

Evidence to Continue Oral Anticoagulant Therapy for Ambulatory Oral Surgery

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Many patients taking coumarin derivatives, such as warfarin, present to the oral and maxillofacial surgeon needing to have teeth extracted. The surgeon is faced with the choice of altering or stopping warfarin and risking thromboembolism or leaving the patient on the warfarin and risking uncontrolled bleeding. A common approach to managing patients with a low risk of thromboembolism needing surgery is to interrupt warfarin therapy for several days before and after surgery.¹⁻⁴ Patients with a high risk of thromboembolism commonly stop warfarin and bridge anticoagulation with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH).¹⁻⁶ However, patients who interrupt warfarin therapy are at risk of developing a thromboembolism with or without bridging therapy.^{1,3,6} On the other hand, warfarin therapy can be continued without interruption for procedures such as dentoalveolar surgeries that rarely cause significant or life-threatening bleeding.^{1-3,5}

Stopping warfarin is problematic because of its slow unpredictable reversal. Warfarin inhibits the enzyme vitamin K epoxide reductase, which converts vitamin K to vitamin K hydroquinone.⁷ The vitamin K hydroquinone is needed to gamma carboxylate the glutamic acids at the N-terminal portion of the clotting factors II, VII, IX, and X and endogenous proteins C and S. If the clotting factors are not carboxylated, they are not biologically active. Return of normal clotting after stopping warfarin requires the elimination of warfarin followed by the synthesis of new clotting factors. Because the elimination half-life of warfarin is 40 hours and the clotting factors have different and sometimes long half-lives (Table 1), it takes days to reverse the effects of warfarin.

The rationale for using UFH or LMWH to bridge anticoagulation while warfarin is temporarily inter-

rupted is to shorten the time that the patient is unprotected from thromboembolism.^{1,3,6} However, even when bridging is done with UFH or LMWH, there will be a period of at least 12 to 24 hours that patients are unprotected (Fig 1). In addition to an interval when anticoagulation is not therapeutic, stopping warfarin may result in a temporary hypercoagulable state.^{5,8,9} Because of these limitations, it is preferable to continue the warfarin without interruption if major bleeding can be prevented.

Risk of Thrombosis and Stopping Warfarin

The risk for thromboembolism depends on several factors, including the clinical indications for anticoagulation.^{1,3,4,6} Anticoagulation is required in the management of patients with prosthetic heart valves, chronic atrial fibrillation, hypercoagulable states (ie, protein C deficiency, protein S deficiency, factor V Leiden mutation, antithrombin III deficiency, antiphospholipid-antibody syndrome), venous or arterial thromboembolism, and cerebrovascular disease with strokes. However, patients who require anticoagulation do not have equal risk of developing thromboembolism.

Thromboembolic risk for prosthetic heart valves is high and depends on the location of the valve and the type of replacement.^{1,6} The incidence of thromboembolism is less for prosthetic aortic valves than for prosthetic mitral valves. The most thrombogenic prosthetic heart valve is the caged ball type (eg, Starr-Edwards), followed by the tilting disc type. Reliable estimates of the absolute risk for temporary interruption of warfarin therapy are difficult to determine. If the risk for thromboembolism in unprotected patients with prosthetic heart valves is 9% to 22% per year, the risk of interrupting warfarin for 6 to 8 days can be extrapolated to be 0.17% to 0.42%.

The risk of thromboembolism in patients with atrial fibrillation increases when patients have multiple thromboembolic risk factors.^{1,4,6} The factors associated with increasing risk are age (>75 years old), hypertension, diabetes mellitus, and left ventricular dysfunction. Patients with atrial fibrillation and previ-

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Table 1. HALF-LIVES OF VITAMIN K-DEPENDENT COAGULATION FACTORS

Coagulation Factor	Half-life (hr)
Factor II	60
Factor VII	4 to 6
Factor IX	24
Factor X	48
Protein C	8
Protein S	30

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ous stroke or transient ischemic attacks (TIAs) have a high risk of thromboembolism (12% to 15% per year). Patients with atrial fibrillations without other risk factors have a low risk of stroke (<1% per year). Most patients with atrial fibrillation fall between the low- and the high-risk categories (3% to 7% per year). The risk of thromboembolism when warfarin is stopped for 6 to 8 days in patients with atrial fibrillation ranges from 0.02% to 0.38%.

