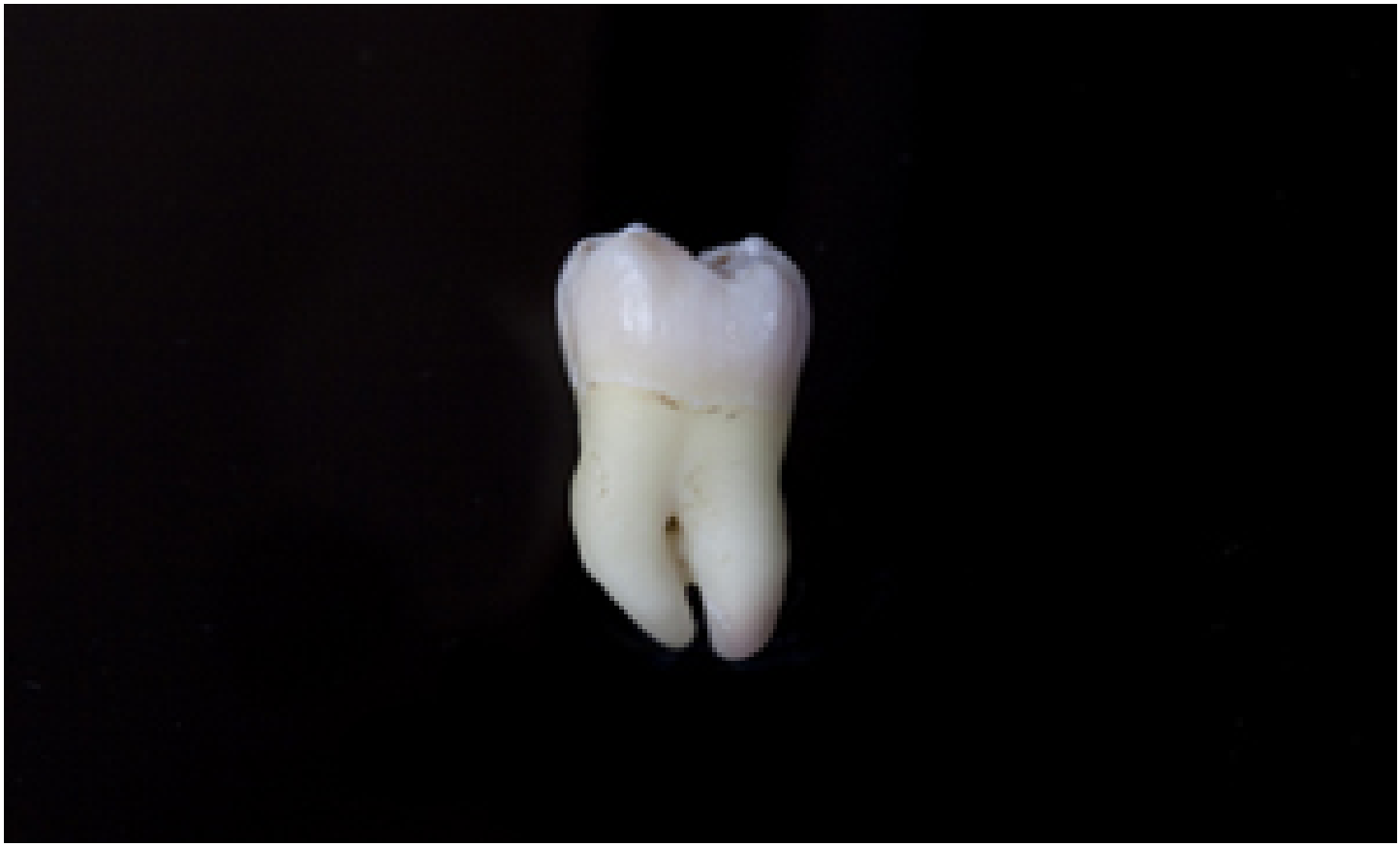
Management of Dental Extractions in Patients taking Warfarin as Anticoagulant Treatment: A Systematic Review



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TOPICS:
adverse reactions / pharmacology / treatment

Objectives: The management of patients on anticoagulation therapy is challenging. The objective of this study was to conduct a systematic review to establish the effectiveness of hemostatic interventions to prevent postoperative bleeding following dental extractions among patients taking warfarin.

Methods: A systematic review of the literature was conducted using PubMed, EMBASE and the Cochrane Central Register of Controlled Trials databases and applying relevant MeSH terms. Identified studies were screened independently by 2 reviewers using the following selection criteria: tooth extraction, patients taking warfarin as the only anticoagulant, randomized controlled trials and a hemostatic intervention.

Results: Six articles were included in the final review, all evaluating different interventions. Oral or local hemostatic agents were compared in 4 studies where patients continued taking warfarin before and after the procedure; in 3 studies, there were no differences between the agents in preventing postoperative bleeding and, in 1, Histoacryl glue was superior to a gelatin sponge. Two studies compared warfarin continuation with temporary discontinuation and found that continuation did not increase the risk of bleeding in patients who had an international normalized ratio (INR) within the therapeutic range.

Conclusions: Patients with an INR within the therapeutic range can safely continue taking the regular dose of warfarin before dental extractions. There is no evidence to support or reject the superiority of local hemostatic agents over warfarin discontinuation.

Current management of dental extractions in patients on anticoagulation therapy is still a challenging and controversial area for dental professionals. The perceived risk of bleeding among these patients is usually weighed against the risk of thromboembolic events, both of which could have severe consequences.[1] Oral anticoagulants are usually prescribed for patients with previous thromboembolic events (e.g., stroke, myocardial infarction, pulmonary embolism), atrial fibrillation, prosthetic heart valves and peripheral vascular disease.[2,3] The clinical management of these patients is generally complex because they are usually older, have multiple comorbid conditions and are taking multiple medications.

