their patients, to appreciate the actual risks associated with antithrombotic medications, and to avoid adverse interactions with drugs the dentist might administer or prescribe.

Key Words: Preoperative assessment; Drug interactions; Drug side effects; Drug toxicity; Anticoagulants; Postoperative bleeding.

ANTIHYPERTENSIVE AGENTS

Total cholesterol and low-density lipoprotein, which contains high amounts of cholesterol, are highly correlated with atherosclerotic cardiovascular disease. Cholesterol is transported in serum as a component of lipoproteins, which in turn are classified according to their cholesterol content. Low-density lipoprotein is rich in cholesterol content, whereas high-density lipoprotein contains relatively sparse amounts of cholesterol. A continuum for risk commences as total cholesterol levels exceed 160 mg/dL, and every 10% decrease in cholesterol is associated with a 20% reduction in atherosclerotic cardiovascular disease. Modifications in diet and lifestyle can realistically lower cholesterol levels by 10%, but greater reductions require the concurrent use of drug therapy.¹ Elevated levels of low-density lipoprotein are understandably viewed as a risk for cardiovascular disease, but an explanation of

why high-density lipoprotein levels are protective remains elusive. Nevertheless, the goals of pharmacological therapy are to lower low-density lipoprotein and raise high-density lipoprotein serum concentrations.

The principal agents used to lower plasma lipoprotein levels include HMG CoA-reductase inhibitors, bile acid-binding resins, and nicotinic acid (niacin). The HMG CoA-reductase inhibitors, nicknamed statins, are the most effective agents currently available and have the lowest incidence of side effects. Although the occurrence of such events is rare, they have been implicated in producing destruction of skeletal muscle cells (rhabdomyolysis). A summary of the lipid-lowering profiles for these agents is presented in Table 1.

Two additional agents may also be used to reduce cholesterol levels. Nicotinic acid reduces the hepatic synthesis of very-low-density lipoprotein but produces significant side effects including gastritis, flushing, hepatotoxicity, and hyperglycemia. Bile acid sequestrants, such as cholestyramine (Questran), bind to bile acids and hasten their elimination. This requires the liver to convert cholesterol into new bile acids. Dyspepsia and foul taste are their principal side effects.

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Table 1. Lipid-Lowering Properties of HMG-CoA Reductase Inhibitors^{1*}

Drug	Mean Change from Baseline (%)				
	TC	LDL	HDL	Apo-B	TG
Atorvastatin (Lipitor)	(-) 44–58	(-) 41–60	(+) 5–7.5	(-) 50	(-) 37–53
Fluvastatin (Lescol)	(-) 25	(-) 33–38	(+) 7–11	(-) 27	(-) 19–25
Lovastatin (Mevacor)	(-) 29–34	(-) 40–42	(+) 8–10	(-) 19–27	(-) 10
Pravastatin (Pravachol)	(-) 27	(-) 37	(+) 3	No data	(-) 19
Rosuvastatin (Crestor)	(-) 40–46	(-) 43–63	(+) 10–17	(-) 54	(-) 28–43
Simvastatin (Zocor)	(-) 31–52	(-) 36–51	(+) 7–16	No data	(-) 24–38

* Data based on maximum daily dose. TC indicates total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; Apo-B, apolipoprotein B; and TG, triglyceride.

For patients with mild hypercholesterolemia, particularly older individuals, the bile acid sequestrants and nicotinic acid can be quite effective, but their side effects are troubling. In most instances, these agents have been relegated as adjuncts to the statins when more aggressive treatment is required.

Dental Implications for Patients Medicated With Antihyperlipidemics

Side effects of these drugs have little impact on dental management, but some consideration must be given to potential drug interactions with certain antimicrobials that may be prescribed by the dentist.¹ Macrolide antibiotics such as erythromycin and azole antifungal agents such as ketoconazole should be avoided in patients taking any of the statins. These antimicrobials elevate the serum levels of statins, which increases their risk for myopathy and possible hepatotoxicity. Tetracycline preparations will be absorbed poorly in patients taking bile acid sequestrants.

ANTITHROMBOTIC AGENTS

Antithrombotic drugs are prescribed extensively in medical practice. Patients who are managed with these agents introduce concerns not only for postoperative hemorrhage but also for their potential for significant drug interactions. To evaluate and understand these risks, it is essential to have a better understanding of the various classes of antithrombotics and their impact on thrombogenesis.

