Oral antithrombotics and dentistry: Current state of affairs and guideline proposal

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Chapter 3

Dental management of patients using antithrombotic drugs: critical appraisal of existing guidelines

Denise van Diermen
Irene Aartman
Jacques Baart
Johan Hoogstraten
Isaäc van der Waal

ABSTRACT

Objectives. The aims were: 1) to identify the guidelines available for management of dental invasive procedures in patients on antithrombotic drugs; 2) to assess their quality with the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument; and 3) to summarize their conclusions and recommendations.

Study design. Systematic literature search for guidelines in several electronic databases. Retrieved guidelines were evaluated with the AGREE instrument for quality assessment.

Results. The systematic search yielded 93 results, of which only 4 were evidence-based practice guidelines. Two of these guidelines could be recommended for clinical use on the basis of the AGREE instrument. These 2 guidelines drew 68 conclusions from the existing literature and provided 58 recommendations.

Conclusions. Two evidence-based clinical practice guidelines, satisfactorily fulfilling the criteria of the AGREE instrument and both published in 2007, advise to not routinely discontinue antiplatelet and anticoagulation medication before dental surgery. The majority of the recommendations, however, were not sufficiently linked to levels of evidence.
INTRODUCTION

Antithrombotic drugs, such as aspirin and warfarin, are frequently prescribed to avoid primary or secondary thromboembolic events. When patients have to undergo invasive dental or maxillofacial treatment, dentists, oral and maxillofacial surgeons, physicians, and patients have to decide whether to continue the use of the antithrombotics or to stop it temporarily to minimize the bleeding risk associated with the surgical procedure. However, stopping this medication may lead thromboembolic events to recur, thus creating potentially hazardous situations, such as myocardial infarction, stroke, or even death1.

In dentistry, most clinical studies on this subject have focused on the risk of bleeding during or after oral surgical procedures in patients who continue their antithrombotic medication. Few studies have prospectively investigated the risk of thromboembolic events after the discontinuation of this medication. Garcia et al.2 prospectively studied the effects of short-term (<5 days) interruption of warfarin in 1,293 episodes before ophthalmic, dental, and colonoscopic procedures. They concluded that a brief periprocedural interruption of warfarin therapy is associated with a low risk of thromboembolism (0.7%) and that the risk of clinically significant bleeding (1.7%) should be weighed against the thromboembolic risk of an individual patient. Other publications advise against routinely stopping antithrombotic medication before invasive dental surgery3-6. For the safe management of patients using antithrombotic medication undergoing an invasive dental procedure, there is obviously a need for an evidence-based clinical practice guideline.

Although the recent shift from practice-based dentistry toward evidence-based dentistry7 has led to the development of numerous practice guidelines to improve the delivery of health care8,9, unfortunately this has not resulted in a practice guideline for the dental management of patients using antithrombotic medication in the Netherlands10. However, practice guidelines may have been developed in other countries. To ensure that these guidelines meet specific standards of quality, the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument11, an internationally validated and accepted instrument to evaluate the quality of the procedure and the impact of clinical practice guidelines in daily practice, can be
used. If evidence-based practice guidelines exist on this topic and they prove to have good standards of quality as appraised by the AGREE instrument, a summary of the conclusions and recommendations of these guidelines can be helpful in constructing new guidelines which can be tailored to the specific needs of different countries. This is important, because even the same conclusions from scientific studies can lead to different recommendations in different countries.

Therefore, the purposes of this study were: 1) to identify the guidelines available on the management of dental invasive procedures in patients on antithrombotic drugs; 2) to assess their quality against the criteria of the AGREE instrument; and 3) to summarize the conclusions and recommendations from these guidelines.