Warfarin, a vitamin K antagonist, remains the most commonly prescribed oral anticoagulant for the prevention and treatment of thromboembolic events.[1,3] Warfarin has a narrow therapeutic index measured by the international normalized ratio (INR), i.e., 2.0–3.0 for most indications,[4] and can cause major and fatal bleeding if not regularly monitored.[5,6] In the past, it has been suggested that the decision to continue or withdraw warfarin among patients undergoing dental extractions be tailored to INR levels: continuing the use of warfarin with local hemostatic agents if INR is within therapeutic range[1,7] and postponing warfarin to make dose adjustments if INR exceeds 3.5[8] or 4.0.[1]

A 2009 systematic review and meta-analysis of 5 randomized controlled trials (RCTs) concluded that continuing the regular dose of warfarin does not increase the risk of bleeding during minor dental procedures compared with altering or discontinuing the dose.[9] However, the analysis did not evaluate the effect of other hemostatic agents used by patients in the study. In contrast, the latest guideline from the American College of Chest Physicians recommended, for patients undergoing minor dental procedures, "continuing VKAs [vitamin K antagonists] with coadministration of an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure instead of alternative strategies," a weak recommendation based on low- or very low-quality evidence (grade 2C).[10]

In dental patients, a variety of oral and local hemostatic agents, such as tranexamic acid oral rinse, cellulose and gelatin foams, applied locally, have been used as physical matrices to aid clotting initiation.[2,11] Although the effectiveness of these agents has been evaluated in various clinical trials, no systematic review has focused specifically on patients taking warfarin and undergoing tooth extraction. Considering the evolving clinical recommendations and the existing gap in the literature, the objective of this study was to conduct such a review to establish the effectiveness of hemostatic interventions in preventing postoperative bleeding following dental extractions among patients taking warfarin.

Methods

We conducted a systematic review of the literature to determine which hemostatic interventions (considering both the use of hemostatic agents and warfarin discontinuation) are effective in preventing postoperative bleeding in patients taking warfarin, who are undergoing dental extractions. We followed the Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12]

Study Selection Criteria

Participants: Patients taking warfarin and undergoing tooth extraction(s). Studies of patients taking forms of anticoagulant medication other than or in addition to warfarin, undergoing oral surgical procedures other than extractions or having an increased bleeding tendency because of chronic liver or renal disease or genetic bleeding disorders were excluded.

Intervention: Discontinuation of warfarin, any hemostatic agent including (but not limited to) tranexamic acid mouthwash, Histoacryl glue, gelatin sponges, resorbable cellulose meshes, resorbable sutures, autologous fibrin glue and commercial fibrin adhesives.

Control: Continuation of warfarin or dose alteration, addition of a hemostatic agent.

Outcome measures: Postoperative bleeding following tooth extraction and outcomes of bleeding events.

Studies: RCTs

Data Sources and Search Methods

A literature search was conducted using PubMed, EMBASE and the Cochrane Central Register of

Controlled Trials databases from the time of their inception to April 2014. This was done with the help of a University of Toronto research librarian. Articles were retrieved by combining database-specific search terms for warfarin, bleeding or hemorrhage, specific hemostatic agents and hemostatic agents in general and tooth extraction. The search was then limited to RCTs and human studies. See **Appendix 1** for the detailed search strategy used in PubMed.

Selection of Studies and Data Abstraction

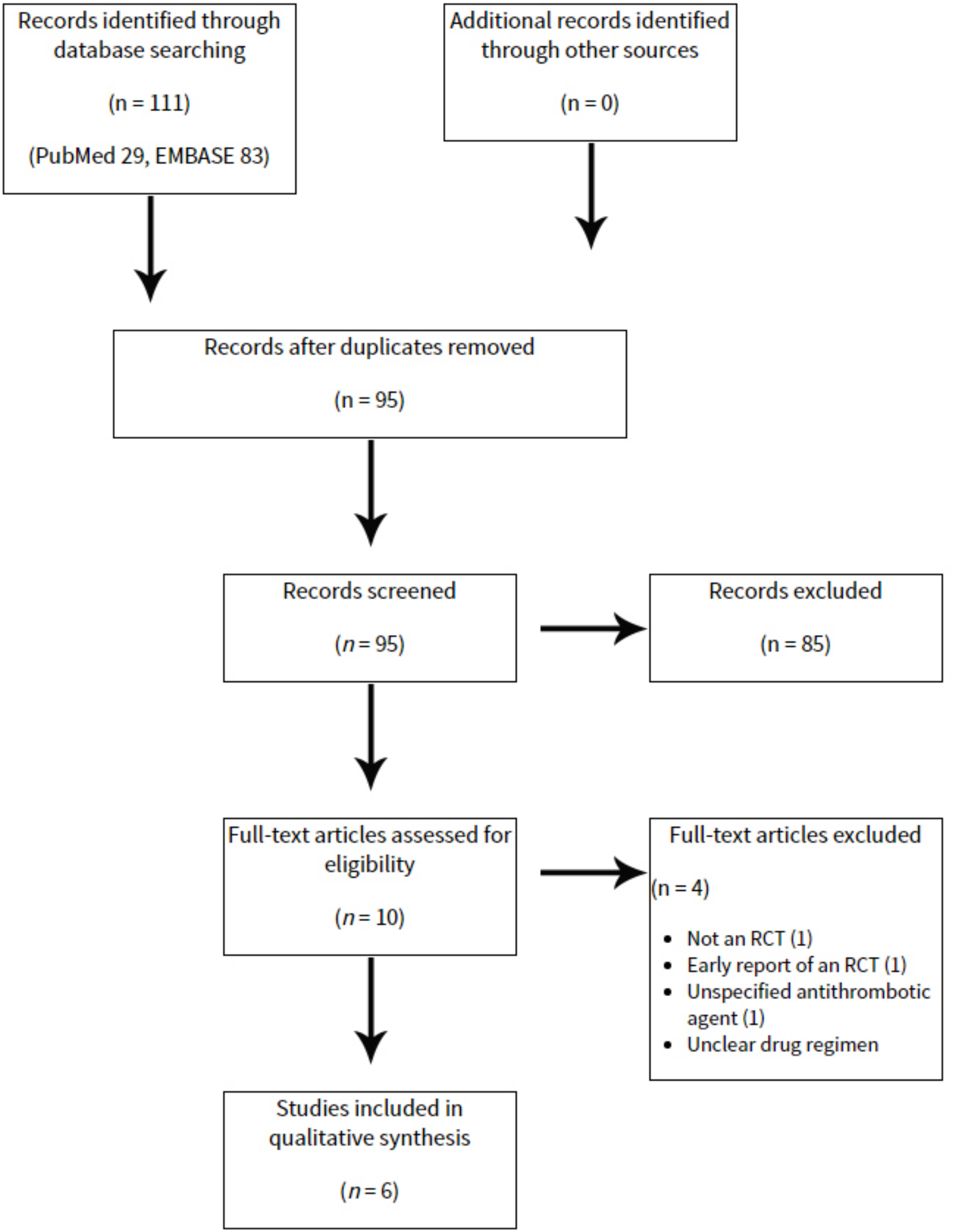
At all stages — review of title, review of abstract, full-text review, assessment of quality and data abstraction — each study was assessed independently by 2 reviewers (4 reviewers in total: NJ, JC, DD, AK). Disagreements were resolved by consensus and consultation with other authors (YA, LA, AA). When deemed necessary, the team contacted the corresponding authors of the published articles.