Thrombogenesis (clot formation) includes 2 principal processes; platelet aggregation and coagulation (Figure 1). Platelet aggregation consists of activated platelets attaching to strands of fibrinogen, whereas coagulation is a complex cascade of enzymatic events leading to the formation of fibrin strands. The sequence of these 2 processes, and their consequences,

differs during thrombogenesis in arteries compared to thrombogenesis in veins.² Platelet activation is the initial event during arterial thrombogenesis. Platelets adhere to damaged vessel walls, aggregate, and provide a core around which fibrin strands accumulate. Arterial thrombi are prone to occlude arterial flow, which leads to ischemia of local tissues. In contrast, venous thrombi commence as fibrin strands and embolize great distances, ultimately lodging in the pulmonary arteries, ie, pulmonary embolism.

Antiplatelet drugs and anticoagulants target each component of clot formation and can be used to prevent thrombogenesis but have no effect on existing clots, other than limiting their progression. Only the fibrinolytic (thrombolytic) drugs can actually dissolve an existing thrombus. Hemorrhage is the principal side effect common to all antithrombotic agents.

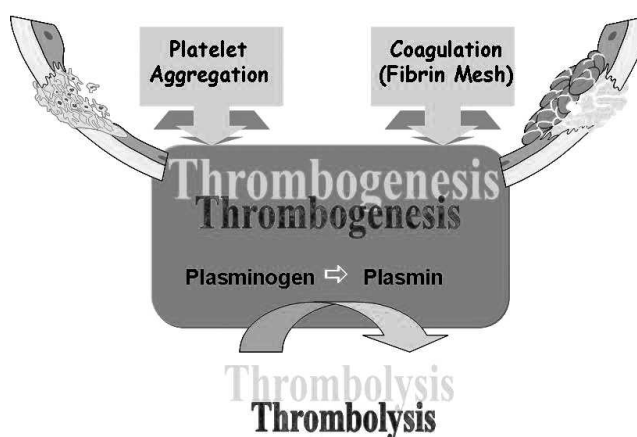


Figure 1. Summary of thrombogenesis and thrombolysis. A thrombus consists of 2 principal components: an aggregate of platelets and a fibrin mesh. Platelet activity consists of adherence to vessel walls (adhesion) and to one another (aggregation). The fibrin mesh is synthesized during a complex cascade of enzymatic reactions leading to the formation of fibrin strands (coagulation). The body also has a natural thrombolytic system, essentially comprised of plasmin, an enzyme that cleaves fibrin strands. Antithrombotic drugs are classified according to action on each of these processes: antiplatelet drugs, anticoagulants, and thrombolytics (fibrinolytics).

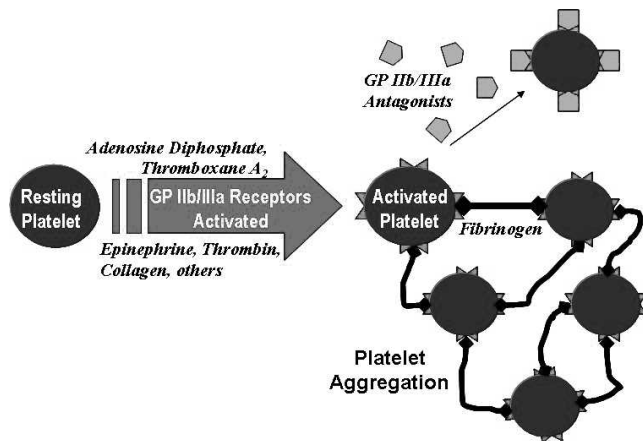


Figure 2. Resting platelets are activated by a variety of chemical mediators, each of which can be targeted by antiplatelet drugs summarized in Table 2. Activated platelets aggregate by binding to strands of fibrinogen, which can be prevented by drugs that block the activated receptors.

Antiplatelet Drugs

Aspirin is the most commonly prescribed antiplatelet drug, and is used to prevent arterial thrombogenesis. It is effective for the prevention of myocardial infarction and thrombotic stroke. Aspirin's antiplatelet effect is achieved using very low doses, <100 mg/d, and this minimizes risk for gastrointestinal side effects. Although 81 mg (baby aspirin) is the most conventional dose, dosages as low as 40 mg/d may also be effective and can be used for patients having poor aspirin tolerance.^{3,4}

Dipyridamole (Persantine) prevents platelet adherence to endothelial surfaces more than it prevents platelet aggregation. When combined with warfarin (Coumadin), it provides an enhanced antithrombotic effect on artificial surfaces. For this reason, the combination may be prescribed for patients having valve and other cardiac prostheses.⁴ However, there is no proven advantage for its addition to aspirin when managing coronary artery and cerebrovascular disease. Dipyridamole is also a coronary vasodilator and is used during diagnostic procedures to assess patency of coronary arteries, ie, dipyridamole-thallium scanning.

