

Managing Warfarin & Antiplatelet Drugs Perioperatively

Background

Patients taking warfarin, aspirin, clopidogrel (*Plavix*), and NSAIDs face an increased risk of bleeding due to surgery. But stopping these medications prior to surgery may put the patient at risk of a thrombotic event (e.g., DVT, stroke). Therefore, the risk of bleeding must be weighed against the risk and consequences of thrombosis. This article reviews recommendations for managing these medications perioperatively, including those from the 2008 American College of Chest Physicians (ACCP) guidelines.

Warfarin

Warfarin can be continued during minor dental procedures (e.g., tooth extraction, root canal) with use of a local hemostatic agent (aminocaproic acid or tranexamic acid mouthwash).¹ One regimen used by some dentists consists of rinsing with 10 mL of the oral aminocaproic acid syrup starting 30 minutes prior to the procedure and continuing every one to two hours after the procedure until the bleeding has stopped. In a study of tranexamic acid 4.8% in oral surgery, patients rinsed with 10 mL of the solution for two minutes at the time of surgery and four times daily for seven days. When utilizing either antifibrinolytic mouthwash, patients should be instructed to hold the solution in the mouth for about two minutes and then expectorate. Vigorous swishing or using a drinking straw should be discouraged to avoid dislodging the forming clot.²

Warfarin can also be continued during minor dermatologic procedures (e.g., excision of basal or squamous cell carcinomas, nevi, or actinic keratoses) or cataract surgery.¹ It can also be continued during diagnostic endoscopy and colonoscopy, although holding warfarin is reasonable if polyp removal is anticipated.³

For most surgeries, an INR of 1.5 is usually safe. An INR <1.2 may be desired for some major surgeries (e.g., neurosurgery).⁴ The INR will usually reach <1.5 if warfarin is discontinued

five days prior to the procedure.^{1,4} Oral vitamin K 1 mg to 2 mg can be given if the INR is still 1.5 or higher one or two days pre-op. If a procedure is urgent, 2.5 mg or 5 mg of IV or oral vitamin K can be given. Fresh frozen plasma can be given in addition for even faster reversal (i.e., within 12 hours).^{1,3}

Warfarin, at the pre-op dose, can be restarted as soon as the evening after the surgery or the next day (i.e., 12 to 24 hours post-op) if bleeding has stopped.^{1,3}

Bridging Therapy

Patients at thromboembolic risk may benefit from use of heparin or low molecular weight heparin (LMWH) as “bridging” therapy after warfarin is discontinued. In most studies, patients received therapeutic-dose LMWH (e.g., dalteparin [*Fragmin*] 200 IU/kg daily or 100 IU/kg twice daily; enoxaparin [*Lovenox*] 1 mg/kg twice daily or 1.5 mg/kg daily).¹ LMWH can be started 36 hours after the last warfarin dose [Evidence level C; expert opinion].³ Unfractionated heparin may be preferred to LMWH in patients over 150 kg or with end-stage renal disease due to risk of overdose [Evidence level C; expert opinion].^{3,4} Also, some experts avoid LMWH in patients with gastrointestinal bleeding within the past ten days or major trauma or stroke within the past two weeks.³ Special consideration is also needed for use of LMWH in patients undergoing regional (e.g., spinal) anesthesia in regard to timing of catheter placement and removal, and must be coordinated with anesthesia services.⁵

Assessing patient risk for thromboembolism: Decisions regarding bridging therapy are based on thromboembolic risk. Patients with a mechanical heart valve are at high risk if they have a mechanical mitral valve, have an older-type aortic valve (e.g., Starr-Edwards or tilting disk), or have had a stroke or TIA within six months. Patients with a bileaflet aortic valve plus atrial fibrillation, previous stroke

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or TIA, hypertension, diabetes, or CHF, or are age over 75 years are at moderate risk. Those with a bileaflet aortic valve with no other stroke risk factors are at low risk.¹

Risk in patients with atrial fibrillation is based in part on the CHADS₂ (CHF, hypertension, age over 75, diabetes, stroke) score. Patients get one point for each of the risk factors except prior stroke or TIA, for which two points are given. Patients are at high risk if they have a CHAD score of five or six, have had a stroke or TIA within three months, or have rheumatic valvular heart disease. Patients with a CHADS₂ score of three or four are at moderate risk. And patients with a CHADS₂ score of zero, one, or two, with no history of stroke or TIA, are at low risk.¹

Risk in patients with a history of a thromboembolic event (e.g., DVT, pulmonary embolism) is based on their indication for warfarin. Patients are at high risk of a thromboembolic event if they have had a thromboembolic event within the past three months, or have a severe thrombophilia. Examples include protein C, protein S, or antithrombin deficiency, antiphospholipid antibodies, homozygous for Factor V Leiden mutation, or multiple thrombophilias. Patients are at moderate risk if they have had a thromboembolic event within the past three to twelve months, or have had recurrent venous thromboembolic events. Other patients at moderate risk are cancer patients receiving palliative care and patients who have undergone cancer treatment within the past six months. Patients with a nonsevere thrombophilia (e.g., heterozygous for Factor V Leiden or Factor II mutation) are also at moderate risk. Patients are at low risk if they had a single thromboembolic event more than a year ago and have no other risk factors.¹

Bridge therapy regimens based on risk: High thromboembolic risk patients can receive heparin by IV infusion to a goal aPTT of 1.5 to 2 times control, or therapeutic-dose subcutaneous LMWH (preferred).¹