We assessed the quality of the trials included in the final review using the Cochrane Risk of Bias Tool.[13] In brief, we evaluated 6 domains (namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues) based on what was reported to have happened in the study. Then, we assigned a judgement of the risk of bias (high, low or unclear) to each domain. Information retrieved from each selected study included sample size, demographic data (age and gender), INR values at baseline, number of teeth extracted per patient, description of the hemostatic interventions, outcomes data and conclusions. The plan was to conduct a meta-analysis to evaluate the effectiveness of hemostasis if any of the studies compared similar hemostatic agents.

Results

Selection of Studies

After removing duplicates, our search identified 95 potentially relevant studies (**Fig. 1**). A review of titles and abstracts eliminated 85 studies, resulting in 10 articles for a full-text review. Four additional studies were excluded at this stage.[14-16] One[14] was not a true randomized study as patients were assigned to treatments on a "simple alternating basis." The second[15] was an early report of a larger RCT[17] subsequently included in our review. The third[16] did not specify which type of anticoagulant treatment patients were taking. The fourth[18] defined patients' antithrombotic drug regimen as "aspirin and coumarin" without clear specification of what proportion of patients used only 1 of these and what proportion, if any, used both. Hence, 6 studies were included in this research synthesis.[17,19-23] (**Table 1**)


Records identified through database searching
(n = 111)
(PubMed 29, EMBASE 83)
Additional records identified through other sources
(n = 0)
Records after duplicates removed
(n = 95)
Records screened
(n = 95)
Records excluded
(n = 85)
Full-text articles assessed for eligibility
(n = 10)
Full-text articles excluded
(n = 4)
Not an RCT (1)
Early report of an RCT (1)
Unspecified antithrombotic agent (1)
Unclear drug regimen
Studies included in qualitative synthesis
(n = 6)

Systematic Reviews

We identified 2 potentially relevant systematic reviews closely related to the topic.[9,24] The systematic review and meta-analysis by Nematullah and colleagues[9] included 5 RCTs and evaluated the effect of continuing versus stopping the regular dose of warfarin on risk of bleeding in patients undergoing minor dental surgical procedures. In this review, the hemostatic agents were not the main focus and were described as "co-interventions." Two of the studies in this systematic review were also identified in our search and were included in our final review.[17,22] The systematic review by Patatanian and Fugate,[24] which included 8 studies (2 prospective observational studies and 6 RCTs), evaluated the efficacy and safety of local hemostatic agents in patients taking oral anticoagulants and undergoing dental extractions. Patients were using warfarin exclusively in only 3 of these studies,[24] 2 of which were also identified in our search and were included in our systematic review.[20,21]

Quality of Selected Studies

Blinding was the single domain where all studies had a high risk of bias (**Table 2**). A low risk of bias was assigned to domains that evaluated completeness of outcome data, selective reporting and other sources of bias.

Table 1: Characteristics of the 6 studies included in the systematic review.

Author, year, country	Treatment groups	Sample size	Age range (mean), years	Male: female	INR range (mean)	Mean no. extracted teeth/ patient*
Al-Belasy and Amer[19] 2003, Egypt	Experimental	15	50–64 (56.5)	10:5	1.9–4.3 (2.5)	6.0
	Control	15	53–65 (58.0)	9:6	1.7–4.1 (2.4)	6.3
	Negative control	10	49–67 (57.2)	5:5	0.9–1.3 (1.0)	6.5
Al-Mubarak et al.[17] 2007, Saudi Arabia	Group 1	48	38.0–66.6 (52.3)	22:26	n/a (1.8)	1–5
	Group 2	58	37.0–66.4 (51.7)	27:31	n/a (2.4)	1–5

	Group 3	56	35.6–61.8 (48.7)	25:31	n/a (1.9)	1–5
	Group 4	52	39.4–66.8 (53.1)	24:28	n/a (2.7)	1–5
Carter and Goss[20] 2003, Australia	Group 1	43	21–77 (65.2)	22:21	n/a (2.7)	2
	Group 2	42	24–86 (65.7)	32:10	n/a (2.8)	3
Carter et al.[21] 2003, Australia	Group 1	26	24–85 (n/a)	16:10	2.3–4.0 (3.0)	1–13
	Group 2	23	40–83 (n/a)	15:8	2.1–4.0 (3.1)	1–18
Evans et al.[22] 2002, UK	Experimental	57	36–92 (67.0)	36:21	1.2–4.7 (2.5)	2
	Control	52	30–93 (66.0)	37:15	1.3–2.3 (1.6)	3
Halfpenny et al.[23] 2001, UK	Experimental	20	33.4–83.4 (66.5)	13:17	2.0–4.1 (2.7)	2
	Control	26	38.2–79.3 (64.8)	17:9	2.1–4.1 (2.9)	1.5

Note: n/a = not available, INR = international normalized ratio, UK = United Kingdom.
*Range is listed when the mean number was not reported.

