Dental Surgery for Patients on Anticoagulant Therapy with Warfarin: A Systematic Review and Meta-analysis

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ABSTRACT

Purpose: To evaluate the effect of continuing warfarin therapy on the bleeding risk of patients undergoing elective dental surgical procedures.

Methods: Data sources were the MEDLINE and EMBASE databases, the Cochrane Central Register of Controlled Trials, a manual citation review of the relevant literature, content experts and relevant abstracts from the proceedings of the International Association for Dental Research. Study selection was carried out independently by 2 reviewers, as was quality assessment. Data extraction was done by 3 reviewers. Differences were resolved by consensus. Eligible studies were randomized controlled trials that compared the effects of continuing the regular dose of warfarin therapy with the effects of discontinuing or modifying the dose on the incidence of bleeding in patients undergoing dental procedures.

Results: Five trials (a total of 553 patients) met the inclusion criteria. Compared with interrupting warfarin therapy (either partial or complete), perioperative continuation of warfarin with patients' usual dose was not associated with an increased risk for clinically significant nonmajor bleeding (relative risk [RR], 0.71; 95% confidence interval [CI]: 0.39–1.28; $p = 0.65$; $I^2 = 0\%$) or an increased risk for minor bleeding (RR, 1.19; 95% CI: 0.90–1.58; $p = 0.22$; $I^2 = 0\%$).

Conclusions: Continuing the regular dose of warfarin therapy does not seem to confer an increased risk of bleeding compared with discontinuing or modifying the warfarin dose for patients undergoing minor dental procedures.

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Warfarin therapy is used by more than 4 million patients in North America for conditions such as atrial fibrillation, mechanical heart valve and venous thromboembolism.[1] Warfarin therapy reduces the risk of arterial thromboembolic events such as stroke by 70%[2,3] and the risk of recurrent venous thromboembolism by 90%.[4] Given these therapeutic benefits, the management of patients on anticoagulant therapy who require surgery or another invasive procedure is a problem because clinicians must weigh the risk of thromboembolism caused by a temporary interruption of warfarin therapy against the risk of perioperative bleeding if the therapy is continued.

In clinical practice, the management of patients on anticoagulant therapy who require

dental procedures varies considerably.[5–8] A 2006 survey[7] of hematologists and dentists revealed no consistent management of perioperative anticoagulation. Perioperative management ranged from the continuation of the regular dose of anticoagulant to reduction of the dose to its complete cessation. Another practice is to stop warfarin 5 days before the procedure and administer bridging anticoagulation, typically low-molecular-weight heparin, for patients at high risk of thromboembolism.[9] This approach, which aims to avoid a residual anticoagulant effect at the time of the procedure, deals with dentists' perception of an increased risk of serious bleeding if warfarin is not interrupted. Dentists' concern about postoperative bleeding may be based, in part, on their observation that for patients not on anticoagulation, bleeding after dental procedures, such as extractions, can be excessive, given the highly vascular supporting structures. Prevention of oral bleeding is also desirable because it can be distressing for patients, presents challenges for the homebound elderly and may deter future dental care. Interruption of warfarin therapy, however, may increase the risk of thromboembolism, such as stroke, which can be associated with mortality and long-term morbidity.[10] Further, bleeding after dental surgery is easily seen and usually self-limiting, and most often can be managed with local measures, such as biting on gauze. Finally, recent editorials and reviews[8,11–13] have suggested that dentists' concerns about the risk of bleeding when procedures are done on patients taking anticoagulation have been overstated.

Against this background, we did a systematic review of studies assessing outcomes for patients treated with anticoagulants who required elective dental procedures. We aimed to determine the risk of bleeding for patients who continued warfarin therapy compared with that for those whose dose was reduced or interrupted.

Methods

Data Sources

We attempted to identify all published and unpublished randomized controlled studies that assessed the management of warfarin therapy in patients undergoing elective dental procedures. We searched MEDLINE and EMBASE databases (1990 to June 2008), and the Cochrane Central Register of Controlled Trials (from its inception to June 2008). We also searched for relevant abstracts from the electronic database of the proceedings of the International Association for Dental Research (from its inception to 2008). We supplemented the search strategy (**Appendix 1**) by manually reviewing the reference lists of the articles retrieved and by contacting content experts.

