Management of dental patients taking common hemostasis-altering medications

Doron J. Aframian, DMD, PhD,[a] Rajesh V. Lalla, BDS, PhD,[b] and
Douglas E. Peterson, DMD, PhD,[c] Jerusalem, Israel, and Farmington, CT
THE HEBREW UNIVERSITY AND THE UNIVERSITY OF CONNECTICUT

Objective. Millions of patients worldwide are taking medications that alter hemostasis and decrease the risk for thromboembolic events. This systematic review is intended to provide recommendations regarding optimal management of such patients undergoing invasive dental procedures. The primary focus of this report is on warfarin therapy, although issues related to heparin and aspirin are briefly discussed because of the frequency with which they are encountered in dental practice.

Study design. The review of literature and development of recommendations was based on the Reference Manual for Management Recommendations for the World Workshop in Oral Medicine IV (WWOM IV). A total of 64 publications were identified for initial review. From these publications, the following types of articles were critically analyzed using WWOM standard forms: randomized controlled trials (RCT), non-RCT studies that assess effects of interventions, and studies that assess modifiable risk factors. Development of recommendations was based on the findings of these reviews as well as expert opinion.

Results. The following evidence-based recommendations were developed: (1) For patients within the therapeutic range of International Normalized Ratio (INR) below or equal to 3.5, warfarin therapy need not be modified or discontinued for simple dental extractions. Nevertheless, the clinician's judgment, experience, training, and accessibility to appropriate bleeding management strategies are all important components in any treatment decision. Patients with INR greater than 3.5 should be referred to their physician for consideration for possible dose adjustment for significantly invasive procedures. (2) A 2-day regimen of postoperative 4.8% tranexamic acid mouthwash is beneficial after oral surgical procedures in patients on warfarin. (3) It is not necessary to interrupt low-dose aspirin therapy (100 mg/day or less) for simple dental extractions.

Conclusion. For most patients undergoing simple single dental extractions, the morbidity of potential thromboembolic events if anticoagulant therapy is discontinued clearly outweighs the risk of prolonged bleeding if anticoagulant therapy is continued. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103(suppl 1):S45.e1-S45.e11)**

The aim of oral anticoagulant therapy (OAT) is to reduce blood coagulability to an optimal therapeutic range within which the patient is provided some degree of protection from thromboembolic events. This is achieved at the cost of a minor risk of spontaneous bleeding. When patients on anticoagulant therapy present for an invasive dental procedure expected to cause bleeding, the question arises as to whether the anticoagulant therapy should be continued, modified, or discontinued at some point before dental treatment. In such situations, clinicians must assess the patient's ability to achieve hemostasis following a procedure if anticoagulation is continued versus the risk of thromboembolism if anticoagulant therapy is decreased or discontinued. To avoid these potential complications, several alternative periprocedural anticoagulation strategies have been proposed; however, each of these techniques may be problematic (Fig. 1).

This topic was selected as 1 of 10 to be reviewed at the Fourth World Workshop in Oral Medicine (WWOM IV). Recommendations for the optimal management of patients taking hemostasis-altering medications put forth in this document are based on the results of a systematic review of the published literature as well as the experience of a panel of experts (consultants). Furthermore, review articles from recent years were consulted.[1-15] The primary focus of this report will be on warfarin, given the relative strength of the literature base for this subject. Issues specifically related to heparin and aspirin will only be briefly discussed, in view of the more limited data available from randomized clinical trials (RCTs) regarding use of these agents in patients in the dental setting.
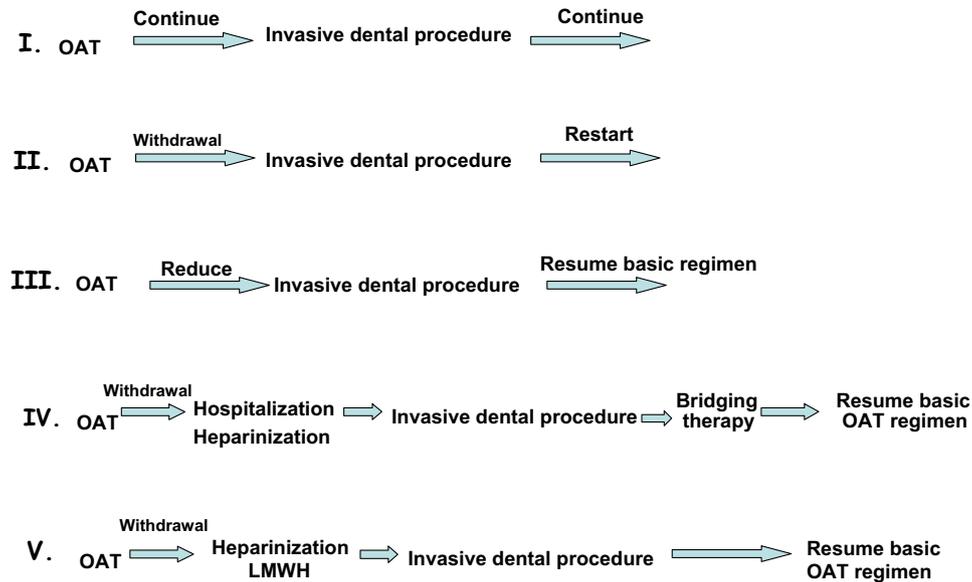
Fig. 1. Potential strategies for treating patients on OAT. LMWH, low molecular weight heparin; OAT, oral anticoagulant therapy.

METHODS

A research librarian performed literature searches using the following online databases: Medline/PubMed, EMBASE, Cochrane Library, and Best Evidence. The period searched was from 1966 to 2005. Search terms included anticoagulants, dentistry, oral health, mouth and mouth diseases, blood coagulation disorders, embolism and thrombosis, platelet aggregation inhibitors, fibrinolytic agents, oral surgical procedures, surgery, oral, mouth surgery. Searches were limited to studies involving human subjects and in the English language. Further, the reviewers identified additional studies from citations in reviewed literature. Publication types included were meta-analyses, systematic reviews, randomized controlled trials (RCT), nonrandomized studies, case studies, and opinion documents.