Table 2: Quality of studies evaluated by the Cochrane Risk of Bias Tool.*

	Al-Belasy and Amer[19]	**Al-Mubarak et al.[17]**	**Carter and Goss[20]**	**Carter et al.[21]**	**Evans et al.[22]**	**Halfpenny et al.[23]**
Random sequence generation	–	–	–	–	+	–
Allocation concealment	?	?	–	?	–	–
Blinding Participants	?	+	+	+	+	+
Personnel	–	?	?	?	+	+
Outcome assessment	+	–	?	+	+	+
Incomplete outcome data	–	–	–	–	–	–
Selective reporting	–	–	–	–	–	–

Other sources of bias	–	–	–	–	–	–
*+ = high risk, − = low risk, ? = uncertain.						

Effectiveness of Hemostatic Interventions after Dental Extraction

Compared interventions and study outcomes are summarized in **Table 3**. Oral or local agents were compared in 4 studies[19-21,23] where patients continued taking warfarin before and after the procedure. Two studies[17,22] compared warfarin continuation with temporary discontinuation. In general, all 6 studies compared different interventions. This heterogeneity in treatment modalities precluded us from conducting a meaningful meta-analysis.

Table 3: Description of interventions and outcomes of the 6 studies reviewed.

<table>
<tr><th>Article</th><th>Compared interventions</th><th>Outcomes: no. (%) patients with postoperative bleeding</th><th>Conclusions</th></tr>
<tr><td>Al-Belasy and Amer[19]</td><td>Experimental: Patients continued warfarin, and sockets were dressed with Histoacryl glue (n-butyl-2-cyanoacrylate) after extractions Control: Patients continued warfarin, and sockets were dressed with gelatin sponge after extractions Negative control: Patients were never on warfarin, and sockets were dressed with gelatin sponge after extractions</td><td>Experimental: 0 (0.0%) Control: n = 5 (33.3%) (2 on day 2; 2 on day 3; 1 on day 5) Negative control: 0 (0.0%) p = 0.016, control vs. experimental p = 0.046, control vs. negative control</td><td>Patients on warfarin can safely undergo extractions without changing their anticoagulant regimen, provided that an effective local hemostatic method is used, such as Histoacryl glue.</td></tr>
<tr><td rowspan="5">Al-Mubarak et al.[17]</td><td>4 study groups were compared:</td><td rowspan="5">Outcomes by group and day after extractions:
<table><tr><th>Group</th><th>Day 1</th><th>Day 3</th><th>Day 7</th></tr><tr><td>1</td><td>12%</td><td>4%</td><td>0%</td></tr><tr><td>2</td><td>21%</td><td>3%</td><td>0%</td></tr><tr><td>3</td><td>17%</td><td>3%</td><td>4%</td></tr><tr><td>4</td><td>29%</td><td>5%</td><td>0%</td></tr><tr><td colspan="4">p > 0.05 for between group comparisons</td></tr></table></td><td rowspan="5">Dental extractions can be carried out safely among patients on warfarin without alteration of the anticoagulant dosage, as long as the INR is ≤ 3.0 and effective hemostasis is achieved. Suturing plays no significant role in achieving hemostasis and should be used only when needed.</td></tr>
<tr><td>Group 1. Stopped warfarin treatment 2 days before extractions and resumed after 12 h; no sutures placed</td></tr>
<tr><td>Group 2. Continued warfarin treatment; no sutures placed.</td></tr>
<tr><td>Group 3. Stopped warfarin treatment 2 days before extractions and resumed after 12 h; sutures placed</td></tr>
<tr><td>Group 4. Continued warfarin treatment; sutures placed</td></tr>
</table>

Carter and Goss[20]	*Group 1:* Patients continued warfarinandused4.8% tranexamic mouthwash for 2 days after tooth extraction, 4 times/day for 2 minutes *Group 2:* Patients continued warfarin and used 4.8% tranexamic mouthwash for 5 days after tooth extraction, 4 times/day for 2 minutes	Bleeding on day 2 after extractions: *Group 1*: 2 (4.7%) *Group 2*: 1 (2.4%) $p = 0.57$	Both regimens of 4.8% tranexamic mouthwash were effective at controlling local hemostasis in patients on warfarin.
Carter et al.[21]	*Group 1:* Patients continued warfarin; sockets were irrigated with 4.8% tranexamic acid mouthwash; resorbable cellulose mesh soaked in the mouthwash was then placed in each socket; and mouthwash rinse was continued for 7 days after extraction, 4 times/day for 2 minutes *Group 2:* Patients continued warfarin; 80 mL blood sample was collected from patients 1–2 weeks before surgery to prepare autologous fibrin glue (AFG), which was then applied to socket walls, wound site and over sutures	Bleeding on day 2 after extractions: *Group 1*: 0 (0.0%) *Group 2*: 2 (8.7%) $p = 0.12$	Dental extractions can be performed without alteration to existing anticoagulant treatment. Both tranexamic acid mouthwash and AFG are similarly effective in preventing postoperative bleeding.
Evans et al.[22]	*Experimental:* Patients continued warfarin *Control*: Patients discontinued warfarin 2 days before extractions and resumed same dose after the extraction	Postoperative days when bleeding occurred were not specified. *Experimental*: 15 (26%) *Control*: 7 (14%) $p = 0.10$	The observed difference in bleeding rates was not clinically significant. Dental extractions can be safely done in a hospital setting without changing warfarin regimen if INR is < 4.1. The routine discontinuation of warfarin before dental extractions should be reconsidered.
Halfpenny et al.[23]	*Experimental:* Patients continued warfarin; after the extraction, sockets were dressed with Beriplast P, a fibrin adhesive *Control:* Patients continued warfarin; after the extraction, sockets were dressed with Surgicel, a	Bleeding on day 1 after extractions (numbers too small to test for significance of difference): *Experimental*:	Both local hemostatic agents, Beriplast P and Surgicel, are effective in achieving local hemostasis among