Recently there has been a dramatic increase in the development of drugs that inhibit platelet aggregation. The final event required for platelet aggregation is the activation of glycoprotein receptors (GP 11b/111a) on their cell membranes that bind with fibrinogen. Platelets attach or aggregate with one another indirectly by sharing attachment to fibrinogen molecules. Antiplatelet drugs act either by preventing activation of platelet GP 11b/111a receptors or by blocking the binding sites on receptors that have been activated. These mechanisms are illustrated and summarized in Figure 2 and Table 2. These varied mechanisms pro-

vide a basis for combining agents in order to inhibit platelet aggregation. For example, the combination of aspirin and clopidogrel (Plavix) is more effective than either agent alone for preventing thrombosis following coronary stent placement. Agents that block the GP 11b/111a receptors impart the most "absolute" inhibition of aggregation and therefore carry the greatest risk for hemorrhage. These drugs are administered intravenously to prevent platelet aggregation during acute coronary syndromes or postoperatively following interventional procedures such as insertion of coronary stents.

Dental Implications for Patients Medicated With Antiplatelet Agents

Ibuprofen has been implicated as a competitive inhibitor of aspirin on platelet cyclooxygenase.⁵ The antiplatelet influence of low-dose aspirin occurs when it contacts platelets within the hepatic portal system following absorption.³ Based on this information, one solution might be to instruct patients to take their daily aspirin upon rising and delay the first dose of ibuprofen for 1–2 hours. By this time the antiplatelet influence of aspirin will have been established.⁶ Consideration regarding this issue may eventually prove moot because actual clinical relevance has been challenged impressively. Cryer et al⁷ found thromboxane inhibition by aspirin to be reduced only 1% after 10 days of concurrent ibuprofen use, and Patel and Goldberg⁸ found no increase in incidence of myocardial infarction over a 10-year period in patients with coronary disease taking ibuprofen with low-dose aspirin.

Although low-dose aspirin does not introduce a major risk for bleeding following minor dental surgery, extensive surgery may require some consideration. This may be of even greater concern for patients medicated with clopidogrel. Both drugs produce an antiplatelet effect that extends for the life of the platelet and requires the drug to be withheld for 10–14 days for platelets to be completely replenished. In general, it is unnecessary to interrupt either drug for dental surgery; risk for thrombotic events outweighs any slight risk for postoperative bleeding, which can be controlled with local measures. However, if the surgical procedure is so extensive that antiplatelet therapy poses a concern, consultation with the patient's physician is essential. Although complete reversal of antiplatelet influence requires approximately 10 days, a recent study found that bleeding time is normal after interrupting aspirin therapy for only 4 days.⁹

Antiplatelet drugs are prescribed for a variety of medical conditions, but the patient having coronary stents is a

Table 2. Summary of Antiplatelet Drugs and Their Mechanisms (see text for explanation)^{1,4*}

<i>Drugs Inhibiting GP 11b/111a Receptor Expression and Activation</i>			
<i>Inhibit Synthesis TBX</i>	<i>Inhibit Phosphodiesterase, Which Increases cAMP and Sustains Resting State</i>	<i>Inhibit ADP Binding to Receptors</i>	<i>Drugs That Block GP 11b/111a Receptors</i>
Aspirin	Dipyridamole (Persantine) Cilostazol (Pletal)	Ticlopidine (Ticlid) Clopidogrel (Plavix)	Abciximab (ReoPro) Tirofiban (Aggrastat) Eptifibatide (Integrilin)

* TBX indicates thromboxane A₂; cAMP, cyclic adenosine monophosphate; and ADP, adenosine diphosphate.

special consideration. In general, these patients are medicated with dual antiplatelet coverage consisting of aspirin and clopidogrel. Acute myocardial infarctions have followed interruption of antiplatelet therapy in such patients.¹⁰ Reports have accumulated and have spawned a scientific advisory from the American Heart Association in collaboration with other professional organizations, including the American Dental Association.¹¹ Antiplatelet coverage for patients having placement of coronary stents must rarely if ever be interrupted, especially if the stent is of the drug-eluting category.