Study Selection

Study selection was done independently by 2 reviewers (AN, JD). A study was included if it was a randomized controlled trial (RCT) assessing anticoagulant management for patients on warfarin therapy who required an elective dental procedure, and the RCT assessed at least 1 of the following outcomes: thromboembolism (arterial or venous) or postoperative bleeding (major, clinically significant nonmajor, or minor). Studies were excluded if they did not have a treatment arm consisting of patients who continued warfarin therapy in its usual dose and a control arm consisting of patients whose usual dose was decreased or whose warfarin therapy was stopped before the dental procedure.

Study Quality Assessment

Two reviewers (AN, SS) independently assessed the quality of included trials using a validated quality scale[14] that is based on the methods used to generate the randomization sequence, the method of double-blinding and the description of patient withdrawals and dropouts. They scored the appropriateness of randomization and double-blinding from 0 to 2 points, and the reporting of withdrawals and dropouts, as 0 or 1 point, for a maximum of 5 points if all criteria were satisfied. Studies with a score > 2 were considered high quality; studies with a score of ≤ 2 were considered low quality. Interrater agreement about the assessment of the quality of included trials was moderate ($\kappa = 0.58$, 95% confidence interval [CI]: 0.21–0.95). Disagreements about the quality of the studies were resolved by consensus between the reviewers.

Study Data Extraction

For each study, 3 reviewers (AN, AA, SS) independently extracted data about study design, patient characteristics, perioperative interventions and the following clinical outcomes: major, clinically significant nonmajor and minor bleeding; thromboembolic events; re-intervention or re-operation; and all-cause mortality. We defined bleeding outcomes a priori. We defined major bleeding as clinically overt bleeding that was associated with at least 1 of the following: a > 2 g/dL decrease in hemoglobin, a transfusion of > 2 units of red blood cells, bleeding that was fatal, or bleeding that required another operation or reversal of anticoagulation. We defined clinically significant nonmajor bleeding as bleeding that was not major, but resulted in a visit to a medical facility or an unplanned procedure or intervention (e.g., suturing). We defined minor bleeding as bleeding that did not satisfy the criteria for major or clinically significant nonmajor bleeding.

We reclassified bleeding events in the selected studies according to our defined criteria to allow pooling of findings across studies based on standardized definitions of bleeding outcomes. This was necessary because no accepted standardized definition of bleeding for patients undergoing surgical procedures exists.[15] We defined thromboembolic events as stroke, transient ischemic

attack, systemic embolism, thrombosis of a mechanical heart valve, thrombosis of the cardiac chamber, deep-vein thrombosis or pulmonary embolism. We defined all-cause mortality as death from any cause. We resolved disagreements about data extraction by consensus and discussion with a fourth reviewer (JD).

Meta-analysis

The outcomes of interest were clinically significant nonmajor bleeding and minor bleeding events as we defined them for this study. We based this decision on our expectation that studies would not be adequately powered or of sufficient duration to detect thromboembolic events and on the paucity of reported major or life-threatening bleeding after elective dental surgery. The risk of bleeding with the continuation of warfarin compared with that for the discontinuation or reduction of the dose of warfarin was expressed as a relative risk (RR) with an associated 95% CI. For this analysis, an RR < 1.0 favoured the continuation of the usual warfarin, a RR > 1.0 favoured the discontinuation or alteration of the warfarin dose, whereas an RR of 1.0 indicated equivalence between the 2 groups. CIs that crossed the line of equivalence indicated that the true RR may be 1 rather than the calculated value. The χ^2 test was used to calculate the percentage variation across studies caused by their heterogeneity. Significance for this test was set liberally at $p \leq 0.1$, since in practice, the test often lacks the power to detect inter-study differences of the treatment effect.[16] DerSimonian and Laird's random effects model of pooling[17] was used to provide a more conservative estimate of the true effect. These analyses were carried out with Review Manager 4.2 (Cochrane Collaboration, Oxford).