	resorbable oxycellulose dressing	2(10%) *Control*: 1(3.8%)	patients on warfarin.

Studies that Compared Oral or Local Hemostatic Agents while Patients Continued Warfarin

The study by Al-Belasy and Amer enrolled patients in experimental, control and negative control (i.e., those never taking warfarin) groups.[19] After extractions, sockets were dressed with Histoacryl glue in the experimental group and with gelatin sponge in the other 2 groups. Minor postoperative bleeding was observed in only 5 patients (33%) in the control group ($p < 0.05$ compared with other groups) and was successfully stopped with local hemostatic treatment with 5% tranexamic acid. The authors concluded that patients taking warfarin can safely undergo dental extractions without any change of regimen if an effective local hemostatic agent, such as Histoacryl glue, is used.[19]

Studies by Carter and Goss[20] and Carter et al.[21] investigated the effect of tranexamic mouthwash after tooth extraction. The first study[20] randomly assigned patients to a 5-day or a 2-day regimen of 4.8% tranexamic acid mouthwash applied 4 times a day. Minor bleeding was observed in only 3 patients and there were no significant differences between the groups. The second study[21] compared a 7-day regimen of 4.8% tranexamic acid mouthwash with autologous fibrin glue that was applied to the extraction sockets and over the sutures. Minor bleeds were observed in only 2 patients in the autologous fibrin glue group, with no significant differences among the groups. Both studies concluded that the compared interventions were similarly effective.

Halfpenny et al.[23] compared the effectiveness of the fibrin adhesive, Beriplast P (CSL Behring, King of Prussia, Penn.), with the resorbable oxycellulose dressing, Surgicel (Johnson & Johnson, New Brunswick, N.J.) after dental extractions. After extraction, sockets were dressed with 1 of the hemostatic agents and then sutured with softgut. Bleeding was observed in 3 patients in total: 2 required additional suturing and 1 required admission to hospital because of more significant bleeding. The low bleeding rate did not allow statistical testing of the difference. The authors concluded that both treatments were equally effective in preventing bleeding after dental extractions.

Studies that Compared Warfarin Continuation and Discontinuation

The study by Evans et al.[22] randomly assigned patients to continue or discontinue warfarin 2 days before dental extraction. The authors reported a higher rate of bleeding in patients who continued warfarin (26%) than in those who stopped (14%), although the difference was neither statistically nor clinically significant. Two patients in the warfarin continuation group required a hospital visit to stop the bleeding. The authors concluded that warfarin can be safely continued in patients who undergo dental extraction in a hospital setting if their INR is below 4.1.

The study by Al-Mubarak et al.[17] applied a factorial design of 4 possible combinations of warfarin continuation and discontinuation and suturing and no suturing. The observed bleeding rate on the first postoperative day was slightly but not significantly higher in the 2 groups that continued warfarin compared with the groups that discontinued warfarin treatment. Bleeding rates

significantly diminished by day 7 with no significant differences among the groups on any of the postoperative days. Suturing did not play any role, and wound healing was similar across the groups. All bleeding events were described as "of the mild transient type."[17] The authors concluded that warfarin therapy can be safely continued in patients during dental extractions if the INR is 3 or lower; however, suturing or any other invasive manipulation should be used only when required.[17]

Discussion

Optimal management strategies for patients taking oral anticoagulants and undergoing dental procedures have been discussed extensively in the past.[2,8-10,24,25] However, there is still a controversy over whether warfarin should be routinely discontinued or if additional hemostatic agents should be used.[9,10] Our systematic review summarizes RCTs that compared any hemostatic management of patients taking warfarin and undergoing single or multiple dental extractions. Only 6 RCTs, conducted between 2001 and 2007, were found; none were conducted in North America.

Although these studies rated highly in terms of quality of evidence, we identified some risks of bias. The most significant source of potential bias was the lack of blinding. The role of patient blinding was crucial in these studies, as bleeding was first reported by patients and then reviewed by treating doctors, if necessary. Although blinding patients to duration of tranexamic acid mouthwash use or to discontinuation of warfarin may seem to be impractical, it is still possible to achieve adequate blinding by using a placebo treatment. Only 1 study reported blinding of outcome assessors,[17] and 1 reported partial blinding of personnel.[19] Inadequate blinding in the included studies could have introduced reporting and measurement biases.

Regular INR monitoring is part of the standard care for patients taking warfarin.[26] For safety, all 6 studies in the review included the requirement for an INR within therapeutic range as an eligibility criterion for patient enrollment. INR was also actively monitored postoperatively. Therefore, our findings are applicable only to patients whose INR is within the therapeutic range before dental extraction. This is in agreement with past clinical care pathways in oral surgery that have recommended measuring INR before the intervention and making a decision about continuation or discontinuation of the anticoagulant or the use of bridging therapy only afterwards.[2,8]

The average number of dental extractions per patient varied from 1.5 to 6.5, a significant range, especially if one considers potential associated risks of surgical intervention and post-surgical complications. However, past studies have not found an association between risk of bleeding and number of extracted teeth among patients on antithrombotic therapy.[27,28] Studies included in our review also varied in type of extractions, such as simple or surgical. For example, extracting molars is generally more traumatic than extracting incisors and may lead to an increased risk of bleeding. Similarly, complex extractions involving the raising of gingival flaps and bone removal may be associated with an increase in bleeding compared with simple extractions. Unfortunately, none of the reviewed studies reported this level of detail.