The review of literature and development of recommendations were based on the Reference Manual for Management Recommendations for the WWOM IV. A total of 53 publications related to warfarin or heparin and 11 related to aspirin were identified for initial review. From these, the following types of studies were critically analyzed using WWOM standard forms: RCTs, non-RCT studies that assess effects of interventions, and studies that assess modifiable risk factors. A total of 23 such studies (RCT and non-RCT studies) related to warfarin, 3 studies related to aspirin, and no studies related to heparin were identified. Each of these 26 studies was independently evaluated by 2 of the authors (D.J.A., R.V.L.). The development of recommendations was based on the findings of these studies as well as expert opinion. In addition, we incorporated recent reviews and opinions.[1-15]

RESULTS

Warfarin

Mechanism of action. Warfarin, a 4-hydroxycoumarin derivative, is one of the most commonly used oral anticoagulants worldwide. It is a vitamin K antagonist, which acts by inhibiting the posttranslational carboxylation of glutamic acid residues that are found at several sites at the N-terminal end of coagulation factors II, VII, IX, and X.[16] Warfarin also inhibits glutamate carboxylation on the amino terminus of the proteins C and S.[17] Warfarin is rapidly and completely absorbed and peak plasma concentrations can be seen within 1 hour of ingestion. Its half-life is approximately 37 hours. Circulating warfarin is almost completely bound to albumin. It is metabolized in the liver into inactive compounds excreted primarily in urine. The measured anticoagulant effect of warfarin results predominantly from reduction in factor II (prothrombin) rather than a cumulative effect of lowering all 4 vitamin K–dependent factors. Prothrombin has a considerably longer half-life, 96 hours, than do the other vitamin K–dependent factors.[16]

Epidemiology. Continuous OAT with warfarin has been used for more than 40 years to decrease the risk for thromboembolism and more than 1 million patients in the United States are currently taking daily warfarin. Based on prescription-centric data reported by the NDC(R) Pharmaceutical Audit Suite (PHAST) monthly audit, warfarin sodium was the 41st most prescribed drug in the United States in 2004 with 16,581,657 prescriptions (http://www.rxlist.com/top200.htm). Many of these patients are taking anticoagulants for varying periods; in some cases, lifelong therapy may be required.

Dose. The international normalized ratio (INR) level to be achieved depends on the condition placing the patient at risk for thromboembolism. The American College of Chest Physicians has recommended an INR of 2.0 to 3.0 for most indications[18-20] with some exceptions requiring higher levels (up to 3.5) (Table I). The basis for development and use of INR is described in the next section.

Diagnosis and testing. The prothrombin time ratio (PTR), defined as the patient's prothrombin time (PT) divided by a laboratory control value, was used to monitor warfarin therapy for many years. However, the PTR has been shown to be imprecise and variable for the following reasons: (1) There may be little comparability of PT values performed in different laboratories; (2) The variability of PT values is attributable to differences in the source of thrombo-

Table I. Recommended Therapeutic Range for Warfarin Therapy*

Low-intensity (INR* goal 2.5 with a range of 2.0 to 3.0)
Prophylaxis of venous thrombosis (high-risk surgery)
Treatment of venous thrombosis
Treatment of pulmonary embolism
Prevention of systemic embolism
Tissue heart valves
Acute myocardial infarction
Atrial fibrillation
Valvular heart disease
High-intensity (INR goal 3.0 with a range of 2.5 to 3.5)
Most mechanical prosthetic heart valves
Prevention of recurrent myocardial infarction

INR = International Normalized Ratio.
*Modified from Little et al. 2002,[8] Lockhart et al. 2003,[9] Carter et al. 2003,[4] Hirsch et al. 1992.[21]
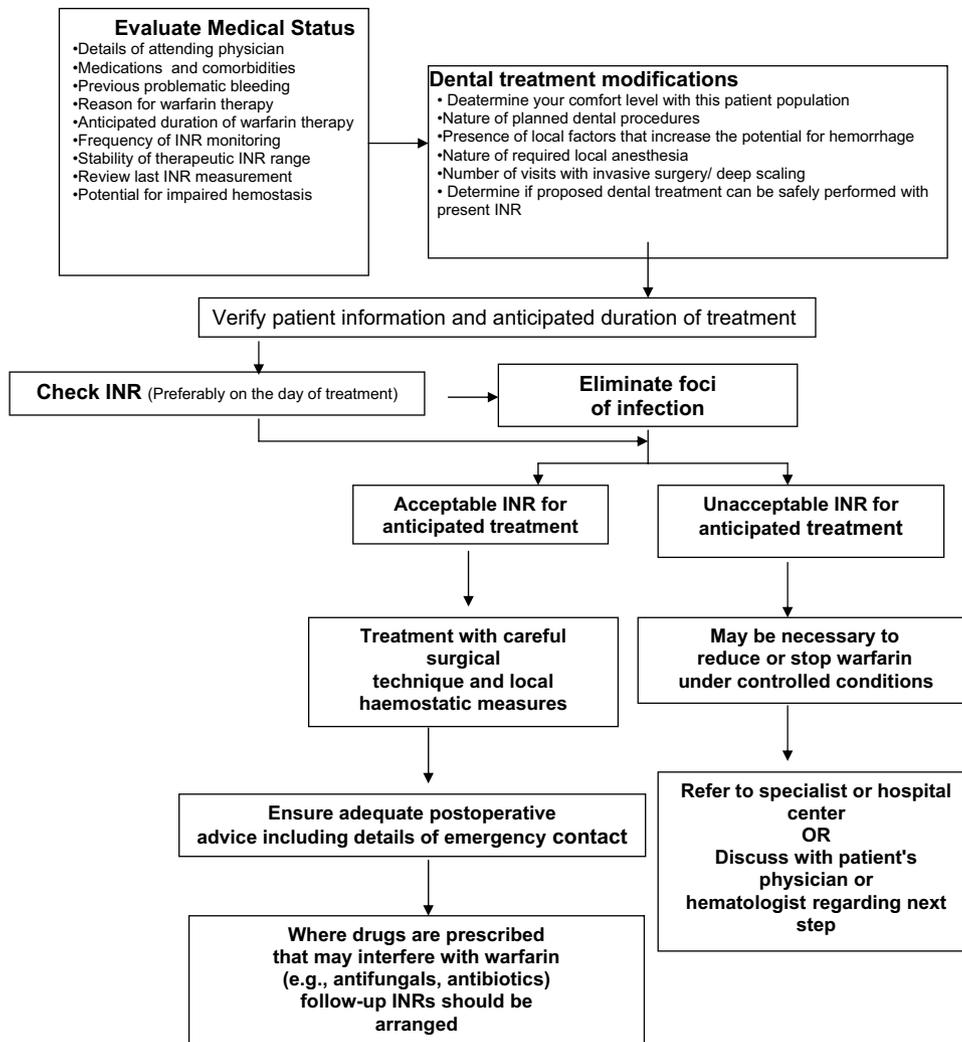