**METHODS**

In October 2007, a systematic literature search for existing guidelines was performed using Medline (1966-), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) database (1980-), the Cochrane Library, and the Science Citation Index (SCI) (1945-). The search strategy consisted of 3 basic components. The MESH terms “guidelines” (i.e., guidelines, recommendations, standards, algorithm, expert consensus, etc), “anticoagulation,” and “dentistry” were used in all possible combinations (see Appendix 1). We also searched Google (first 100 hits) and several guideline websites, including the National Guideline Clearinghouse (www.guidelines.gov), the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk), the Canadian Medical Association Infobase for Clinical Practice Guidelines (http://www.mdm.ca/cpgsnew/cpgs/index.asp), the Guidelines International Network (www.g-i-n.net), Evidence-Based Medicine Guidelines (www.ebm-guidelines.com), the National Institute for Clinical Excellence (www.nice.org.uk), and the Canadian Collaboration on Clinical Practice Guidelines in Dentistry (www.cda-cdc.ca/en/dental_profession/practising/clinical_practice_guidelines/index.asp).

**Inclusion/exclusion criteria**

Guidelines were included if they were developed for the dental management of patients using antiplatelet or oral anticoagulation medication on the basis of
consensus or evidence-based methods. If the guidelines had been updated the latest version was included. Guidelines based on commentaries and narrative reviews were excluded. Only guidelines written in English were reviewed.

**Quality and content assessment**

Two investigators (J.B. and I.A.) appraised the quality of the guidelines using the AGREE instrument\(^{15}\), which comprises 23 items in 6 domains: 1) scope and purpose of the guideline; 2) stakeholder involvement; 3) rigor of development; 4) clarity and presentation; 5) applicability; and 6) editorial independence (Table I). Each item was awarded a score from 1 to 4, in which 1 meant the guideline did not fulfill this criterion or was not properly described and 4 meant the guideline fulfilled this criterion well. Each appraiser scored each guideline independently. The results were then collected and analyzed by the lead investigator (D.v.D.), who did not take part in the assessment. Each domain was awarded a final score by adding the individual item scores of the 2 independent appraisers. The domain scores were then standardized as a percentage of the maximum possible score for that domain\(^{15}\) as follows: standardized domain score = \((\text{obtained score} - \text{minimum possible score})/\text{maximum score} - \text{minimum possible score}) \times 100\). The balance between the domains and the number of rated items determined the overall assessment of the guidelines (Table II) and could lead to a strong recommendation or no recommendation for use of the guideline in clinical dental practice. Next, the guidelines were analyzed for the conclusions they had drawn from the scientific literature and for their subsequent recommendations. If evidence levels for these conclusions were provided in the guideline text, they were assembled as well as the levels of recommendation.
Chapter 3

Table I. Appraisal of Guidelines for Research and Evaluation (AGREE)

The AGREE instrument consists of 23 key items organized in 6 Domains\textsuperscript{15}. Each domain is intended to capture a separate dimension of guideline quality.

1. **Scope and purpose** (items 1-3) is concerned with the overall aim of the guideline, the specific clinical question, and the target patient population.

2. **Stakeholder involvement** (items 4-7) focuses on the extent to which the guideline represents the views of its intended users.

3. **Rigor of development** (items 8-14) relates to the process used to gather and synthesize the evidence and the methods to formulate the recommendations and to update them.

4. **Clarity and presentation** (items 15-18) deals with the language and format of the guideline.

5. **Applicability** (items 19-21) pertains to the likely organizational, behavioral, and cost implications of applying the guideline.

6. **Editorial independence** (items 22-23) is concerned with the independence of the recommendations and acknowledgement of possible conflict of interest from the guideline development group.

Table II. Overall recommendation of guidelines following the AGREE criteria\textsuperscript{15}

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly recommended</td>
<td>Rates 3 or 4 in the majority of items; most domain scores &gt;60%</td>
</tr>
<tr>
<td>Recommended (with modifications)</td>
<td>Rates 3 or 4 and 1 or 2 on a similar number of items; most domain scores 30%-60%</td>
</tr>
<tr>
<td>Not recommended</td>
<td>Rates 1 or 2 in the majority of items; most domain scores &lt;30%</td>
</tr>
</tbody>
</table>
RESULTS

Identification of existing guidelines
The systematic literature search yielded 93 citations (Medline 73, CINAHL 3, CSI 4, Google and guideline websites 13). Of these, only 4 met the inclusion criteria. Two guidelines were found through Medline\textsuperscript{16,17} and 2 were only found by Google\textsuperscript{18,19}. These 4 guidelines were all published in 2007.