The hemostatic agents (not considering sutures) compared in the studies were Histoacryl glue,[19] gelatin sponge,[19] 4.8% tranexamic acid mouthwash,[20,21] autologous fibrin glue,[21] a fibrin adhesive

(Beriplast P)[23] and a resorbable oxycellulose dressing (Surgicel).[23] Patients in these studies continued to receive warfarin pre- and postoperatively (except the negative control group in 1 of the studies whose members had never been on warfarin). In only 1 study was a significant difference in postoperative bleeding observed: Histoacryl glue was found to be more effective than gelatin sponge.[19] A 2-day regimen of 4.8% tranexamic mouthwash compared with a 4-day regimen,[20] a 7-day 4.8% tranexamic mouthwash regimen compared with autologous fibrin glue[21] and Beriplast P compared with Surgicel[23] did not result in any differences in the risk of postoperative bleeding in patients taking warfarin. The availability and applicability of all these agents in Canada must be further considered. For example, Beriplast P is not available in Canada. Similarly, tranexamic acid mouthwash is not readily available, is relatively expensive and largely relies on patient compliance as multiple mouth rinses are required. The fabrication of autologous fibrin glue involves the acquisition of the patient's blood 1–2 weeks in advance,[21] limiting its practicality. Histoacryl glue is only effective for wounds in which the edges can be approximated, its use is technique sensitive (an exothermic reaction may occur during polymerization) and it may pose an occupational hazard for dental staff.[29] Surgicel, in contrast, is more widely available, is easier to administer and is less costly compared with other local agents.

No study compared the use of hemostatic agents (while continuing warfarin) with warfarin discontinuation, limiting any conclusion regarding the effectiveness of these agents in preventing postoperative bleeding as stated in the American College of Chest Physicians' guideline.[10] The 2 studies that evaluated warfarin continuation versus discontinuation 2 days before extractions[17,22] did not report any significant difference in postoperative bleeding between the groups, supporting the conclusion that dental extractions can be performed safely without alteration of warfarin dose if INR is within the therapeutic range.

Whether to discontinue warfarin therapy is a question of balancing the risk of thromboembolism associated with stopping warfarin with the risk of bleeding associated with continuing warfarin. The perceived risk of bleeding has caused many clinicians, including dentists, to interrupt warfarin therapy before surgical interventions.[30,31] However, the results of this systematic review indicate that the risk of postoperative bleeding is not significant after dental extractions. In the reviewed studies, most bleeding occurred within 1 week of dental extraction, was minor in nature and was successfully treated with local measures. In addition, no thromboembolic event was reported in any of the included studies. Fatal or non-fatal thromboembolic events after a short-term withdrawal of warfarin have been reported in several past studies; the incidence of such events varied from 0.02% to 1% and the duration of withdrawal varied from 2 to 30 days or was unknown.[30-36]

We acknowledge the limitations of our study. The literature search was limited to 3 major medical databases and peer-reviewed publications. There could be a publication bias, where studies with negative results were not published. We were suspicious about this possibility, as studies were from the United Kingdom, Australia, Saudi Arabia and Egypt, but not from North America. Considering that dental procedures, materials and accessibility may differ vastly in different parts of the world, a North American study would have added value to this review. Finally, this review is limited to patients who were taking warfarin only and does not consider the new generation of oral anticoagulants (e.g., dabigatran, rivaroxaban and apixaban), which are more effective than warfarin,

have fewer side effects and are increasingly used to prevent thromboembolism.[37-39] In contrast to warfarin, these medications do not require regular INR monitoring and do not have an antidote in case of bleeding.[39]

With the increasing global burden of atrial fibrillation[40] and stroke,[41] future research should address the management of patients undergoing tooth extraction whose INR values are above the therapeutic range. In addition, future trials should compare the addition of a hemostatic agent to the current anticoagulant regimen with its discontinuation. Currently, warfarin is still the most widely used medication in patients who need continuous anticoagulation therapy. However, as the new oral anticoagulants are increasingly becoming part of the recommended standards of care,[37,42,43] new clinical trials should evaluate their impact on dental patient outcomes and their optimal management.

Conclusions

In conclusion, the results of our systematic review indicate that a patient whose INR is within the therapeutic range can safely continue taking the regular dose of warfarin. Local hemostatic agents were not significantly different in reducing the risk of postoperative bleeding, except for gelatin sponges, which appear superior to Histoacryl glue. There is no evidence to support or reject the superiority of local hemostatic agents to warfarin discontinuation. Although not specifically supported in our review, a more careful approach should be taken to patients with INR outside the therapeutic range, where an additional consultation with the treating physician would further guide optimal management. Further evidence is needed to evaluate the risk of postoperative bleeding in dental patients with specific reference to the new generation of anticoagulants.