Fig. 2. Algorithm for treatment of patient taking warfarin (Modified from: Herman et al. 1997,[23] Lockhart et al. 2003[9]).

Table II. Grade A warfarin studies: Randomized placebo-controlled trials evaluating the effect of tranexamic acid mouthwash in warfarin-treated patients undergoing oral surgery

Source	No. of patients (M/F; age)	Comparison group	No. of extraction (median; range)	INR (range)	Treatment algorithm	Complications
Sindet-Pedersen et al, 1989[26]	19 (11/8; mean 58)	Placebo	TA(1; 1-17) Placebo; (1, 1-14)	2.5-4.8	Sutures + TA7d	None
Carter and Goss, 2003[27]	43 (22/21; med. 65.2)	TA5d	Range 1-13	2-4	Sutures + TA2d	Delayed bleeding in 2 patients
Carter and Goss, 2003[27]	42 (32/10; med. 65.7)	TA2d	Range 1-16	2-4	Sutures + TA5d	Delayed bleeding in 1 patient

TA, tranexamic acid; med, median; 2d, 2 days; 5d, 5 days; 7d, 7 days.

plastin (human brain, rabbit brain), the brand of thromboplastin, and the type of instrumentation used. This variability has contributed to hemorrhagic events in OAT patients and has historically been a source of concern about invasive dental procedures in these patients.

In 1985, the International Committee on Thrombosis and Homeostasis requested that all lots of thromboplastin have an indication of their international sensitivity index (ISI). 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 INR, which is calculated by the formula $INR = (PTR)^{ISI}$, where the PTR corresponds to the patient's PT divided by that of reference control plasma. Consequently, INR value should be used to assess the level of PT.[22]

Management recommendations. Several strategies have been proposed over the years for managing patients on OAT before, during, and after invasive dental procedures (Fig. 1). Before the initiation of dental treatment, specific consideration must be given to the issue of whether OAT should be unaltered, modified, or stopped (Fig. 2). If warfarin is stopped, the coagulation status for almost all patients returns to near normal in about 4 days.[24] However, there is some evidence that suggests a rebound hypercoagulability effect owing to increased thrombin production or platelet activation if warfarin is abruptly discontinued.[25]

The 23 studies related to warfarin that were critically reviewed were graded according to the potential for bias as follows:

Grade A = low risk of bias (2 articles)

Grade B = low to moderate risk of bias (10 articles)

Grade C = moderate to high risk of bias (6 articles)

Grade D = high risk of bias (5 articles)

The 12 studies rated as Grade A and Grade B are summarized in Tables II and III, respectively, and were used to support management recommendations.

Evidence from these studies indicates that for patients whose INR is within the therapeutic range, bleeding after a simple dental extraction can typically be controlled with local hemostatic measures. In contrast, there have been documented episodes of thromboembolic events when warfarin was discontinued for a dental procedure. In a retrospective review of 197 patients presenting over a 12-month period with nonfatal cardioembolic cerebral infarction, 14 (7.1%) of the infarcts were related to discontinuation of warfarin therapy for invasive medical procedures (one of which was a dental procedure).[1] The average INR at admission for these 14 patients was 1.4 (range 1.0-2.0), and all had been on chronic anticoagulation for over a year. Although we could find no data concerning the overall risk of thromboembolic events from withholding or reducing the dose of warfarin for surgical procedures, there is a clear risk with this practice.

Recommendation. For patients within the therapeutic range of INR of 3.5 or below, warfarin therapy need not be modified or discontinued for simple single dental extractions. More complicated and invasive oral surgical procedures would represent an exception to this recommendation for patients with an INR on the high end of the scale, and they should be discussed with the physician managing the condition requiring warfarin. Nevertheless, the clinician's judgment must always be considered for all treatment decisions (Fig. 2). Since the benefit of preventing a thromboembolic episode clearly outweighs the risk of a significant bleeding episode, this is a Class I recommendation. This recommendation