A sensitivity analysis omitting studies of low quality was planned to assess the effect of the methodological quality of the primary studies on the overall outcome. Two subgroup analyses were done after the fact. One analysis assessed the risk of bleeding for patients maintained at higher international normalized ratios (INRs) and included studies in which the mean INR of the study group was > 3. A larger treatment effect was hypothesized for these studies. Another analysis was done for studies that used antifibrinolytic agents; a smaller treatment effect was hypothesized for these studies.

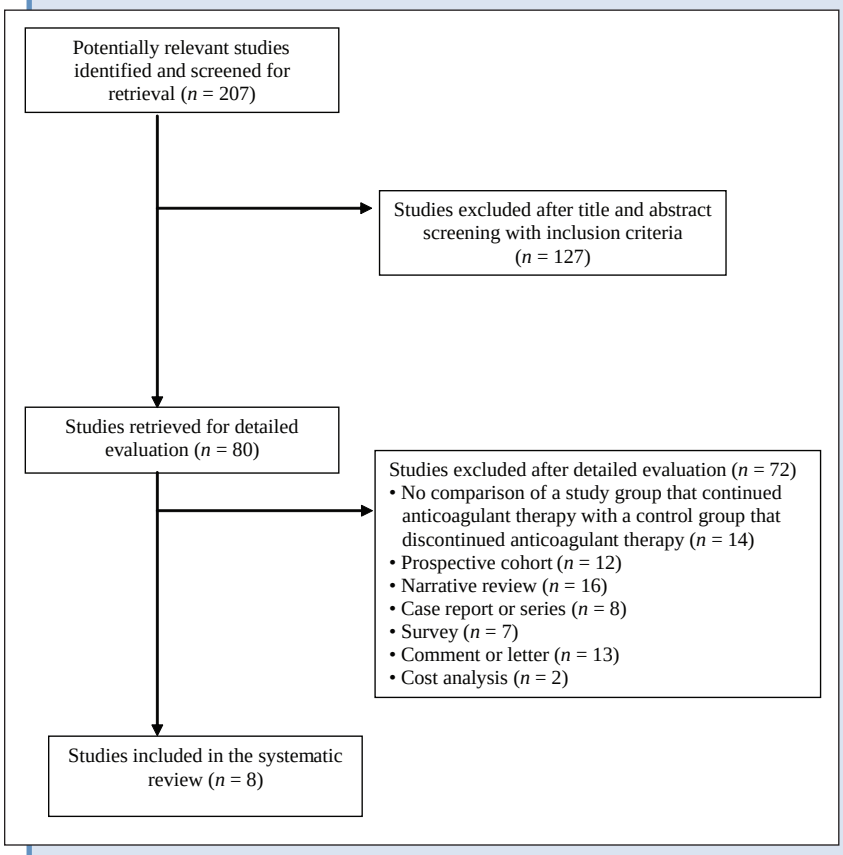


Figure 1: Study identification and selection.

Results

Data Sources

Study Identification and Selection

As shown in **Fig. 1**, 207 potentially eligible studies were identified, 127 of which were excluded after the study titles and abstracts were screened with the predefined inclusion and exclusion criteria. The remaining 80 studies were retrieved for more detailed evaluation. Communication with content experts did not identify any additional eligible studies. Of the retrieved 80 studies, 72 were excluded: 14 did not compare the treatment group that continued anticoagulant therapy with a control group that discontinued or reduced such treatment; 16 were narrative reviews; 7 were surveys; 8 were case series or case reports; 12 studies were prospective cohort studies; 2 were cost analyses; and 13 were comments or letters to the editor. Therefore, 8 RCTs[18–24] were included. Three of these 8 RCTs were initially reported as letters, followed by more comprehensive publications. The latter reports were used for data extraction. Therefore a total of 5 studies, reported as 8 publications, were included in our review.