In moderate-risk patients, therapeutic-dose subcutaneous LMWH is preferred, but low-dose subcutaneous LMWH or IV heparin infusion are options. In patients with low thromboembolic risk, low-dose LMWH or no bridging therapy are options.¹

LMWH can be started as an outpatient to reduce costs associated with hospitalization. For patients receiving therapeutic-dose LMWH, the last preoperative dose should be given 24 hrs prior to surgery. The last preoperative dose should be half the total daily dose. For once-daily regimens, give 50% of the dose; for twice-daily regimens, give only the morning dose. IV heparin should be stopped 4 hours pre-op.¹

Post-op management: The decision if, when, and what anticoagulant to resume post-op should take into account adequacy of hemostasis and bleeding risk. For minor procedures, therapeutic-dose LMWH can be restarted the day after surgery (i.e., 24 hrs post-op) if bleeding has stopped. In the case of major surgery or high bleeding risk, heparin can be resumed 48 to 72 hours post-op if bleeding has stopped. Other options in high bleeding risk scenarios include administering low-dose heparin or low-dose LMWH when bleeding is controlled, or not resuming either LMWH or heparin.¹ Discontinue LMWH when the INR has been therapeutic for two days in a row.⁴

Aspirin or Clopidogrel

For patients requiring surgery within six weeks of placement of a bare metal coronary stent or within 12 months of placement of a drug-eluting stent, it is recommended that aspirin and clopidogrel be continued. If possible, delay elective noncardiac surgery for six weeks post bare metal stent placement and 12 months post drug-eluting stent placement.¹

In patients undergoing minor dental procedures, minor dermatologic procedures, or cataract surgery, aspirin can be continued. Clopidogrel can be discontinued at least five days (preferably ten days) prior to the procedure in patients not at high cardiac risk. Patients who have had a bare metal coronary stent placed within the previous six weeks, and those who have had a drug-eluting stent placed within the past 12 months should continue clopidogrel.¹

In patients not at high risk of cardiac events undergoing a noncardiac procedure, it is recommended that aspirin, aspirin-containing medications (e.g., *Aggrenox*), and clopidogrel should be stopped seven to ten days prior to surgery.¹

For patients at high risk of cardiac events undergoing noncardiac surgery or percutaneous

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coronary intervention (PCI), it is suggested that aspirin be continued. It is suggested that clopidogrel be stopped five or preferably ten days pre-op.¹

For patients undergoing coronary bypass (CABG), it is recommended that aspirin be continued. It is recommended that clopidogrel be stopped five or preferably ten days pre-op.¹

For most post-op patients, it is recommended that antiplatelets, if held, be restarted 24 hours after surgery or the morning after surgery if hemostasis is achieved. If clopidogrel is interrupted in PCI patients, it is suggested that patients be reloaded with a single 300 mg to 600 mg dose. If aspirin is held prior to CABG, it is recommended that it be resumed six to 48 hours post-CABG.¹

NSAIDs, Cilostazol, and Dipyridamole

NSAIDs, including COX-2 inhibitors, have reversible antiplatelet effects. To ensure absence of antiplatelet effect, NSAIDs should be discontinued five half-lives before surgery. The following chart shows how long before surgery each NSAID should be discontinued.¹

| NSAID | Time to hold before surgery |
|---|------------------------------------|
| Diclofenac (e.g., <i>Voltaren</i>) Ibuprofen (e.g., <i>Motrin</i>) Indomethacin (e.g., <i>Indocin</i>) Ketoprofen (e.g., <i>Orudis, Oruvail</i>) | One day |
| Celecoxib (<i>Celebrex</i>) Diflunisal (<i>Dolobid</i> ; <i>Novo-Diflunisal</i> [Canada]) Naproxen (e.g., <i>Naprosyn</i>) Sulindac (<i>Clinoril</i> ; <i>Novo-Sundac</i> [Canada]) | Two to three days before surgery |
| Meloxicam (<i>Mobic</i>) Nabumetone (<i>Relafen</i>) Piroxicam (<i>Feldene</i> ; <i>Pexicam</i> [Canada]) | Ten days before surgery |

Cilostazol (*Pletal*) would need to be stopped two to three days prior to surgery to ensure absence of effect at surgery time. Although

dipyridamole alone could be stopped two to three days prior to surgery, it is usually taken in combination with aspirin (i.e., *Aggrenox*), so it would need to be stopped seven to ten days prior to surgery due to the aspirin component. Antiplatelet drugs can be restarted 24 hours after surgery or the morning after surgery if adequate hemostasis is achieved.¹

Commentary

High-quality studies of perioperative management of anticoagulation and antiplatelet agents are lacking, and many questions remain. For example, cohort studies show that with bridging therapy the risk of recurrent venous thromboembolism is 0.6% (95% CI 0.13 to 1.7). However, we do not know what the risk is without bridging therapy. There is no standard bridging regimen with therapeutic-dose LMWH, and more study is needed of the efficacy of low-dose LMWH as bridging therapy.¹

Most published recommendations on perioperative management of anticoagulation and antiplatelet therapy are based on expert opinion or lower-quality evidence. It is therefore important to consider the individual's risk of bleeding versus risks and consequences of thromboembolism in making management decisions.

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Project Leader in preparation of this Detail-Document: *Melanie Cupp, Pharm.D., BCPS*

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Levels of Evidence

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| B | Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study |
| C | Consensus Expert opinion |
| D | Anecdotal evidence In vitro or animal study |

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