Table III. Grade B warfarin studies

Source	No. of subjects (M/F, age)	Comparison group	No. of extractions (mean, range)	INR mean (range)	Treatment Algorithm	Complications
Blinder et al., 1999[28]	Grp I: 50 (35/15, 40-86 yrs) Grp II: 50 (33/ 17, 35-79 yrs) Grp III: 50 (18/ 32, 40-93 yrs)		I: 119 II: 117 III: 123	I: 2.38 II: 2.70 II: 2.19	I: gelatin sponge and sutures II: gelatin sponge, sutures and TA MW III: fibrin glue, gelatin sponge and sutures	Post-op bleeding in: 3 subjects from I 6 subjects from II 4 subjects from III.
Al-Belasy et al., 2003[29]	Study grp: 15 subjects on AC (10/5, 50-64 yrs)	Control: 15 subjects on AC (6/9, 53-65 yrs) Negative control (never on AC): 10 subjects (5/5, 49-67 yrs)	Range per subject 5-7 for all grps. Mean: 6 for study grp, 6.33 for control, 6.5 for negative control)	Study grp: 2.5 (1.9-4.3) Control grp: 2.4 (1.7-4.1) Neg control: 1.0 (0.9-1.3)	Study grp: Histoacryl glue and sutures Control and neg control: Gelatin sponge and sutures	5 post-op bleeding cases in control grp, none in study grp or neg control grp.
Carter et al., 2003[30]	Grp A: 26 (16/ 10, 24-85)	Grp B: 23 (15/8, 40-83)	Grp A: 71 (1-13 per subject) Grp B: 81 (1-18 per subject)	Grp A: 3.0 (2.3-4.3) Grp B: 3.1 (2.1-4.0)	Grp A: 4.8% TA MW qid $\times$ 7 days postoperatively. Grp B: Fibrin glue intraoperatively	Post-op bleeding: None in Grp A, 2 in Grp B. Both had unexplained elevated INR on day of bleeding.
Evans et al., 2002[31]	AC grp: 57 (36/ 21, 36-92)	Control grp: 52 (37/ 15, 30-93)	AC grp: (2, 1-7) Control: (3, 1-9)	AC: 2.5 (1.2-4.7) Control: 1.6 (1.2-2.3)	AC: warfarin continued Control: warfarin stopped 2 days before extraction	Bleeding complications: AC grp: 15 cases, 26%, Control grp: 7 cases, 14% ($p = 0.1$)
Gaspar et al., 1997[32]	AC withheld: 15 (7/8, 35-72)	AC continued: 32 (17/15, 34-85)	AC withheld: 15 AC continued: 32	AC withheld: 1.4 (1.3-1.9) AC continued: 2.5 (1.9-3.5)	AC withheld: Stopped warfarin 3 days before surgery. AC continued: no reduction.	Post-op bleeding: AC withheld: 1 case AC continued: 2 cases (no significant difference)
Halfpenny et al., 2001[33]	Study grp: 20 (13/7, 33-83)	Control grp: 26 (17/ 9, 38-79)	Study: (2, 1-6) Control: (1.5, 1-4)	Study: 2.7 (2.0-4.1) Control: 2.9 (2.1-4.1)	Study: Fibrin adhesive dressing (Beriplast C) Control: Oxycellulose dressing (Surgicel)	Post-op bleeding: 1 case in study grp, 0 in control.
Bodner et al., 1998[34]	69 subjects (age, sex not given)	none	(2.87, 1-7)	Low: 1.0-2.0 (20 subjects) Medium: 2.1-3.0 (26 subjects) High: 3.1-5.0 (23 subjects)	No change in warfarin, gelatin sponge and sutures	Minor bleeding: 2 in medium grp, 1 in high grp.
Zanon et al., 2003[35]	Study grp: 250 (59/191, 44-88)	Control: 250 (84/ 166, 42-92)	Study: 525 Control: 513	Study grp: 1.8-4.0 Control grp: not given	Study grp: Warfarin continued, oxidized cellulose and silk suture. Control grp: never on warfarin, suture in some cases.	Bleeding complications: 4 in study grp, 3 in control grp ($p = 0.7$)

Table III. Continued

Source	No. of subjects (M/F, age)	Comparison group	No. of extractions (mean, range)	INR mean (range)	Treatment Algorithm	Complications
Souto et al., 1996[36]	Grps G0-G4: 64 (30/34, mean age 59.7)	Grp G5: 28 (12/16, mean age 56.3)	82 single tooth extractions, 10 cases extraction of 2 adjacent teeth.	G0: 2.5 G1: 2.9 G2: 2.5 G3: 3.3 G4: 3.5 G5: 2.8	G0: AC reduced, heparin, EACA systemic, water irrigation post op. G1: AC reduced, heparin, TA MW, water irrigation post op. G2: AC reduced, heparin, EACA MW, water irrigation post op. G3: AC not changed, no heparin, TA MW, water irrigation post op. G4: AC not changed, no heparin, EACA MW, water irrigation post op. G5: AC not changed, no heparin, EACA MW, TA irrigation post op.	INR adjusted odds ratio for hemorrhagic risk: G1: 4.95 G2: 3.17 G3: 0.88 G4: 1.64 G5: 0.12
Ramstrom et al., 1993[37]	TA grp: 44 (25/19, 53-87 yrs)	Placebo grp: 45 (28/17, 35-83 yrs)	Mean 1.5 in both grps	2.1 to 4.0 in both grps	No change in AC for both grps. TA or placebo MW qid for 7 days postoperatively	Bleeding requiring treatment: 10 in placebo grp, 0 in TA grp ($p < 0.01$)

AC, Anticoagulant; TA, Tranexamic acid; MW, Mouthwash; EACA, epsilon-amino caproic acid (Amicar); Grp, group; Neg, negative; N/A, not available; Post-op, postoperative.

is supported by multiple RCTs and is based on Level of Evidence A. This recommendation was also supported by the expert consultants.

The high end of the therapeutic range of INR is 3.5. Therefore, patients with INR above the therapeutic range are at increased risk of prolonged bleeding. For this reason, patients with INR greater than 3.5 should be referred to their physician for dose adjustment before invasive dental procedures.

Expert opinion suggests that INR values should be obtained within 24 hours before the dental procedure. Portable INR monitors are now available that can measure INR from a finger-stick sample of whole blood and provide results within seconds. Such devices may be useful in cases when INR values are known to fluctuate significantly. Recently, a study by Brennan et al.[38] evaluated the role of a portable INR monitor and found that 18% of OAT patients were above their therapeutic range for INR and 50% were below, emphasizing the

beneficial use of such devices (from the abstract by Brennan et al.[39]). Therefore, 68% of patients were outside their target range.

An algorithm for managing patients on OAT is listed in Fig. 2. An accurate medical history is essential to assess the general health status of OAT patients and to ensure that the condition for which the patient is being anticoagulated is stable. Comorbid conditions that may potentiate an existing bleeding problem include liver disease, bone marrow disorders, biliary tract obstruction, malabsorption, renal disease, and cancers such as leukemia. Increased inflammation of the oral tissues in patients on OAT can contribute to excessive bleeding even with minor procedures. The use of concomitant medications, including antibiotics,[40] antifungals,[41] nonsteroidal anti-inflammatory drugs (NSAIDs), and other platelet aggregation inhibitors (e.g., clopidrogel) may affect a patient's ability to achieve adequate hemosta-

sis after a routine dental procedure. According to the expert consultants, a single dose of prophylactic antibiotics will not impair a patient's ability to achieve adequate hemostasis after a routine dental procedure. However, prolonged therapy with certain antibiotics creates the potential for increased bleeding because of vitamin K deficiency secondary to effects on gastrointestinal flora.