Table 1 Study characteristics

Study	Indication for anticoagulant therapy	No. of pts	Anticoagulant therapy	INR, mean ± SD or mean (range)	Co-interventions	Dental procedure	Follow-up (days)
Al-Mubarak and others[19]	NR	214	**T:** continued OAC **C:** OAC d/c 2 days preop; usual dose 12 hours postop	**T:** 1.85 (1.4–2.3) **C:** 2.55 (1.9–3.1)	Sutures for groups 3 and 4	Extractions, nature not specified (single tooth, 63.3%; 2 teeth, 25%; 3 teeth, 7.5%; 4 teeth, 3.3%; 5 teeth, 0.8%)	7
Borea and others[20]	PHV (100%)	30	**T:** continued OAC **C:** d/c OAC, duration not specified	**T:** 3.09 ± 0.20 **C:** 1.69 ± 0.20	**T:** TXA irrigation at surgery and mouth rinse qid for 7 days **C:** physiologic (placebo) irrigation at surgery and mouth rinse qid for 7 days	Single extraction **T:** 4/15 complicated (mucosal flap, bone removal) **C:** 0/15 complicated	7
Evans and others[21]	NR	114	**T:** continued OAC **C:** OAC d/c 2 days preop; resumed usual dose same day postop	**T:** 2.5 (1.2–4.7) **C:** 1.6 (1.2–2.3)	Oxycellulose dressing applied at surgery for all patients	Extractions, nature not specified Mean no. (range): **T:** 2 (1–7) **C:** 3 (1–9)	7
Sacco and others[23]	PHV (45%), atrial fibrillation (30%), DVT (12%), valvulopathy (10%), other (3%)	131	**T:** continued OAC **C:** OAC reduced to target INR range 1.8	**T:** 2.89 ± 0.42 **C:** 1.77 ± 0.26	**T:** TXA q6h for 2 days, gelatine and oxidized cellulose sponges **C:** none	Extractions, nature not specified (average 4 teeth per patient) Implant placement (6 fixtures) Excision of cysts (6)	7
Souto and others[24]	PHV (73%), valvulopathy (27%)	64	**T:** acenocoumarol full dose **C:** acenocoumarol half dose 2 days preop; usual dose day of surgery	**T:** 3.40 **C:** 2.64	**T:** cold water or TXA irrigation at surgery; antifibrinolytic mouth rinses (EACA or TXA) qid for 2 days **C:** heparin bridging plus cold water or TXA irrigation at surgery; antifibrinolytic mouth rinses (EACA or TXA) qid for 2 days	Extraction single teeth or 2 adjacent teeth, nature not specified	NR

No. of pts = Number of patients; INR = international normalized ratio; NR = not reported; T = treatment group; C = control group; OAC = oral anticoagulant; d/c = discontinued; preop = preoperatively; postop = postoperatively; PHV = prosthetic heart valve; TXA = tranexamic acid; qid = 4 times a day; q6h = every 6 hours; DVT = deep venous thrombosis; EACA = epsilon-aminocaproic acid.

Table 2 Quality scores (based on Jadad and others[14])

Study	Randomized			Double-blinded		Patient withdrawals	Total score (out of 5)
	Method not described (Score, 1)	Method appropriate (Score, 2)	Method not appropriate (Score, 0)	Method not described (Score, 1)	Method described (Score, 2)	Adequate description (Score, 1)	
Al-Mubarak and others[19]	X						1
Borea and others[20]			X		X		2
Evans and others[21]		X				X	3
Sacco and others[23]	X						1
Souto and others[24]		X					2

Table 3 Comparison of bleeding outcomes

Source	No. of patients (n = 553)		Nonmajor bleeding		Minor bleeding	
	Treatment (n = 275)	Control (n = 278)	Treatment (n = 275)	Control (n = 278)	Treatment (n = 210)	Control (n = 212)
Al-Mubarak and others[19]	110	104	0	0	8	7
Borea and others[20]	15	15	1	2	1	0
Evans and others[21]	60	54	2	0	13	7
Sacco and others[23]	65	66	6	10	NR	NR
Souto and others[24]	25	39	6	13	19	26

No. = number; nonmajor bleeding = clinically significant nonmajor bleeding; NR = not reported.