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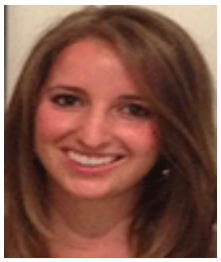	**Ms. Katchky** is a student, faculty of dentistry, University of Toronto, Toronto, Ontario.
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References

1. 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.
2. Doonquah L, Mitchell AD. Oral surgery for patients on anticoagulant therapy: current thoughts on patient management. *Dent Clin North Am.* 2012;56(1):25-41, vii.
3. Cavallari LH, Shin J, Perera MA. Role of pharmacogenomics in the management of traditional and novel oral anticoagulants. Pharmacotherapy. 2011;31(12):1192-207.
4. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest.* 2008;133(6 Suppl):160-98S.
5. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med.* 2003;139(11):893-900.
6. Kamoh A, Swantek J. Hemostasis in oral surgery. *Dent Clin North Am.* 2012;56(1):17-23, vii.
7. Randall C. Surgical management of the primary care dental patient on warfarin. *Dent Update.* 2005;32(7):414-6, 19-20, 23-4 passim.
8. Aframian DJ, Lalla RV, Peterson DE. Management of dental patients taking common hemostasis-altering medications. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103 Suppl:S45.e1-11.
9. Nematullah A, Alabousi A, Blanas N, Douketis JD, Sutherland SE. Dental surgery for patients on anticoagulant therapy with warfarin: a systematic review and meta-analysis. *J Can Dent Assoc.* 2009;75(1):41.
10. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e326-50S.
11. McBee WL, Koerner KR. Review of hemostatic agents used in dentistry. *Dent Today.* 2005;24(3):62-5; quiz 65, 61.
12. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535.
13. Higgins JPT, Altman DG, Sterne JAC, editors. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration: 2011. Available from www.cochrane-handbook.org.
14. Devani P, Lavery KM, Howell CJ. Dental extractions in patients on warfarin: is alteration of anticoagulant regime necessary? *Br J Oral Maxillofac Surg.* 1998;36(2):107-11.
15. Al-Mubarak S, Rass MA, Alsuwyed A, Alabdulaaly A, Ciancio S. Thromboembolic risk and bleeding in patients maintaining or stopping oral anticoagulant therapy during dental extraction. *J Thromb Haemost.* 2006;4(3):689-91.
16. Borea G, Montebugnoli L, Capuzzi P, Magelli C. Tranexamic acid as a mouthwash in anticoagulant-treated patients undergoing oral surgery. An alternative method to discontinuing anticoagulant therapy. *Oral Surg Oral Med Oral Pathol.* 1993;75(1):29-31.

17. Al-Mubarak S, Al-Ali N, Abou-Rass M, Al-Sohail A, Robert A, Al-Zoman K, et al. Evaluation of dental extractions, suturing and INR on postoperative bleeding of patients maintained on oral anticoagulant therapy. *Br Dent J.* 2007;203(7):E15; discussion 410-1.
18. Cakarer S, Eyüpoğlu E, Günes ÇÖ, Küseoğlu BG, Berberoğlu HK, Keskin C. Evaluation of the hemostatic effects of Ankaferd blood stopper during dental extractions in patients on antithrombotic therapy. *Clin Appl Thromb Hemost.* 2013;19(1):96-9.
19. 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.
20. 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.
21. 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.
22. 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.
23. 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.
24. Patatanian E, Fugate SE. Hemostatic mouthwashes in anticoagulated patients undergoing dental extraction. *Ann Pharmacother.* 2006;40(12):2205-10.
25. 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.
26. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *Circulation.* 2003;107(12):1692-711.
27. Morimoto Y, Niwa H, Minematsu K. Risk factors affecting postoperative hemorrhage after tooth extraction in patients receiving oral antithrombotic therapy. *J Oral Maxillofac Surg.* 2011;69(6):1550-6.
28. Morimoto Y, Niwa H, Minematsu K. Risk factors affecting hemorrhage after tooth extraction in patients undergoing continuous infusion with unfractionated heparin. *J Oral Maxillofac Surg.* 2012;70(3):521-6.
29. Leggat PA, Kedjarune U, Smith DR. Toxicity of cyanoacrylate adhesives and their occupational impacts for dental staff. *Ind Health.* 2004;42(2):207-11.
30. Kovich O, Otley CC. Thrombotic complications related to discontinuation of warfarin and aspirin therapy perioperatively for cutaneous operation. *J Am Acad Dermatol.* 2003;48(2):233-7.
31. Wahl MJ. Myths of dental surgery in patients receiving anticoagulant therapy. *J Am Dent Assoc.* 2000;131(1):77-81.
32. Blacker DJ, Wijdicks EF, McClelland RL. Stroke risk in anticoagulated patients with atrial fibrillation undergoing endoscopy. *Neurology.* 2003;61(7):964-8.
33. Dodson TB. Managing anticoagulated patients requiring dental extractions: an exercise in evidence-based clinical practice. *Evid Based Dent.* 2002;3:23-6.
34. Dunn AS, Turpie AG. Perioperative management of patients receiving oral anticoagulants: a systematic review. *Arch Intern Med.* 2003;163(8):901-8.
35. Garcia DA, Regan S, Henault LE, Upadhyay A, Baker J, Othman M, et al. Risk of thromboembolism

with short-term interruption of warfarin therapy. *Arch Intern Med.* 2008;168(1):63-9.
36. Todd DW. Anticoagulated patients and oral surgery. *Arch Intern Med.* 2003;163(10):1242.
37. Skanes AC, Healey JS, Cairns JA, Dorian P, Gillis AM, McMurtry MS, et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol.* 2012;28(2):125-36.
38. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. *Am J Cardiol.* 2012;110(3):453-60.
39. Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation.* 2012;126(20):2381-91.
40. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation.* 2013;129(8):837-47.
41. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet.* 2014;383(9913):245-54.
42. Kirchhof P, Ammentorp B, Darius H, De Caterina R, Le Heuzey JY, Schilling RJ, et al. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events — European Registry in Atrial Fibrillation (PREFER in AF). *Europace.* 2014;16(1):6-14.
43. Wann LS, Curtis AB, Ellenbogen KA, Estes NA, Ezekowitz MD, Jackman WM, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation.* 2013;127(18):1916-26.