Quality assessment
The results of the quality rating of the 4 guidelines are shown in Table III. The domain scores varied from 0\% for domain 6 (editorial independence) in both the U.K. Medicine Information (UKMI) guidelines\textsuperscript{18,19}, to 83\% for domain 4 (clarity and presentation) in the UKMI guideline on warfarin\textsuperscript{19}. Guideline overall assessment resulted in a strong recommendation of the guideline by Perry et al.\textsuperscript{16} and a recommendation with modifications of the guideline by Aframian et al.\textsuperscript{17}, whereas both of the UKMI guidelines\textsuperscript{18,19} were not recommended for clinical use.

Table III. AGREE analysis of 4 guidelines on the management of patients using antithrombotic drugs in dental surgery (\%)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Perry et al.\textsuperscript{16}</th>
<th>Aframian et al.\textsuperscript{17}</th>
<th>UKMI warfarin\textsuperscript{19}</th>
<th>UKMI antiplatelet\textsuperscript{18}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Scope and purpose</td>
<td>72</td>
<td>39</td>
<td>33</td>
<td>67</td>
</tr>
<tr>
<td>2. Stakeholder involvement</td>
<td>63</td>
<td>38</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>3. Rigor of development</td>
<td>67</td>
<td>64</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>4. Clarity and presentation</td>
<td>58</td>
<td>42</td>
<td>83</td>
<td>81</td>
</tr>
<tr>
<td>5. Applicability</td>
<td>22</td>
<td>72</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>6. Editorial independence</td>
<td>17</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Recommendation
- Strongly recommended
- Recommended with alterations
- Not recommended
- Not recommended


Conclusions and recommendations in the evaluated guidelines

The 4 guidelines draw 68 conclusions from the existing literature (Appendix 2). These conclusions lead to a total of 58 recommendations (Table IV). Of these 58 recommendations, only 13 are linked to levels of evidence, of which 4 are classified as “expert opinion.” The guidelines by Perry et al.\textsuperscript{16} and Aframian et al.\textsuperscript{17} use a slightly different scale to classify levels of evidence and recommendation levels. The UKMI guidelines\textsuperscript{18,19} do not clearly provide levels of evidence.
Table 4. Review of the recommendations from four guidelines on patients undergoing dental surgery using antithrombotic drugs (aspirin, clopidogrel, heparin, oral anticoagulants).

<table>
<thead>
<tr>
<th>1. Continuation of anticoagulant drugs</th>
<th>Level of evidence*</th>
<th>Recommendations Class or Grade**</th>
</tr>
</thead>
<tbody>
<tr>
<td>When the International Normalized Ratio (INR) is less than 3.5 do not modify or discontinue warfarin therapy for simple single dental extractions.</td>
<td>Level A</td>
<td>Class I</td>
</tr>
<tr>
<td>When INR is 3.5 or more and complicated or invasive oral surgery procedures are planned, discuss with physician.</td>
<td>Level A</td>
<td>Class I</td>
</tr>
<tr>
<td>Consult physician of patient on Low Molecular Weight Heparin (LMWH) for advise on continuing, altering or stopping of medication before dental procedure.</td>
<td>Level C</td>
<td></td>
</tr>
<tr>
<td>If LMWH should be discontinued, do it 4-6 hours before dental treatment.</td>
<td>Level B</td>
<td>Class I</td>
</tr>
<tr>
<td>If unfractionated heparin needs to be discontinued, do an aPTT test before the dental procedure.</td>
<td>Level B</td>
<td>Class I</td>
</tr>
<tr>
<td>Do not interrupt low-dose aspirin therapy (100 mg or less) for outpatient dental procedures.</td>
<td>Level B</td>
<td>Class I</td>
</tr>
<tr>
<td>Oral anticoagulants should not be discontinued in the majority of patients requiring out-patient dental surgery, including extraction.</td>
<td>Level Ib</td>
<td>Grade A</td>
</tr>
<tr>
<td>Warfarin does not need to be stopped before primary care dental surgical procedures when INR &lt; 4.0.</td>
<td>Level A</td>
<td></td>
</tr>
<tr>
<td>A primary care dentist should not advise to alter the warfarin but the general practitioner (GP), anticoagulant clinic or hematologist must do this.</td>
<td>Level B</td>
<td></td>
</tr>
</tbody>
</table>