Study Characteristics

As shown in **Table 1**, 5 RCTs, with a total of 553 patients, were included in our meta-analysis. In 2 studies,[19,21] warfarin was discontinued 2 days before the procedure. In one study,[24] a half dose of warfarin was taken 2 days before and the day before the procedure. Two remaining studies[20,23] did not specify the length of time warfarin was discontinued, although one[23] stated the target INR for control patients.

Methodological Quality

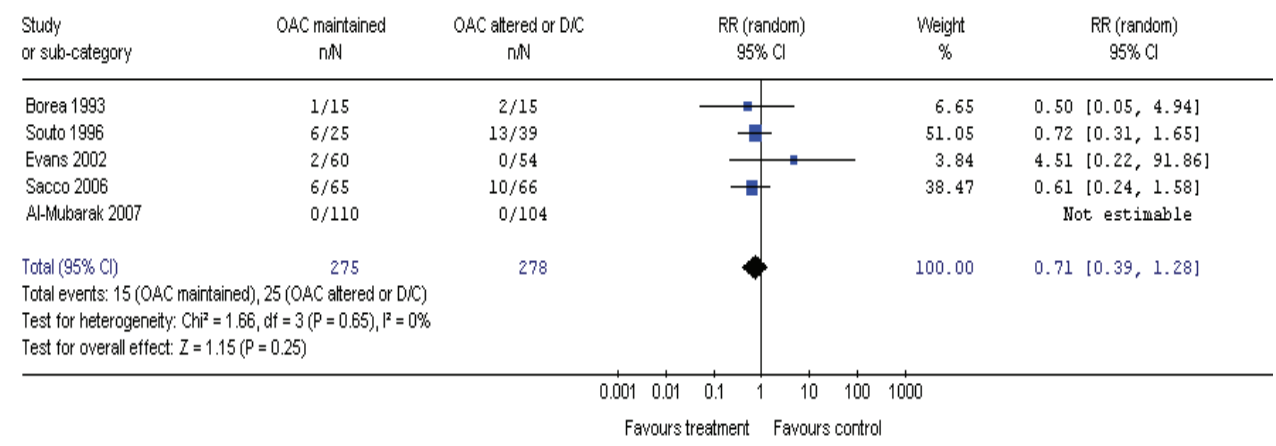
As shown in **Table 2**, the median quality score was 2.0. Assessment indicated that 4[19,20,23,24] of 5 trials were low quality, scoring 1 or 2 on the Jadad scale[14]; the remaining study[21] was higher quality, scoring 3 on the Jadad scale. This study was the only one in which the randomization method was appropriate, and that included a description of withdrawals and dropouts. Two studies[19,23] did not describe the method of randomization; 1 study[20] described the method of randomization, but because allocation concealment was not adequate, randomization was not considered appropriate. Two studies[21,24] described the randomization method appropriately.

Data Synthesis

Data relating to our presumptive outcomes of interest, namely, data for clinically significant nonmajor bleeding and minor bleeding, are summarized in **Table 3**. Some authors considered bleeding at 1-, 3- and 7-day intervals. For these studies, only bleeding on day 3 was analyzed.

Clinically Significant Nonmajor Bleeding

As shown in **Fig. 2**, clinically significant nonmajor bleeding occurred in 15 of 275 (5.5%) patients who continued their regular dose of warfarin and in 25 of 278 (9.0%) patients who discontinued or altered their dose of warfarin before dental surgery. The risk of clinically significant nonmajor bleeding was not significantly lower for patients who discontinued or altered their warfarin dose (RR = 0.71, 95% CI 0.39–1.28; $p = 0.25$; $I^2 = 0\%$). Data from 1 study[19] could not be included in the analysis for this outcome because no incidents of clinically significant nonmajor bleeding were reported.



OAC = anticoagulant therapy; n= number of patients with the outcome of clinically significant nonmajor bleeding; N = number of patients in study; D/C = discontinued; RR = relative risk; CI = confidence interval; df = degrees of freedom; P = probability; I^2 = the extent of inconsistency among results; Z = a calculation of the number of standard deviations from the mean to the value of interest.

Figure 2: Forest plot comparing the outcome of clinically significant nonmajor bleeding for patients who were taking anticoagulant therapy with the outcome for patients who had their anticoagulants discontinued or their dose altered.