Surgical management recommendations from the expert consultants include minimizing trauma and minimizing the size of the surgical field. For example, removing a limited number of teeth at each visit would allow for an evaluation of the coagulation status.

Tranexamic acid

Several studies have examined the use of tranexamic acid mouthwash in anticoagulated patients undergoing oral surgery, including the 2 grade A warfarin studies in this review.

Sindet-Pedersen et al.[26] conducted a placebo-controlled, double-blind, randomized study on the use of 4.8% tranexamic acid mouthwash after oral surgery (extractions, removal of retained teeth, periapical surgery) in patients on warfarin (INR range 2.5-4.8) (Table II). Nineteen subjects were randomized to tranexamic acid and 20 to placebo. After the surgical procedure, the operated field of surgical intervention was irrigated with 4.8% tranexamic acid mouthwash or placebo for 2 minutes followed by suturing if needed. Thereafter, patients rinsed their mouths for 7 days, 4 times a day, for 2 minutes with 4.8% tranexamic acid mouthwash or placebo. Eight patients in the placebo group experienced a total of 10 postoperative bleeding episodes, while only 1 subject in the tranexamic acid group had a bleeding episode ($P = .01$).[26] This study and similar studies[30,37] have established the efficacy of tranexamic acid mouthwash in this setting.

Carter et al.[27] compared the efficacy of a 2-day and a 5-day regimen of 4.8 % tranexamic acid mouthwash postoperatively after dental extractions in anticoagulated patients with INR between 2 and 4 (mean 2.7 and 2.8 corresponding to the 2-day group and the 5-day group, respectively). After the surgical procedure, the operative field was irrigated with 4.8% tranexamic acid mouthwash. Thereafter, an oxidized cellulose mesh was soaked with 4.8% tranexamic acid and placed in the base of each tooth socket followed by suturing. At home patients continued rinses with 4.8% tranexamic acid mouthwash for 2 minutes, 4 times a day, for 2 or 5 days. Eighty-two of the 85 subjects had no postoperative bleeding. Two subjects in the 2-day group and 1 subject in the 5-day group had minor postoperative bleeding that required minimal intervention to control. The common factor in these 3 cases was severe peri-

odontitis. These results indicate that a 2-day regimen of postoperative 4.8% tranexamic acid mouthwash is as effective as a 5-day regimen.[27]

Recommendation. For patients on OAT, the use of a 2-day regimen of postoperative 4.8% tranexamic acid mouthwash is beneficial to achieve adequate hemostasis after simple oral surgery procedures. Since the benefit to patients (preventing postoperative bleeding) clearly outweighs any risk, this is a Class I recommendation. This recommendation is supported by multiple RCTs; therefore, it is based on Level of Evidence A.

Other hemostatic agents including gelatin sponge, fibrin glue or fibrin adhesive dressing, oxidized cellulose, or epsilon-amino caproic acid (EACA) mouthwash can also be used (Table III). This is a Class I recommendation and is based on data derived from a single randomized trial or nonrandomized studies and is therefore Level of Evidence B.

Although there is no evidence base, there is strong opinion that aspirin prescription for pain control in these patients is contraindicated and caution should be taken with other NSAIDs also because of the risk for bleeding.

Prolonged inter- or postoperative bleeding following oral surgery is an uncommon phenomenon and it rarely requires anything more than local measures. This situation is corrected by transfusing fresh frozen plasma, which contains all of the coagulation proteins, including factors II, VII, IX, and X, and can be used to rapidly lower the INR. Recombinant activated factor VIIa can also lower INR quickly and effectively.[17]

It is important to emphasize that recommendations for management of OAT during invasive dental procedures have also been disseminated among the professional groups of physicians who manage the diseases for which warfarin therapy is indicated. The American Heart Association and American College of Cardiology Scientific Statement states that for patients undergoing dental procedures, tranexamic acid or EACA mouthwash can be applied without interrupting anticoagulant therapy.[18] In addition, the Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy made several limited recommendations (risk/benefit unclear) as follows[42]: (1) For patients undergoing dental procedures who are not considered to be at high risk for bleeding, ACCP recommends that warfarin therapy not be discontinued. In patients at high risk for bleeding, ACCP recommends that warfarin therapy be discontinued. (2) For patients undergoing dental procedures who need local bleeding to be controlled, tranexamic acid or EACA mouthwash can be administered without interrupting anticoagulant therapy.

Standard heparin and low molecular weight heparin

Overview. Treatment with standard heparin (unfractionated) usually involves intravenous infusion and therefore is used primarily as a rapid onset anticoagulation management technique for hospitalized patients. An increasing proportion of dental patients who would have required admission to the hospital for bridging therapy with intravenous heparin infusions may now be treated with subcutaneous injections of low molecular weight (fractionated) heparin (LMWH) as outpatients. The introduction of fractionated heparins with molecular weights in the range of 5,000 daltons, compared with the average 15,000-dalton molecular weight of unfractionated heparin, has produced another effective management strategy to prevent thromboembolism. Although the risk of spontaneous bleeding is assumed to be less with the LMWH, this does not mean that an oral surgical procedure will result in less bleeding than with standard heparin therapy. These patients are anticoagulated and should also be evaluated for the risk of impaired hemostasis as one would evaluate a patient on warfarin therapy.

Indications for the use of heparin include the treatment of venous thrombosis or thromboembolism, acute myocardial infarction, and for patients undergoing cardiopulmonary bypass, vascular surgery, and percutaneous coronary and peripheral vascular procedures.[17]

Unfractionated heparin binds to antithrombin III by unique pentasaccharide chains randomly distributed throughout the molecule.[43] While only about one third of circulating heparin binds to antithrombin, this fraction is enough to produce heparin's anticoagulant effect.[44] The heparin-antithrombin complex inactivates thrombin, as well as factors IIa, Xa, IXa, XIa, and XIIa. However, of all these, thrombin is the most sensitive to inactivation. The inactivation of thrombin requires a complex between heparin, antithrombin, and thrombin. The mechanism of action of the LMWH is the same as that of heparin.