There are little data on the absolute risk of recurrent embolism in patients with venous thromboembolism. The greatest risk for thromboembolism is soon after starting anticoagulation treatment for pulmonary embolism or deep venous thrombosis (DVT).^{1,3,4,6} After 2 to 3 months of anticoagulation, the risk of thromboembolism decreases. The risk remains high for patients with major pulmonary or cardiac disease, active cancer, and inherited hypercoagulability states.³

Anticoagulated patients can be stratified into high, intermediate (moderate), and low risk for thromboembolism (Table 2).^{1,6} High- and intermediate-risk patients should maintain anticoagulation without change or have a minimal interval of subtherapeutic anticoagulation. High-risk patients have a 10% yearly risk of arterial embolism and a greater than 10% 1-month risk of venous embolism. Intermediate-risk patients have a 5% to 10% yearly risk of arterial embolism or a 2% to 10% 1-month risk of venous embolism. Low-risk patients have a less than 5% yearly risk for arterial embolism and a less than 2% 1-month risk of venous embolism.

Some clinicians argue that patients with low risk of thromboembolism who need surgery can stop warfarin for 4 to 5 days without UFH or LMWH bridging therapy.¹⁻⁴ The low-risk group includes patients with atrial fibrillation without other associated risk factors (previous stroke, TIAs, left ventricular dysfunction, age >75 years old, hypertension, and diabetes), newer prosthetic aortic valve replacements, one venous thromboembolic episode more than 6 months before surgery, and intrinsic cerebrovascular disease without recurrent strokes or TIAs. High- and intermediate-risk patients, however, must maintain anticoag-

ulation therapy with minimal to no unprotected intervals if possible.

Potential Risk of Bleeding With Continuous Anticoagulation

The goal of managing anticoagulated patients who need surgery is to prevent major or life-threatening bleeding while protecting against thromboembolism. Some procedures such as intra-abdominal, intrathoracic, major cancer surgery, removal of head and neck tumors, and extraoral open reduction of facial fractures are associated with considerable bleeding. Life-threatening or major bleeding in patients who need high-risk surgery is avoided by stopping warfarin with or without bridging therapy.¹⁻⁶ Bridging therapy with UFH or LMWH is recommended for patients with a high risk of thromboembolism, whereas patients with a low risk of thromboembolism can stop warfarin without bridging therapy. Intermediate-risk patients may or may not require bridging. The international normalized ratio (INR) is used to monitor the status of anticoagulation when warfarin therapy is stopped and restarted.² The Food and Drug Administration has not approved bridging therapy with LMWH in patients with prosthetic heart valves, and UFH is frequently recommended for bridging therapy in these high-risk patients who develop arterial thromboembolism.¹⁻³

Many surgical procedures have a low risk of major or life-threatening bleeding and can be done without

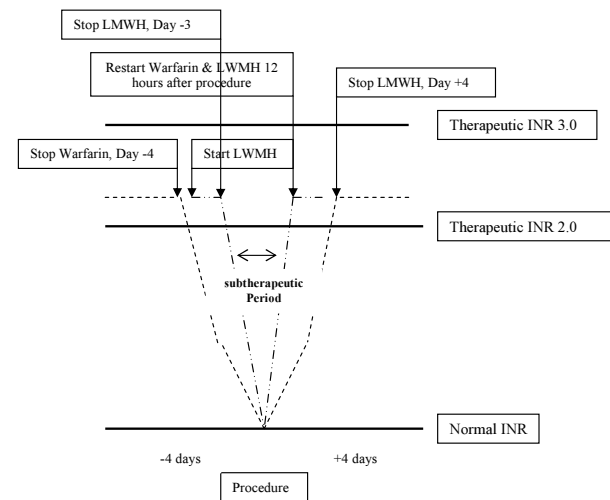


FIGURE 1. Bridging therapy. Warfarin is stopped 3 to 5 days before surgery and low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) is started 1 to 2 days after stopping warfarin. The LMWH is stopped 18 to 24 hours before surgery and restarted 12 to 24 hours after the surgery. UFH can be stopped 6 to 8 hours before surgery and restarted 6 to 24 hours after surgery. LMWH or UFH is continued until the INR returns to therapeutic levels. When the LMWH or UFH is stopped, the patients will be unprotected for 12 to 24 hours.