Understanding graphs (forest plots) of meta-analyses (Figs. 2 and 3)

For each study, the box in the column labelled *RR (random)* of the forest plot represents the study result or point estimate (RR = relative risk). This result or point estimate is the best estimate of the true value for the population from which the sample of patients was taken.

The horizontal bars on either side of the point estimate are the 95% confidence intervals that represent the uncertainty due to chance associated with the estimate: the true result may lie anywhere within that interval. Wide confidence intervals indicate a large amount of uncertainty about the estimate. Narrow confidence intervals provide more confidence that the estimate is close to the true result — that greater precision is associated with the result.

The vertical line through the boxes (point estimates) and horizontal lines (95% confidence intervals) is the line of equivalence where there is no difference between the effect of the treatment and the effect of the control. A point estimate that lies on the side of the vertical line labelled *favours treatment* indicates that the intervention may be beneficial (in this study, the treatment is the continuation of OAC). The point estimate that lies on the side labelled *favours control* indicates that the control (in this study, discontinuation of OAC) may be more beneficial than the treatment being studied. However, if the confidence interval for the estimate crosses the vertical line of the graph, one of the possible values for the true estimate is zero. In this case, the result is deemed to be not statistically significant.

The diamond at the lower end of the graph represents the combined results of all studies and the associated 95% confidence interval.

Minor Bleeding

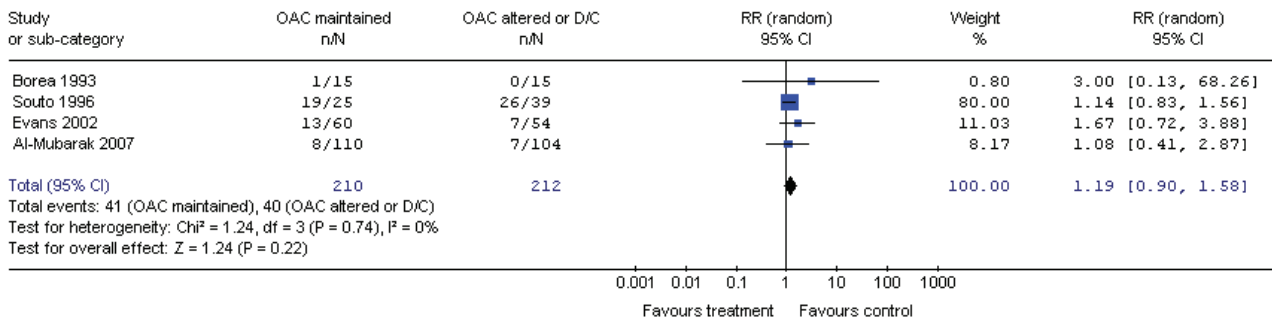
As shown in **Fig. 3**, minor bleeding occurred in 41 of 210 (19.5%) patients who continued their regular dose of warfarin and in 40 of 212 (18.9%) patients who discontinued or altered their dose of warfarin before dental surgery. The risk of minor bleeding was not significantly lower for patients who discontinued or altered their warfarin dose (RR = 1.19, 95% CI 0.90–1.50; p = 0.22; I^2 = 0%). One[23] of 5 RCTs did not record minor bleeding and was therefore excluded from this analysis.

Sensitivity and Subgroup Analyses

A sensitivity analysis excluding studies of low quality was planned, but was not conducted because 4 of the 5 included studies were of low quality, scoring ≤ 2 on a validated quality scale.[14] The results of the primary analyses were supported by the subgroup analyses done in studies[20,24] with a mean INR > 3.0 (RR = 0.50, 95% CI 0.21–1.68; p = 0.21; I^2 = 0%). Results from the subgroup analyses on studies[20,23,24] that used antifibrinolytic agents were also not significant (RR = 0.65, 95% CI 0.36–1.19; p = 0.16; I^2 = 0%).