Appendix 1: Detailed search strategy used in PubMed

Step	Search string	Results
1	Search ((((((((((("Therapeutics" [MeSH]) OR "Hemostasis" [MeSH]) OR "Tranexamic Acid" [MeSH]) OR "Fibrin Tissue Adhesive" [MeSH]) OR "Enbucrilate" [MeSH]) OR "Chlorhexidine" [MeSH]) OR "chlorhexidine gluconate" [supplementary concept]) OR "6-Aminocaproic Acid" [MeSH])))) AND (((((("Anticoagulants" [MeSH]) OR "Hemorrhage" [MeSH]) OR "Warfarin" [MeSH]) OR "Blood Coagulation Disorders" [MeSH])))) AND ((("Surgery, Oral" [MeSH]) OR "Tooth Extraction" [MeSH]))	638
2	Search ((((((((((("Therapeutics" [MeSH]) OR "Hemostasis" [MeSH]) OR "Tranexamic Acid" [MeSH]) OR "Fibrin Tissue Adhesive" [MeSH]) OR "Enbucrilate" [MeSH]) OR "Chlorhexidine" [MeSH]) OR "chlorhexidine gluconate" [supplementary concept]) OR "6-Aminocaproic Acid" [MeSH])))) AND (((((("Anticoagulants" [MeSH]) OR "Hemorrhage" [MeSH]) OR "Warfarin" [MeSH]) OR "Blood Coagulation Disorders" [MeSH])))) AND ((("Surgery, Oral" [MeSH]) OR "Tooth Extraction" [MeSH])) Filters: Randomized Controlled Trial; Humans	29

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Article	Standard of Care
Al-Belasy and Amer[19]	2 g amoxicillin or 500 mg azithromycin was administered orally 1 h before surgery. Simple multiple tooth extractions were performed and involved raising of a mucoperiosteal flap as well as alveoloplasty under local anesthesia, using 3% mepivacaine HCl. Post-surgical hemostasis and primary closure were achieved using a gelatin sponge and resorbable sutures (catgut 000) in all patients. Patients received postoperative instructions and were prescribed either amoxicillin (500 mg every 8 h), or azithromycin (250 mg twice daily for 3 days). Patients were instructed to use acetaminophen for postoperative analgesia, and to avoid aspirin and other NSAIDs for 10 days postoperatively. Patients were also instructed to contact the oral surgeon in the advent of uncontrolled bleeding (not controlled by 20 minutes of local compression with a gauze pad).
Al-Mubarak et al.[17]	Dental extractions were performed under local anesthesia using 2% lidocaine HCl with 1:100 000 epinephrine. Gauze and finger pressure was applied for 6–10 minutes on the wound site and gauze was changed when needed. Clean gauze was kept on the extraction site for a minimum of 30 minutes and replaced with a new one at the end of the appointment. Wound closure procedures for patients in groups 3 and 4 included non-resorbable sutures. Patients were provided written and verbal postoperative instructions. Patients returned for 3 follow-up sessions (1, 3 and 7 days after extractions). Postoperative blood tests were performed to measure INR at day 1, 3 and 7.
Carter and Goss[20]	Patients with cardiac valvular disease received antibiotic prophylaxis according to the institutional protocol. Dental extractions were done under local anesthetic, using 2% lignocaine with epinephrine 1:80 000. After tooth extraction, the region was irrigated with 4.8% tranexamic mouthwash. An oxidized cellulose mesh (Surgicel, Johnson & Johnson), soaked in tranexamic acid, was also placed in the base of the sockets prior to suturing with resorbable sutures (4.0 Vicryl, Ethicon, Johnson & Johnson). Patients also received a bag containing a supply of tranexamic solution (for their intervention), analgesics (paracetamol or paracetamol/codeine), gauze pads, a list of postoperative appointments and instructions. Patients were asked to maintain a liquid diet the first day after surgery and to refrain from eating or drinking for the first hour following rinsing with tranexamic acid.
Carter et al.[21]	Patients with cardiac valvular disease received antibiotic coverage in accordance with the institutional protocol. Extractions were performed under local anesthesia using 2% lignocaine with 1:80 000 epinephrine. Post-extraction analgesics included paracetamol or paracetamol/codeine. All patients were instructed to not eat or drink during the first hour post-extraction and were advised to maintain a liquid diet on the first day postoperatively. Patients were also provided with a list of other postoperative instructions.
	Antibiotic prophylaxis was provided to patients at risk of endocarditis in accordance with British National Formulary guidelines. Dental extractions were done under local anesthetic, using 2% (20 mg/mL) lignocaine HCl with 1/80 000 (12.5 μg/mL) epinephrine. Where necessary, a minimum sized mucoperiosteal flap was raised and a

Evans et al.[22]	minimum amount of bone was removed. Each extraction socket was packed with oxycellulose dressing (Surgicel) and sutured with 3/0 polyglactin 910 (Vicryl) sutures. Patients were then given a gauze swab to bite on for 10 minutes and were observed for another 10 minutes before being discharged. All patients were given verbal and written instructions, as well as contact information in case of emergency. Paracetamol was prescribed as a postoperative analgesic (1 g every 6 h, as required), and patients were advised not to use any other forms of analgesia. All patients were given a review appointment 1 week after surgery.
Halfpenny et al.[23]	Antibiotic prophylaxis was used when indicated according to the British National Formulary guidelines. Where necessary, the extraction included raising a mucoperiosteal flap, removing some bone and dividing the root with a drill. Extractions were performed under local anesthesia using 2% lignocaine with 1:80 000 epinephrine or 3% prilocaine with felypressin. All extraction sites were sutured with softgut. Patients were instructed to bite on gauze to apply pressure and achieve hemostasis. For post-extraction analgesia, patients were instructed to avoid ASA and NSAIDs. In addition, patients were given instructions on what to do in case of postoperative bleeding, and arrangements for emergency treatment were reviewed. All patients were given a review appointment at 1 week, in the absence of any complications requiring earlier review.
Note: NSAID = non-steroidal anti-inflammatory drug.	