2. Antibiotics

A single dose of prophylactic antibiotics will not need an alteration of anticoagulation regimen. | Level IV | Grade C |
Patients receiving more than 1 dose of antibiotics should have their INR measured after 2-3 days.\textsuperscript{16}

Advise patients who require a course of amoxicillin to be vigilant for any signs of increased bleeding.\textsuperscript{19}

Avoid metronidazole whenever possible. If not possible the warfarin dose may need to be reduced by a third to a half by the GP or anticoagulant clinic.\textsuperscript{19}

A patient must seek advice from the person managing their anticoagulant before taking metronidazole.\textsuperscript{29}

Advise patients who use erythromycin to be vigilant for any sign of increased bleeding.\textsuperscript{19}

### 3. Preoperative measures

Obtain INR values < 24 hours before dental procedure.\textsuperscript{17}

Assess general health status by taking an accurate medical history to ensure the condition of the patient is stable.\textsuperscript{17}

Assess co-morbid conditions as liver disease, bone marrow disorders, biliary tract obstruction, malabsorption, renal disease, cancers (leukemia) or increased inflammation of oral tissues.\textsuperscript{17}

Do not perform a bleeding time test in patients on aspirin preoperatively.\textsuperscript{17}

Check INR prior to dental surgery 72 hours before dental surgery in patients that have stable INR’s.\textsuperscript{16}

INR must be measured prior to dental procedures, ideally within 24 hours before the procedure.\textsuperscript{29}

In patients with a stable INR, an INR measured 72 hours before the procedure is acceptable.\textsuperscript{29}

### 4. Operative measures

Minimize trauma and site of surgical field.\textsuperscript{17}

When more than 3 teeth need to be extracted, schedule more visits.\textsuperscript{18}

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**Table 4. Continued**

<table>
<thead>
<tr>
<th>Level of evidence*</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class or Grade**</td>
<td></td>
</tr>
<tr>
<td>Level Ib Grade A</td>
<td></td>
</tr>
</tbody>
</table>

---

\*Level of evidence: R1-23 represent levels of evidence according to best evidence available. R1 indicates the highest level of evidence, and R23 the lowest. 

\*Class or Grade: Recommendations are based on the class or grade of the evidence. Class 1 represents high-quality evidence, while Grade A indicates strong recommendations. Class 2 represents medium-quality evidence, and Grade B indicates moderate recommendations. Class 3 represents low-quality evidence, and Grade C indicates weak recommendations.
<table>
<thead>
<tr>
<th>Level of evidence*</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class or Grade**</td>
<td></td>
</tr>
</tbody>
</table>

Restrict scaling and gingival surgery to a limited area to assess bleeding.18
Make the procedure as atraumatic as possible.18-19
Minor surgical procedures (such as: simple extraction of up to 3 teeth, gingival surgery, crown and bridge procedures, dental scaling and surgical removal of teeth) can be safely carried out without altering the warfarin dose.19
When more than 3 teeth need to be extracted, plan multiple visits, 2-3 teeth at the time or by quadrant.19
Limit scaling and root planing to a limited area e.g. one quadrant, to assess if the bleeding is problematic.19
Plan surgery at the beginning of the day and early in the week.19

5. Management of postoperative bleeding
Remove non-resorbable sutures after 4-7 days.18
Apply pressure to the socket by using a gauze pad that the patient bites on for 15-30 minutes.18
Pack sockets gently with absorbable haemostatic dressing (oxidized cellulose, collagen sponge, resorbable gelatin sponge).19
Carefully suture the socket.19
Apply pressure to the socket(s) by using a gauze pad that the patient bites down for 20 minutes.19
Manage any bleeding using local measures.19