Over the past 20 years LMWH has been used to prevent deep venous thrombosis and pulmonary emboli, angina, myocardial infarctions, and graft thrombosis in vascular surgery. LMWH is now the treatment of choice for patients undergoing total hip or knee replacement because of its superior efficacy compared with subcutaneous standard heparin in the prevention of thromboembolism.

Enoxaparin is the most widely used LMWH but there are 5 other LMWH preparations: ardeparin, dalteparin, nadroparin, reviparin, and tinzaparin.

LMWHs possess several advantages compared to unfractionated heparin. These include its relatively longer half-life allowing for more predictable dosing regimens. Moreover LMWHs cause less in the way of bleeding complications than standard heparin.[45] LMWHs are also more bioavailable (90% compared with 30% to 40% for standard heparin) and they have a reduced binding affinity to plasma proteins. Additionally, LMWHs have been associated with a lower frequency of idiosyncratic and autoimmune-mediated thrombocytopenia.

Administration and dose. The LMWHs are administered subcutaneously in the abdomen. The dose is based on body weight and no laboratory monitoring is necessary. The half-life of the LMWHs is approximately 2 to 4 hours. Treatment with the LMWHs can occur on an outpatient basis.

Monitoring heparin levels. The anticoagulant effect of intravenous infusion of unfractionated heparin is monitored by the activated partial thromboplastin time (aPTT) test. Laboratory monitoring of LMWH therapy is usually not necessary because they do not significantly influence platelet aggregation or affect global clotting tests (i.e., PT or aPTT). Monitoring is advised for selected patient populations such as those with morbid obesity or renal failure. The recommended monitoring assay is the level of anti-Xa factor, since LMWH has more anti-Xa activity than antithrombin III activity.

Management recommendations. Risk of bleeding during and following invasive dental procedures in patients on LMWH and the risk of thromboembolism as a result of stopping the LMWH temporarily is not well established in the dental literature; therefore, no evidence-based management recommendations for LMWH and dental procedures can be made. Expert consensus opinion (Evidence level C) suggests that when a patient on LMWH is to undergo invasive dental procedures, it is advisable to consult with the patient's physician regarding continuing, altering, or stopping the medication.

Since the half-life is relatively short, the LMWH can usually be discontinued 4 to 6 hours before dental treatment. For the typical patient on twice-daily subcutaneous injection, this means withholding the morning dose on the day of the dental procedure and resuming with the evening dose. The plan will vary depending on the patient's risk for thromboembolism. If intravenous unfractionated heparin is used, then appropriate laboratory testing (aPTT) should be done after discontinuation of the drug and before the procedure.[13] Alternatively, normal clotting can be expected 6 to 8 hours after heparin is administered because of its 6-8 hour half-life.

Although there is no evidence base, there is expert opinion that aspirin prescription for pain control in these patients is contraindicated and caution should be

taken with other NSAIDs also because of the risk for bleeding.

Aspirin

Aspirin is the most commonly used preventive and therapeutic agent for vascular ischemic events.[46] Moreover, aspirin is indicated in other conditions such as inflammatory joint diseases.

Overview. In the United States, the 3 doses of aspirin most frequently recommended for the prevention of stroke and myocardial infarction are 81, 160, and 325 mg per day. In Europe and other countries, 75, 150, or 300 mg per day are commonly recommended.[47]

Aspirin acts by irreversibly inactivating, for the lifespan of the platelet, the enzyme cyclooxygenase. The enzyme is responsible for formation of prostaglandins and thromboxane A2, which are involved in platelet activation and aggregation. Aspirin is rapidly absorbed from the proximal intestine and stomach and converted to salicylate, which has peak circulating levels within 2 hours after ingestion.[17] The half-life of salicylate is 2 to 15 hours, depending on the dosage.

Clinical evaluation, diagnosis, and testing. Laboratory monitoring is not typically recommended for patients taking aspirin. The bleeding time test is not at all useful to assess oral bleeding after invasive dental procedures. A pilot study of 30 patients undergoing dental extraction showed that cutaneous bleeding time did not correlate with oral bleeding time or any measures of postoperative hemostasis.[38]

Management recommendations. Ardekian et al.[48] randomized 39 patients, receiving 100 mg aspirin daily and scheduled for dental extractions, into 2 groups: 1 group continued aspirin therapy while the other group stopped aspirin 7 days before extractions and resumed it the day after surgery. Although the bleeding time was higher in the group that continued aspirin, for both groups the bleeding time was within the normal range. No episodes of uncontrolled intraoperative bleeding or postoperative bleeding were noted.[48]

Madan et al.[49] examined the effects of continuing aspirin therapy (75-100 mg per day) in 51 subjects receiving oral surgical procedures. Only one case (third molar surgery) had increased intraoperative bleeding that was controlled by local measures. There was no postoperative bleeding in any of the 51 cases.[49]

In an abstract presented at the American Academy of Oral Medicine meeting in 2006, Valerin[50] reported results regarding 36 patients randomized to 325 mg aspirin or placebo 2 days before and 2 days after a single tooth extraction. There were no differences in any bleeding outcomes between the 2 treatment groups. This appears to be the first randomized, double-blind, placebo-controlled trial evaluating the impact of aspirin

on bleeding complications from invasive dental procedures. In contrast, Schrodi et al.[51] had demonstrated increased bleeding on probing in patients who received 325 mg aspirin daily for 7 days.

Recommendation. We recommend that low-dose aspirin therapy (100 mg per day or less) should not be interrupted for outpatient dental procedures. When intraoperative or postoperative bleeding does occur, local hemostatic methods are generally effective.[48,49] Because the benefit to patients (preventing a thromboembolic episode) clearly outweighs the risk (bleeding episode), this is a Class I recommendation. This recommendation is supported by 1 RCT and a nonrandomized study; therefore, it is based on Level of Evidence B. This recommendation is also supported by the expert consultants.

AREAS FOR FUTURE RESEARCH
Heparins

Data are lacking to support any evidence-based recommendations for dental patients on LMWHs. The risk of excessive bleeding secondary to dental procedures in patients on LMWH, as well as the risk of thromboembolism if LMWH is stopped for a dental procedure is not well established.