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Table 2. RISK OF THROMBOEMBOLISM

Low Risk	Moderate Risk	High Risk
Atrial fibrillation without stroke	Bileaflet tilting disc aortic valve with ≥ 2 stroke risk factors	Mechanical mitral valve
Cardiomyopathy without atrial fibrillation	Chronic atrial fibrillation with >2 stroke risk factors	Ball-cage valve replacement
Venous thrombosis >6 months	Venous thrombosis <6 months	Venous thrombosis <3 months
Bileaflet aortic valve and <2 stroke risk factors		Hypercoagulable state
		Atrial fibrillation with history of stroke
		Acute myocardial infarction <3 months
		Recent (1 month) stroke or transient ischemic attack

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altering anticoagulation.^{1,3,5} Ophthalmic procedures like cataract extraction and trabeculectomies can be performed without altering anticoagulation therapy.^{1,3,5} The American Society of Gastrointestinal Endoscopy guidelines recommend continuing anticoagulation without change for low-risk procedures like colonoscopy with or without biopsy and flexible sigmoidoscopy with or without biopsy.¹⁰ Dermatologic surgery like Mohs' micrographic surgery and simple excisions and repairs can be done without stopping warfarin therapy.

Oral Surgery Procedures

Procedures including single and multiple dental extractions, full mouth extractions, and alveolectomies are associated with very few bleeding episodes in patients who continue warfarin therapy. Wahl¹¹ published a review of perioperative management of patients receiving oral anticoagulants in 1998. He summarized the outcome of 2,014 dental surgical procedures in patients who continued oral anticoagulation. Serious bleeding occurred in only 12 of the procedures, and 5 of the 12 bleeds were associated with INRs above therapeutic levels. Wahl also examined reports including 493 patients who discontinued warfarin; 5 of these patients developed serious thromboembolic complication, resulting in 4 deaths. He concluded that as long as the surgery was done when the INR was within therapeutic range, 2.0 to 4.0, the chance of serious bleeding following dentoalveolar surgery was low in patients who continue their oral anticoagulation therapy.

Since Wahl's review, several clinical trials describing the outcome of patients maintaining oral anticoagulation therapy and having teeth removed have been published. Blinder et al evaluated the outcome of 150 patients having 359 dental extractions.¹² All of the patients continued taking coumarin and their

INRs on the day of surgery ranged from 1.5 to 4.0. The patients were divided into 3 groups according to the type of local hemostasis. Resorbable gelatin sponges and sutures were used in one group, resorbable gelatin sponge and sutures with tranexamic acid mouthwash 4 times a day for 4 days following surgery were used in a second group, and gelatin sponge, fibrin glue, and multiple sutures were used in a third group. Postoperative bleeding developed in 11 patients who were equally divided between the different groups. Bleeding was stopped in these patients using pressure or curettage of the extraction site and placement of gelatin sponges, fibrin glue, and sutures. None of the patients required hospital admission, transfusions, or reversal of anticoagulation.

Martinowitz et al¹³ followed 40 patients having 63 teeth removed without altering the oral anticoagulation. Local hemostasis was obtained using a biological adhesive after placing a thrombin soaked gauze into the socket for 3 minutes. The INRs on the day of surgery ranged from 2.5 to 4.0. There were no incidences of prolonged or excessive bleeding. One patient had hemorrhage on the third postoperative day that was controlled by biting on gauze.

Bodner et al¹⁴ followed 69 patients who needed single teeth and multiple teeth removed with and without alveoloplasty. Oral anticoagulation was maintained and the INRs in 49 of the 69 patients was greater than 2.0. Local hemostasis was achieved using absorbable gelatin sponges, fibrin sealant, and sutures. There were no cases of prolonged or excessive bleeding. Three patients had minor bleeding on the first postoperative day that was controlled with pressure.