Discussion

From the results of our meta-analysis, continuing warfarin without any dose adjustment before a dental procedure does not seem to confer an increased risk of clinically important bleeding, compared with stopping or reducing the dose of warfarin. The validity of this finding is supported by several factors. Findings for both of the prespecified bleeding outcomes were consistent: continuing warfarin was not associated with a significantly



OAC = anticoagulant therapy; n= number of patients with the outcome of clinically significant nonmajor bleeding; N = number of patients in study; D/C = discontinued; RR = relative risk; CI = confidence interval; df = degrees of freedom; P = probability; I^2 = the extent of inconsistency among results; Z = a calculation of the number of standard deviations from the mean to the value of interest.

Figure 3: Forest plot comparing the outcome of minor bleeding for patients who were taking anticoagulants with the outcome for patients who had their anticoagulants discontinued or their dose altered.

increased risk of either clinically important nonmajor bleeding (RR = 0.71, 95% CI 0.39–1.28) or minor bleeding (RR = 1.19, 95% CI 0.90–1.58). None of the 275 patients who continued warfarin experienced serious (or major) bleeding. The mean INR across studies of patients who continued warfarin was between 1.8 and 3.4 **(Table 1)**, suggesting that patients were therapeutically anticoagulated at the time of the dental procedure; therefore, the observed low rates of bleeding are not likely attributable to a systematically lower intensity of anticoagulation. Further, the follow-up period after dental procedures was at least 6 days for all studies, the time frame during which most procedure-related bleeding events occur,[25] thus reducing the likelihood that bleeding events were missed.

Of significance in the interpretation of our findings is the potential for a type II error (a false negative result) because most included studies were underpowered to detect an increased risk of major bleeding with a continued warfarin strategy. The true incidence of major bleeding for patients who undergo dental procedures without a reduction in the dose or anticoagulant or interruption of the therapy is not well established. Similarly, the finding that none of the 553 patients studied experienced thromboembolic events was expected because of the lack of the studies' power and inadequate follow-up to detect such events. Since most patients studied underwent dental extractions, our findings pertain to this patient population and may not be generalizable across the spectrum of oral surgical procedures. Perioperative management of patients on anticoagulation therapy for other dental surgical procedures requires further study.

The secondary subgroup analyses of patients' mean INR and those taking antifibrinolytic agents were based on a hypothesized difference in treatment benefit in each of these 2 patient groups. In 2 studies[20,24] in which most patients were anticoagulated for prosthetic heart valves and whose mean INR was > 3.0, the subgroup analysis did not show the expected increased risk of bleeding. In 3 studies[20,23,24] that used antifibrinolytic agents, subgroup analysis did not show the benefit anticipated from these agents. The perils of basing conclusions on subgroup analyses, especially secondary analyses, have been well documented.[26,27] Further study is needed to evaluate the upper cut-off point for the discontinuation of warfarin and the use of bridging therapy[9] for patients whose therapeutic INR range is higher, and to assess the benefit of antifibrinolytic agents across a range of INR levels.

The findings of our overall analysis are substantiated by other reports in the literature. The most comprehensive review of cases pertaining to dental surgery in patients on anticoagulant therapy was carried out by Wahl, who reported on 2,014 dental surgical procedures in 774 patients[11] and subsequently on an additional 386 procedures in 176 patients.[12] Surgery included a number of cases of full-mouth extractions and alveoplasties. In these cases, 12 patients (1.3%) experienced major (uncontrolled with local measures) bleeding, of which 4 might be explained by anticoagulation above the therapeutic range at the time of the surgery.[11] For the 8 remaining patients, 3 had above-therapeutic INR levels after the surgery; concomitant administration of antibiotics in multiple doses may have enhanced the effect of warfarin.[12] In 2 of the remaining patients, rinsing with placebo several times a day immediately after surgery may have been the cause of bleeding. The remaining 3 cases were unexplained, although it was not clear whether appropriate local measures had been instituted before administration of vitamin K.

Wahl[12] estimated a risk of thromboembolism of 1.0% for patients who discontinue or alter their warfarin dose,

based on his original report, in which 4 patients experienced fatal and 1 patient experienced 2 nonfatal thromboembolic events. These data have been criticized because the period of withdrawal of anticoagulation was either unknown or ranged from 5 to 19 days.[28] Thromboembolic events, although less common than clinically significant bleeding episodes, pose a greater threat to the patient. A clinically significant bleeding episode may result in an unplanned office visit with institution of further local measures, but thromboembolic events are life-threatening.