Antifibrolytic drugs to support hemostasis

Although a 4.8% tranexamic acid mouthwash proved beneficial in small trials of subjects on warfarin therapy, it has not been approved by the US Food and Drug Administration for use in the United States. Additional clinical trials are thus needed to support the approval of this formulation in the United States. An alternative topical antifibrinolytic agent to tranexamic acid solution is 25% epsilon-aminocaproic acid (EACA) elixir. Additional studies to confirm the positive findings of Souto et al.[36] are needed to assess the effectiveness of 25% EACA elixir in patients maintained on therapeutic anticoagulation with warfarin.

Aspirin

Recent data from RCTs indicate that the optimal dose of aspirin to prevent myocardial infarction and stroke is 160 mg per day.[47] Therefore, more trials with daily aspirin doses greater than 100 mg per day should be conducted to examine bleeding secondary to dental procedures. Such studies will allow the future development of evidence-based guidelines for the management of these patients.

Nonaspirin antiplatelet drugs and the glycoprotein IIb/IIIa antagonists

It is anticipated that there will be increasing use of platelet antiaggregation (antiplatelet) agents for pa-

tients with a history of noncardioembolic stroke or transient ischemic attack, such as ticlopidine, clopidogrel, dipyridamole, extended-release dipyridamole and aspirin, and triflusal.[52] These agents are also used to maintain cardiac stent patency following angioplasty. No studies have been published on postoperative bleeding risk or dental surgery management for patients taking these drugs. Studies are needed to provide data on the proper management for surgical procedures for those patients. Regardless of the initial stimulus, binding of activated glycoprotein IIb/IIIa complex, a platelet surface integrin, to fibrinogen is the final step leading to platelet aggregation. Thus, many researchers have focused on development of drugs that would antagonize this integrin. Currently 3 intravenous glycoprotein IIb/IIIa antagonists are marketed for the prevention of myocardial infarction in patients undergoing percutaneous intervention: abciximab, eptifibatide, and tirofiban, and orally delivered agents are under investigation.[53] No studies have been conducted to assess the bleeding risk among patients on these drugs during invasive dental procedures.

REFERENCES

1. Akopov SE, Suzuki S, Fredieu A, Kidwell CS, Saver JL, Cohen SN. Withdrawal of warfarin prior to a surgical procedure: time to follow the guidelines? Cerebrovasc Dis 2005;19(5):337-42. Epub April 8, 2005.
2. Alexander R, Ferretti AC, Sorensen JR. Stop the nonsense not the anticoagulants: a matter of life and death. N Y State Dent J 2002;68(9):24-6.
3. Beirne OR. Evidence to continue oral anticoagulant therapy for ambulatory oral surgery. J Oral Maxillofac Surg. 2005;63(4):540-5.
4. Carter G, Goss AN, Lloyd J, Tocchetti R. Current concepts of the management of dental extractions for patients taking warfarin. Aust Dent J 2003;48(2):89-96; quiz 138.
5. Chugani V. Management of dental patients on warfarin therapy in a primary care setting. Dent Update 2004;31(7):379-82, 384.
6. Dunn AS, Turpie AG. Perioperative management of patients receiving oral anticoagulants: a systematic review. Arch Intern Med 2003;163(8):901-8.
7. Jeske AH, Suchko GD. Lack of a scientific basis for routine discontinuation of oral anticoagulation therapy before dental treatment. J Am Dent Assoc 2003;134(11):1492-7.
8. Little JW, Miller CS, Henry RG, McIntosh BA. Antithrombotic agents: implications in dentistry. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;93(5):544-51.
9. Lockhart PB, Gibson J, Pond SH, Leitch J. Dental management considerations for the patient with an acquired coagulopathy. Part 2: Coagulopathies from drugs. Br Dent J 2003;195(9):495-501.
10. Patton LL, Ship JA. Treatment of patients with bleeding disorders. Dent Clin North Am 1994;38(3):465-82.
11. Rice PJ, Perry RJ, Afzal Z, Stockley IH. Antibacterial prescribing and warfarin: a review. Br Dent J 2003;194(8):411-5.
12. Scully C, Wolff A. Oral surgery in patients on anticoagulant therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;94(1):57-64.
13. Schardt-Sacco D. Update on coagulopathies. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90(5):559-63.
14. Wahl MJ. Dental surgery in anticoagulated patients. Arch Intern Med 1998;158(15):1610-6.
15. Wahl MJ. Myths of dental surgery in patients receiving anticoagulant therapy. J Am Dent Assoc 2000;131(1):77-81.
16. Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 2001;119(1 Suppl):8S-21S.
17. Owens CD, Belkin M. Thrombosis and coagulation: operative management of the anticoagulated patient. Surg Clin North Am 2005;85(6):1179-89, x.
18. Hirsh J, Fuster V, Ansell J, Halperin JL; American Heart Association/American College of Cardiology Foundation. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. J Am Coll Cardiol 2003;41(9):1633-52.
19. Salem DN, Stein PD, Al-Ahmad A, Bussey HI, Horstkotte D, Miller N, et al. Antithrombotic therapy in valvular heart disease—native and prosthetic: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:457-82.
20. Büller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic yherapy for venous thromboembolic disease: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy . Chest 2004;126:401-28.
21. Hirsh J, Dalen JE, Deykin D, Poller L. Oral anticoagulants. Mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 1992;102(4 Suppl):312S-326S.
22. Steinberg MJ, Moores JF 3rd. Use of INR to assess degree of anticoagulation in patients who have dental procedures. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;80(2):175-7.
23. Herman WW, Konzelman JL Jr, Sutley SH. Current perspectives on dental patients receiving coumarin anticoagulant therapy. J Am Dent Assoc 1997;128(3):327-35.
24. White RH, McKittrick T, Hutchinson R, Twitchell J. Temporary discontinuation of warfarin therapy: changes in the international normalized ratio. Ann Intern Med 1995;122(1):40-2.
25. Genewein U, Haeberli A, Straub PW, Beer JH. Rebound after cessation of oral anticoagulant therapy: the biochemical evidence. Br J Haematol 1996;92(2):479-85.
26. Sindet-Pedersen S, Ramstrom G, Bernvil S, Blomback M. Hemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. N Engl J Med 1989;320(13):840-3.
27. Carter G, Goss A. Tranexamic acid mouthwash—a prospective randomized study of a 2-day regimen vs 5-day regimen to

prevent postoperative bleeding in anticoagulated patients requiring dental extractions. Int J Oral Maxillofac Surg 2003; 32(5):504-7.