Finally, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) always carries a risk for mucosal damage in the gastrointestinal tract. Risk for subsequent bleeding is increased in patients taking any antithrombotic medication, including the more powerful antiplatelet drugs. Risk for gastrointestinal bleeding is increased twofold to threefold in patients medicated with clopidogrel who are prescribed an NSAID concurrently.¹² Patients receiving monotherapy with low-dose aspirin are not a concern.

Anticoagulants

Warfarin and heparin are most effective in preventing venous thrombosis. However, they may also be combined with aspirin when managing patients at great risk for arterial thrombotic events, because fibrin strands reinforce and stabilize these platelet-rich clots. The coagulation pathway and activity of the anticoagulants are illustrated in Figure 3.

Warfarin is the only oral anticoagulant in current use. It acts in the liver by inhibiting the activity of vitamin K, which is essential for the synthesis of factors VII, IX, X, and II (prothrombin). Following warfarin administration, a mild anticoagulant effect is evident within 24 hours, but the peak effect is not realized for 72 hours, pending the consumption of previously synthesized factors.¹³ Conversely, vitamin K can be administered as an antidote for bleeding, but synthesis of replacement factors generally requires 24–72 hours. Serious hemorrhage must be managed by transfusion. The anticoagulant activity of warfarin is monitored using an international normalized ratio

(INR), which is essentially a standardized prothrombin time (PT). Warfarin is contraindicated during pregnancy. It crosses the placenta, where it may produce fetal or intrauterine hemorrhage, and is also associated with fetal malformations. Pregnant patients at risk for thrombotic events must be managed using subcutaneous heparin injections.

Antithrombin is the body's endogenous anticoagulant. It circulates in plasma acting as a "suicide substrate" for several activated factors, but thrombin (Factor IIa) and Factor Xa are most relevant. By consuming these 2 essential clotting factors, antithrombin prevents conversion of fibrinogen to fibrin. Heparin binds to antithrombin, potentiating its activity instantly. Likewise, its action can be reversed immediately by administering protamine sulfate, which neutralizes heparin molecules in a simple acid-base reaction. Generally, 1 mg protamine will neutralize 100 U heparin. The anticoagulant activity of heparin is monitored using an activated partial thromboplastin time.

Heparin can be administered subcutaneously or intravenously, either as an intermittent bolus or as a continuous infusion. Other than hemorrhage from its anticoagulant influence, the principal side effect attributed to short term use of heparin is heparin-induced thrombocytopenia.¹⁴ This is attributed to an immune-mediated reaction whereby antibodies are generated against a complex formed by heparin and a platelet product called platelet factor 4. Before platelet numbers actually decline, arterial thrombosis is common because the antibodies initially trigger existing platelets to aggregate. These platelet-rich clots have a white appearance, which has spawned the term "white-clot syndrome." (Fibrin-rich clots entrap red blood cells and are red in appearance.) Eventually platelets are consumed, resulting in thrombocytopenia, and for this reason platelet counts are ordered periodically during treatment. It must also be mentioned that chronic use of heparin (>1 month) is associated with an increased incidence of osteoporosis.

Although heparin is a large polysaccharide, its anticoagulant action is imparted by a mere pentasaccharide segment. This information led to the development of low-molecular-weight heparins such as enoxaparin