Carter et al¹⁵ examined the efficacy of 2 different local measures in patients taking oral anticoagulants who required dental extractions. A group of 49 patients having 152 extractions were randomized to use either tranexamic acid mouth rinses or autogenous

fibrin glue for local hemostasis. The INRs on the day of surgery ranged from 2.0 to 4.0. None of the patients in the tranexamic group had postoperative bleeding, and 3 patients in the fibrin glue group had minor bleeding that occurred 2 days postoperatively. The bleeding was controlled with pressure and additional fibrin glue.

These clinical studies evaluated patients who maintained oral anticoagulation. There was no control group who stopped anticoagulation or was not anticoagulated. Some recent reports have compared bleeding in patients who continue oral anticoagulants with patients who stop therapy without bridging the anticoagulation with UFH or LMWH. Devani et al¹⁶ divided 65 patients requiring 133 extractions into 2 groups. One group was asked to stop warfarin 2 days prior to extraction and the other group continued warfarin therapy. All extraction sites were packed with absorbable oxycellulose and sutured. Patients who stopped taking warfarin resumed the warfarin on the day of surgery. The average INR on the day of surgery was 1.6 for patients who stopped warfarin and 2.7 for patients who continued taking the warfarin. One patient in each group had postoperative bleeding that was controlled using local measures.

Campbell et al¹⁷ evaluated bleeding following dental extractions in patients who were not taking anticoagulants compared with patients who were taking oral anticoagulants. The patients taking oral anticoagulants were divided into a group who continued taking oral anticoagulants and another group who stopped anticoagulant therapy 3 to 4 days before surgery. Twelve patients continued their anticoagulation, 13 patients stopped anticoagulation therapy, and 10 control patients were not taking anticoagulants. The INR in the 2 groups taking anticoagulants was 2.0. There was no description of local hemostasis for these patients. None of the patients needed treatment for bleeding following the extractions, and intraoperative bleeding was not excessive in any of the patients.

Evans et al¹⁸ randomly divided patients into a group who continued warfarin therapy and a group who stopped warfarin 2 days before tooth extraction. The warfarin was resumed on the day of surgery. The INR was between 2.0 and 4.0 on the day of surgery in patients who continued warfarin and less than 2.0 in the patients who stopped the warfarin. Extraction sites were packed with oxycellulose dressing and sutured. A total of 117 patients were divided into the 2 groups. The overall bleeding rate was 26% in anticoagulated patients and 14% in the patients who stopped warfarin. The difference was not significant. Biting on gauze at home controlled delayed bleeding in all but 2 patients. None of the patients developed life-threatening bleeding or required transfusions.

Zanon et al¹⁹ examined bleeding in patients taking oral anticoagulants using a case-control study design. A total of 250 patients on warfarin requiring dental extractions was compared with a matched control group of 250 patients who were not taking anticoagulants. Following the extractions, oxidized cellulose was inserted and silk sutures were used for closure in the anticoagulated patients while only the silk sutures were placed in the patients not taking anticoagulants. A gauze saturated with tranexamic acid was kept in place 30 to 60 minutes in the anticoagulated patients. The INR on the day of surgery was greater than 2.0 in 172 patients taking warfarin and less than 2.0 in the remaining 78 patients. Four patients in the anticoagulation group and 3 patients in the control group had bleeding. Local measures were used to control all postoperative bleeding.