28. Blinder D, Manor Y, Martinowitz U, Taicher S, Hashomer T. Dental extractions in patients maintained on continued oral anticoagulant: comparison of local hemostatic modalities.Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;88(2):137-40.

29. Al-Belasy FA, Amer MZ. Hemostatic effect of n-butyl-2-cyanoacrylate (histoacryl) glue in warfarin-treated patients undergoing oral surgery. J Oral Maxillofac Surg 2003;61(12):1405-9.

30. Carter G, Goss A, Lloyd J, Tocchetti R. Tranexamic acid mouthwash versus autologous fibrin glue in patients taking warfarin undergoing dental extractions: a randomized prospective clinical study. J Oral Maxillofac Surg 2003;61(12):1432-5.

31. Evans IL, Sayers MS, Gibbons AJ, Price G, Snooks H, Sugar AW. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. Br J Oral Maxillofac Surg 2002;40(3):248-52.

32. Gaspar R, Brenner B, Ardekian L, Peled M, Laufer D. Use of tranexamic acid mouthwash to prevent postoperative bleeding in oral surgery patients on oral anticoagulant medication. Quintessence Int 1997;28(6):375-9.

33. Halfpenny W, Fraser JS, Adlam DM. Comparison of 2 hemostatic agents for the prevention of postextraction hemorrhage in patients on anticoagulants. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92(3):257-9.

34. Bodner L, Weinstein JM, Baumgarten AK. Efficacy of fibrin sealant in patients on various levels of oral anticoagulant undergoing oral surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;86(4):421-4.

35. Zanon E, Martinelli F, Bacci C, Cordioli G, Girolami A. Safety of dental extraction among consecutive patients on oral anticoagulant treatment managed using a specific dental management protocol. Blood Coagul Fibrinolysis 2003;14(1):27-30.

36. Souto JC, Oliver A, Zuazu-Jausoro I, Vives A, Fontcuberta J. Oral surgery in anticoagulated patients without reducing the dose of oral anticoagulant: a prospective randomized study. J Oral Maxillofac Surg 1996;54(1):27-32; discussion 323.

37. Ramstrom G, Sindet-Pedersen S, Hall G, Blomback M, Alander U. Prevention of postsurgical bleeding in oral surgery using tranexamic acid without dose modification of oral anticoagulants. J Oral Maxillofac Surg 1993;51(11):1211-6.

38. Brennan MT, Shariff G, Kent ML, Fox PC, Lockhart PB. Relationship between bleeding time test and postextraction bleeding in a healthy control population. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;94(4):439-43.

39. Brennan MT, Fox PC, Lockhart PB. Role of an INR device in a hospital dental practice. Paper presented at: 60th Annual Meeting of the American Academy of Oral Medicine; May 4, 2006; San Juan, Puerto Rico.

40. Davydov L, Yermolnik M, Cuni LJ. Warfarin and amoxicillin/clavulanate drug interaction. Ann Pharmacother 2003;37(3):367-70.

41. Pemberton MN, Oliver RJ, Theaker ED. Miconazole oral gel and drug interactions. Br Dent J 2004;196(9):529-31.

42. Ansell J, Hirsh J, Dalen J, Bussey H, Anderson D, Poller L, et al. Managing oral anticoagulant therapy. Chest 2001;119(1 Suppl):22S-38S.

43. Choay J, Petitou M, Lormeau JC, Sinay P, Casu B, Gatti G. Structure-activity relationship in heparin: a synthetic pentasaccharide with high affinity for antithrombin III and eliciting high anti-factor Xa activity. Biochem Biophys Res Commun 1983; 116(2):492-9.

44. Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001;119(1 Suppl):64S-94S.

45. Hewitt RL, Chun KL, Flint LM. Current clinical concepts in perioperative anticoagulation. Am Surg 1999;65(3):270-3.

46. Hennekens CH, Dyken ML, Fuster V. Aspirin as a therapeutic agent in cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 1997;96(8):2751-3.

47. Dalen JE. Aspirin to prevent heart attack and stroke: what's the right dose? Am J Med 2006;119(3):198-202.

48. Ardekian L, Gaspar R, Peled M, Brener B, Laufer D. Does low-dose aspirin therapy complicate oral surgical procedures? J Am Dent Assoc 2000;131(3):331-5.

49. Madan GA, Madan SG, Madan G, Madan AD. Minor oral surgery without stopping daily low-dose aspirin therapy: a study of 51 patients. J Oral Maxillofac Surg 2005;63(9):1262-5.

50. Valerin M. Relationship between aspirin use and postoperative bleeding from dental extractions in a healthy population. Paper presented at: 60th Annual Meeting of the American Academy of Oral Medicine; May 4, 2006; San Juan, Puerto Rico.

51. Schrodi J, Recio L, Fiorellini J, Howell H, Goodson M, Karimbux N. The effect of aspirin on the periodontal parameter bleeding on probing. J Periodontol 2002;73(8):871-6.

52. Jamieson DG, Parekh A, Ezekowitz MD. Review of antiplatelet therapy in secondary prevention of cerebrovascular events: a need for direct comparisons between antiplatelet agents. J Cardiovasc Pharmacol Ther 2005;10(3):153-61.

53. Hanson J, de Leval X, David JL, Supuran C, Pirotte B, Dogne JM. Progress in the field of GPIIb/IIIa antagonists. Curr Med Chem Cardiovasc Hematol Agents 2004;2(2):157-67.

Reprint requests:

Douglas E. Peterson, DMD, PhD
Department of Oral Health and Diagnostic Sciences
School of Dental Medicine
University of Connecticut Health Center
Farmington, CT 06030-1605
Peterson@nso.uchc.edu