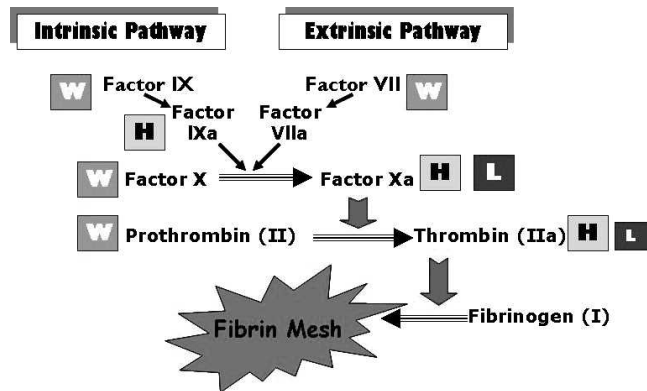


Figure 3. The coagulation pathway and target sites for anticoagulant drugs.¹⁴ The coagulation pathway is a cascade of enzymatic conversions, each activating the next enzyme (Factor) in the sequence. The final enzyme in this pathway is thrombin, also called Factor IIa, which catalyzes the conversion of fibrinogen to fibrin strands. Warfarin (W) acts by inhibiting synthesis of factors in the liver. In contrast, heparin (H) acts to inhibit factors that have become activated within the bloodstream. Thrombin can be activated by either of 2 pathways. The intrinsic pathway is initiated within the bloodstream by platelet thromboplastin. H influences this pathway by inhibiting Factor IXa. However, it also inhibits Factors Xa and IIa within the common pathway, and its activity must be monitored using the activated partial thromboplastin time (aPTT). The extrinsic pathway functions outside the bloodstream, initiated by tissue thromboplastin. This pathway is influenced most by W because it inhibits hepatic synthesis of Factor VII, the most essential factor in this pathway. The anticoagulant activity of W is monitored using the prothrombin time (PT), which is now standardized as the international normalized ratio (INR). Newer agents, commencing with the low-molecular-weight Hs (L) have greater specificity for inhibiting Factor Xa and thrombin within the common pathway and generally do not require therapeutic monitoring.

(Lovenox) and dalteparin (Fragmin).¹⁴ These agents are as effective as heparin but are more selective in inhibiting factor Xa than thrombin (IIa). (See Figure 3.) They require less frequent dosing, they necessitate virtually no activated partial thromboplastin time monitoring, and they are less likely to induce immunological responses that contribute to thrombosis or thrombocytopenia. In certain cases, these advantages offset their cost, which is 10–20 times that of heparin. The success of the low-molecular-weight heparins has ignited research and development of anticoagulants having even greater specificity on the coagulation pathway. Fondaparinux (Arixtra) is a selective Factor Xa inhibitor with no action on thrombin, whereas bivalirudin (Angiomax) is selective in inhibiting thrombin.

Thrombolytic (Fibrinolytic) Drugs

Thrombi are normally dissolved by the action of an endogenous fibrinolytic system. This consists of plas-

minogen, which circulates free in the plasma and binds to both fibrinogen and fibrin. When activated, plasminogen is converted to the proteolytic enzyme, plasmin, which inactivates fibrinogen and lyses any existing fibrin strands. All thrombolytic drugs in current use act by converting plasminogen to plasmin, either in the circulation or on the surface of existing thrombi.

There are several thrombolytic agents currently available that have subtle differences in their precise mechanisms, but all stimulate plasmin production in plasma and on the surface of existing thrombi. None are truly clot specific. All are effective “clot busters” during the early stages of myocardial infarction or ischemic stroke and thus preserve viable tissues. Currently, tissue plasminogen activator is the most common agent in use.

Dental Implications for Anticoagulated Patients

Many antibiotics enhance the anticoagulant activity of warfarin. However, the most significant evidence implicates metronidazole, tetracycline, and macrolide derivatives.¹ These antibiotics should be avoided when managing odontogenic and periodontal infections, but do not present a concern for single-dose prophylactic regimens.

Anticoagulant therapy presents a contraindication to the use of NSAIDs for postoperative pain and inflammation, but the reasoning for this concern is often misstated. Generally, it is believed that the added antiplatelet effect of NSAIDs enhances antithrombotic influences. However, with the exception of aspirin, most NSAIDs have minimal influence on platelet aggregation. In fact, most physicians actually combine the antiplatelet influences of aspirin with those of warfarin when managing patients at significant risk for thromboembolic events. The actual concern with NSAIDs is their risk for producing erosion and ulceration of gastric mucosa, which may bleed more profusely in patients who are anticoagulated. This is rarely a consideration with low-dose aspirin, but is significant with analgesic and anti-inflammatory doses of aspirin or other NSAIDs. The use of NSAIDs by patients receiving warfarin therapy increases the risk for gastrointestinal bleeding fourfold to fivefold.¹²

Patients receiving warfarin are a special concern for the dentist because some degree of hemorrhage is associated with many dental procedures. The anticoagulant influence of warfarin is monitored every 3–6 weeks using either of 2 laboratory tests. The PT is most familiar, and is expressed as a ratio compared to normal. If the normal PT is 12 seconds, a PT ratio of 1.5 would correspond to 18 seconds. Unfortunately, the thromboplastins used by laboratories vary in their sensitivity, and results cannot be compared. In 1983, the World Health

Table 3. Suggested Guidelines for Anticoagulated Patients*

Treatment Risk	Examples	Protocol
Low	Supragingival prophylaxis or restorations, infiltration anesthesia	PT <2.0 or INR <4.0, no change, delay treatment
Moderate	Subgingival scaling or restorations, simple extraction, nerve block injections	PT >2.0 or INR >4.0, no change, delay treatment
High	Extensive surgery, including multiple extractions and those requiring extensive mucosal flaps.	Base decision on consultation; many options, including “bridging” with LMW heparins (see text)

* A PT ratio or INR should be assessed 1 or 2 days before treatment if previous INRs have been inconsistent. Otherwise, stable anticoagulated patients can be managed based on INR values within a week of treatment. PT indicates prothrombin time; INR, international normalized ratio; and LMW, low-molecular-weight.