6. Postoperative pain control
Do not prescribe aspirin for pain control.17
Be cautious with prescribing Non-Steroidal Anti-Inflammatory Drugs (NSAID’s) for pain control.17
Do not prescribe NSAID’s and Cox-2 inhibitors as analgesic.16
Avoid aspirin in analgesic doses and NSAID’s for pain control.18
Table 4. Continued

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level of evidence*</th>
<th>Class or Grade**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid aspirin as an analgesic.19</td>
<td>Class I</td>
<td>level B</td>
</tr>
<tr>
<td>Avoid NSAID's as an analgesic.19</td>
<td>Class I</td>
<td>level A</td>
</tr>
</tbody>
</table>

7. Postoperative measures

Consider using gelatin sponges, fibrin glue, fibrin adhesive dressing, oxidized cellulose or epsilon-amino caproic acid mouthwash.17

Give patients on oral anticoagulation (OAC) a 2-day regimen of postoperative 4.8% Tranexamic Acid Mouthwash (TAM).17

Give clear instructions to the patient on self-management in postoperative period:
- Do not eat/drink in first 2-3 hours
- Do not rinse mouth for 24 hours
- No hard sucking
- No hot liquids/hard food for rest of day
- Chew on other side
- When rebleeding occurs: press for 20 minutes with gauze.
- When bleeding doesn’t stop: contact dentist.18-19

Give clear instructions to patient who to contact with telephone numbers.18-19

Provide a facility for urgent treatment.18-19

Give clear instructions on pain control.18-19

TAM should not be used routinely in primary dental care.19

8. Referral

Refer patients with an INR above 3.5 to physician for dose adjustment before dental invasive procedures.17

Do not perform surgical dental procedures in primary care in patients on OAC and

- Liver disease
- Renal disease
- Thrombocytopenia
- On antiplatelet drugs.16

Refer patients in whom extensive surgery is planned.16
Dentistry and antithrombotics: critical appraisal of guidelines

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level of evidence*</th>
<th>Class or Grade**</th>
</tr>
</thead>
</table>

Refer patients whose INR is unstable.\textsuperscript{16}

Patients who are maintained with an INR $> 4.0$ or who have a very erratic control may need to be referred to a dental hospital or hospital based oral/maxillofacial surgeon.\textsuperscript{19}

Patients presenting with an INR much higher than their normal value, even if it is less than 4.0, should have their procedure postponed and be referred back to the clinician maintaining their anticoagulant therapy.\textsuperscript{19}

**9. Local anaesthesia**

Check INR when performing an inferior alveolar nerve block and use an aspirating syringe at INR $< 3$.\textsuperscript{36}

Use local anesthetic containing a vasoconstrictor.\textsuperscript{18-19}

Avoid regional nerve blocks or cautiously use an aspirating syringe.\textsuperscript{18-19}
DISCUSSION

Our systematic search for guidelines on the management of dental patients who use antithrombotic drugs and who require dental surgery, yielded 4 evidence-based guidelines, all published in 2007. It was remarkable that 2 guidelines were found only by Google, because they had not been published in peer-reviewed scientific journals. Use of the AGREE instrument in assessing the quality of these 4 guidelines showed that only 1, by Perry et al.\textsuperscript{16} performed well enough to receive a strong recommendation for clinical use. This is in agreement with the appraisal of this same guideline by Richards\textsuperscript{20}. Although the guideline by Aframian et al.\textsuperscript{17} performed best regarding the domain of applicability, only a recommendation with modifications could be assigned to it, because 4 out of the 6 domains scored <60%. Although the 2 guidelines from the UKMI\textsuperscript{18,19} had the highest domain scores on clarity and presentation, low-to-moderate domain scores on ≥4 other domains meant that these 2 guidelines cannot be recommended for clinical use in dental practice. This is in accordance with a study by Faggion\textsuperscript{21}, who used the AGREE instrument to evaluate 9 distinct clinical guidelines in dentistry and found that only 1 of them could be considered for use in clinical dental practice.