There are potential weaknesses of our systematic review. First, we searched only the English-language literature. However, the degree of bias introduced by the exclusion of non-English literature is debatable. A study[30] of a number of disease areas showed that language-restricted meta-analyses, compared with language-inclusive meta-analyses, did not differ in their estimate of the benefit or the effectiveness of an intervention. Second, in our meta-analysis, 4 of 5 trials were of low methodological quality, scoring only 1 or 2 on a validated quality assessment scale (**Table 2**). Only 1 study included a description of withdrawals and dropouts. Two[19,21] of the 5 trials did not report the indication for warfarin therapy for their patient population, which determines the therapeutic range of the INR at which patients are normally maintained and gives a sense of the risk of bleeding and thromboembolism. Studies that include a majority of patients anticoagulated for atrial fibrillation or native valvulopathy maintained at lower INRs (2.0–3.0) would be expected to show a lower incidence of bleeding than studies that include patients on anticoagulant therapy who have prosthetic heart valves and are therapeutically maintained at higher INRs (2.5–3.5). In addition to INR, surgical skill, complexity of the surgical procedure, comorbid conditions such as liver disease or blood dyscrasias, and the effect of combined therapy with antiplatelet and nonsteroidal anti-inflammatory agents can increase the risk of bleeding during a surgical procedure. Further, 4[19,21,23,24] of the 5 studies included in this systematic review were conducted in a hospital setting. In 1 study,[20] the setting was not specified. It is possible that the results from this review may not be generalizable to private practice.

Our findings question the current practice of interrupting warfarin therapy for dental procedures. However, a number of pragmatic questions from everyday dental practice preclude an across-the-board recommendation to continue warfarin therapy around the time of dental procedures. For example, questions arise about management of patients with comorbid factors; the use of additional local measures and antifibrinolytic agents; and the need for referral to specialists, hospital care, or bridging therapy. Nonetheless, this is a clinical dilemma that is too prevalent and too important to defer because of insufficient evidence, with resulting continued ambiguous guidance for practitioners. Clinical experts from both medicine and dentistry must review the available evidence, apply their collective knowledge and clinical expertise, and develop concrete practice guidelines to assist practitioners in the management of the dental patient on anticoagulation therapy.

In conclusion, continuing the regular dose of warfarin therapy does not seem to confer an increased risk of bleeding when compared with discontinuing or modifying warfarin dose in patients undergoing minor dental procedures.

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Appendix 1 MEDLINE search strategy

#	Searches	Results
1	warfarin.mp. [mp=ti, ot, ab, nm, hw, kw, tx, sh, ct, tn, dm, mf]	48,603
2	anticoagulants.mp. [mp=ti, ot, ab, nm, hw, kw, tx, sh, ct, tn, dm, mf]	52,515
3	exp Dentistry/ or exp Dentistry, Operative/	300,913
4	exp Tooth Extraction/	16,690
5	exp Surgery, Oral/	16,723
6	exp Thromboembolism/	171,738
7	exp Thrombosis/	210,924
8	exp Hemorrhage/	422,538
9	risk.mp. or exp Risk/	1,850,601
10	adverse event.mp.	15,380
11	adverse events.mp.	79,996
12	complication.mp.	353,683
13	complications.mp.	918,113
14	thrombotic complication.mp.	291
15	thrombotic complications.mp.	3,937
16	1 or 2	91,731
17	3 or 4 or 5	310,779
18	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	3,266,425
19	16 and 17 and 18	413
20	limit 19 to English language [Limit not valid in CDSR, ACP Journal Club, DARE, CCTR, CLCMR; records were retained]	300
21	limit 20 to humans [Limit not valid in CDSR, ACP Journal Club, DARE, CCTR, CLCMR; records were retained]	289
22	limit 21 to yr = "1990 - 2008" [Limit not valid in: DARE; records were retained]	259
23	remove duplicates from 22	207