Organization adopted the INR, which was designed to improve patient monitoring. Now most laboratories standardize their results by using a computation that adjusts the sensitivity of their particular thromboplastin to that of an international standardized thromboplastin. (These sensitivities are expressed as an International Sensitivity Index.) The INR is the result of this calculation, and the value is identical to the value that would have resulted had a universal standard thromboplastin been used for the test. Actual intensity of anticoagulation varies according to risk for thromboembolic events. For example, INR values as low as 1.3–2.0 are effective prophylaxis for deep vein thrombosis, but 2.0–3.0 is required for atrial fibrillation and 3.5–4.5 may be required for patients with prosthetic heart valves.¹³

There are no formal guidelines for managing anticoagulated patients during dental treatment. Decisions are empiric and, if in doubt, should be made in consultation with the patient’s physician. However, risks for hemorrhage are generally overestimated, and adjustments have been excessive in the past. This is due largely to poor communication on the part of the dentist; the physician has little insight into the nature of the anticipated dental treatment. Provided the PT ratio is ≤ 2.0 or the INR is ≤ 4.0 , risks for significant hemorrhage are minimal unless extensive surgical procedures are planned. Mild hemorrhage is easily managed using local measures such as gauze-packing or sutures. My personal experiences managing anticoagulated

Table 4. Exemplary Protocol for Patient Management Using LMW Heparin*

Intervention	Explanation
Discontinue warfarin 3–4 days preoperatively	Synthesis of renewed factors requires 3–4 days after warfarin discontinued
Commence LMW heparin 3 days preoperatively	Provides anticoagulant effect as influence of warfarin declines
Skip PM dose of LMW heparin night before surgery	Assures no anticoagulant influence at surgery
Restart warfarin and LMW heparin PM on day of surgery	Anticoagulant effect commences immediately with LMW heparin
Continue LMW heparin for 3 days postoperatively and check INR to confirm warfarin activity	Anticoagulant protection is provided by the LMW heparin while warfarin effects develop
Discontinue LMW heparin when INR confirms warfarin activity	

* So-called “bridge therapy” must be in consultation with and managed by the patient’s physician. This regimen limits the time patient is not anticoagulated to the perioperative period. LMW indicates low-molecular-weight; and INR, international normalized ratio.

patients are consistent with guidelines proposed by others.^{15–17} (See Table 3.)

For patients requiring extensive surgery, but at significant risk for thromboembolic events, consideration should be given to the use of “bridge therapy” in consultation with the physician. This strategy employs injectable anticoagulants while the patient discontinues and restarts treatment with warfarin. In the extremely high-risk patient this may require hospital admission, but the introduction of low-molecular-weight heparins has allowed bridging to be accomplished safely on an outpatient basis. An exemplary protocol is presented in Table 4. The introduction of fondaparinux may be substituted for the low-molecular-weight heparins, but at even greater expense. This agent is more selective in inhibiting factor Xa and may prove even safer than the low-molecular-weight heparins.

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CONTINUING EDUCATION QUESTIONS

1. The risk for myopathy attributed to HMG CoA-reductase inhibitors ("statins") is enhanced when they are combined with which of the following?
 - A. clindamycin
 - B. erythromycin
 - C. ibuprofen
 - D. hydrocodone
2. Serum levels of warfarin may be increased by concurrent use of all the following medications EXCEPT:
 - A. ibuprofen
 - B. metronidazole
 - C. erythromycin
 - D. doxycycline
3. The use of NSAIDs for postoperative pain is contraindicated in patients taking warfarin. Which of the following is the basis for this contraindication?
 - A. added antiplatelet influence of NSAIDs may prolong bleeding
 - B. NSAIDs may elevate warfarin serum levels
 - C. gastrointestinal irritation may be more likely to result in excessive bleeding
 - D. NSAIDs inhibit renal excretion of warfarin
4. Which of the following provides the rationale for "bridging" anticoagulant therapy?
 - A. enhances anticoagulation by combining 2 mechanisms
 - B. minimizes the time in which a patient is not anticoagulated
 - C. provides greater protection from surgically-induced thrombosis
 - D. minimizes the risk for drug interactions that enhance bleeding

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