Bridging Therapy

Bridging with UFH or LMWH is done to shorten the interval of subtherapeutic anticoagulation while waiting for the reversal of oral anticoagulation. For patients with a low risk of thromboembolism, bridging is not recommended because the efficacy of bridging with UFH and LMWH does not outweigh the risk of postoperative bleeding.¹⁻³ Patients with a low risk of thromboembolism can stop the oral anticoagulant and restart it after the surgery. Stopping oral anticoagulant and bridging is not recommended for procedures for which major bleeding is not likely to develop. If major bleeding is unlikely, the oral anticoagulant is continued without alteration.^{1-3,10,11}

Bridging with LMWH may not protect against arterial thrombosis in patients with prosthetic heart valves or atrial fibrillation with multiple risk factors for stroke.^{2,3,5} UFH is recommended for these patients who have a high risk of arterial thromboembolism.^{2,3,5} Administration of UFH requires several days of hospitalization and costly monitoring of coagulation status before and after the surgery.^{2,4,6,20} Bridging therapy can also be complicated by severe postoperative bleeding.^{1,4}

Bridging with LMWH is less costly than with UFH because it can be administered without hospitalization and does not require costly laboratory monitoring.^{1,20} However, LMWH must be given subcutaneously and patients must learn to administer the injections and be willing to take the medication for 4 to 8 days while stopping and restarting oral anticoagulation. The patients' INRs need close monitoring after restarting the oral anticoagulant to determine when the LMWH can be stopped.^{1,6}

Recommendations

Stopping warfarin with or without bridging for dentoalveolar surgery is not supported by clinical evidence.^{3-5,11} The risk of developing life-threatening bleeding or bleeding that cannot be controlled using local measures following dental extractions, alveoloplasties, or dental implants is so low that there is no need to stop warfarin.

Patients continuing to take oral anticoagulants for dentoalveolar surgery may develop postoperative bleeding that cannot be stopped with pressure alone and may require local homeostasis to control. On the day of surgery, the patient's INR should be obtained to verify that it is within or below the therapeutic range (2.0 to 4.0). After surgery, local measures should be taken to prevent postoperative bleeding. Patients should receive instructions regarding local pressure to control bleeding and to return if local pressure does not stop the bleeding.

The most effective local homeostatic techniques have not been established.^{1,2,4,12-16} Minimally, a hemostatic matrix such as oxycellulose, absorbable gelatin, or collagen with sutures can be used to prevent bleeding. Some clinicians have found that fibrin glue can decrease postoperative bleeding.^{12,15,21,22} Rinsing with an antifibrinolytic agent like tranexamic acid or ϵ -aminocaproic acid (5%) 4 times a day for 2 minutes 4 to 5 days after surgery is recommended by some clinicians for patients continuing warfarin.^{2,3,15} Tranexamic acid has been shown to decrease bleeding in patients taking warfarin, but it is difficult to obtain and must be made into a mouth rinse. ϵ -Aminocaproic acid can be substituted for tranexamic acid, but there are no well-controlled clinical trials confirming that rinsing with ϵ -aminocaproic acid prevents postoperative bleeding in anticoagulated patients.

The clinician must carefully select postoperative medications for patients taking oral anticoagulants.^{7,23,24} The cyclooxygenase (COX) I/II nonsteroidal anti-inflammatory agents should be avoided. The newer COX II selective agents may be safer than the COX I/II nonsteroidal anti-inflammatory agents, but the newer COX II agents may alter warfarin metabolism and its effects.^{7,23,25,26} Acetaminophen can be used in low doses but can affect warfarin metabolism in high doses. Narcotic analgesics can safely be used in patients taking oral anticoagulants. Postoperative antibiotics should be avoided as much as possible.^{7,27} A prophylactic dose of antibiotics to prevent subacute bacterial endocarditis is safe, but a 5- to 10-day course of antibiotic following surgery may alter the intestinal bacterial flora and decrease vitamin K, resulting in elevation of the INR.²⁷ Dicloxacillin and nafcillin enhance warfarin's metabolism and decrease the INR. The INR must be closely monitored when anticoagu-

lated patients are prescribed antibiotics following the surgery.

The evidence from clinical trials and focused reviews supports continuing oral anticoagulation for patients needing dentoalveolar surgery. As long as the INR is within the therapeutic range and local hemostatic measures are taken following the surgery, these patients will have little chance of developing uncontrolled bleeding following the surgery. Local hemostasis will control the bleeding in the few patients who develop postsurgical bleeding. The risk of uncontrolled life threatening bleeding following dentoalveolar surgery is so low that it is not necessary to stop anticoagulation even for a short interval and risk thromboembolism in patients on oral anticoagulants.

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