The AGREE instrument was devised to evaluate the quality of guidelines, but not to assess the quality of the underlying evidence\textsuperscript{15}. Examination of the domain score for rigor of development reflects the soundness of the evidence that was used in constructing the guidelines. Because the guidelines by Perry et al.\textsuperscript{16} and Aframian et al.\textsuperscript{17} scored 67% and 64%, respectively on this domain, these guidelines can be considered to be sufficiently evidence based. The guidelines by Perry et al.\textsuperscript{16} and Aframian et al.\textsuperscript{17} both provided clear insight into their methods of systematic evidence gathering. Although they produced several treatment recommendations that were based more or less on evidence from clinical studies, only 3 recommendations were based on multiple randomized controlled trials (RCTs) (level of evidence A or Ia). Similarly, 5 recommendations were based on only 1 RCT (level of evidence B or Ib), 1 was based on a well-designed nonexperimental study (level of evidence III), and 3 were based on expert opinion alone (Table IV). Evidence levels were therefore lacking for 46 of the 58 recommendations (Table IV). A lack of a definitive standard
of care, which over recent years has been reflected in a large variation of treatment
double protocols, might be indicative of the lack of underlying evidence\textsuperscript{22}.

The 2 guidelines that can be recommended either strongly or with modifications on
the basis of the AGREE evaluation give rather similar key recommendations (Table
IV). Both Perry et al.\textsuperscript{16} and Aframian et al.\textsuperscript{17} advise to not modify or discontinue low-
dose aspirin or warfarin therapy for single tooth extractions. They differ slightly when
the international normalized ratio (INR) of the patient is considered. Aframian et
al.\textsuperscript{17} advise to have the patients’ INR checked <24 hours before the dental operative
procedure, and Perry et al.\textsuperscript{16} recommend to check 72 hours before dental surgery.
Preferred INR before extraction should be ≤3.5 or ≤4.0. This seems to be important
advice, because a study by Brennan et al.\textsuperscript{22} has shown that in-office INR testing
revealed a high incidence of elevated INR in patients visiting the dental office with
a potentially higher risk of bleeding, as has been shown by Oake et al.\textsuperscript{1} in a meta-
analysis on the intensity and outcomes among patients on oral anticoagulant therapy.
Because the clinical dilemma of whether or not stop the oral antithrombotic drugs
before invasive surgical procedures is not solely a problem for dentists and oral and
maxillofacial surgeons, clinical guidelines have been developed in other fields as well.
The American College of Chest Physicians has published an evidence-based clinical
practice guideline on the perioperative management of antithrombotic therapy\textsuperscript{23}.
Also the American Heart Association, American College of Cardiology, Society for
Cardiovascular Angiography and Interventions, American College of Surgeons,
and American Dental Association have presented a collaborative statement on
antiplatelet therapy in patients with coronary artery stents\textsuperscript{24}. Both guidelines advise
against routinely stopping antithrombotic medication before dental treatment,
where dental procedures are defined as single or multiple tooth extractions and
endodontic procedures. Unfortunately, no specific advice is given for major dental
procedures or periodontal and implant surgery when patients are maintained on oral
antithrombotic medication. Elad and Findler\textsuperscript{25} commented on a study in which they
investigated the bleeding tendency in 500 patients treated with oral anticoagulants
after various dental and oral surgical procedures. Of 43 procedures performed in
30 patients from the periodontal surgery subgroup, unusual bleeding complications
occurred in only 2 patients, who had an INR >3.5, and in 2 patients in whom warfarin
sodium was substituted by low-molecular-weight heparin. In these 4 cases, bleeding was controlled by local measures.

CONCLUSIONS

In conclusion, we can state that a systematic search revealed 4 clinical practice guidelines of which 2 can be recommended after a quality assessment with the AGREE instrument. Key recommendations of these 2 guidelines advise against routinely stopping oral antithrombotic medication when performing limited invasive dental procedures; however, the guidelines for more complicated dental procedures are not clearly specified. Furthermore, if a patient uses oral anticoagulants such as warfarin, it is advised to check INR 24-72 hours before the dental procedure. When the INR is ≤3.5-4.0 there is no need to adjust the warfarin dose. However, more clinical studies, especially RCTs, are needed to provide a more solid scientific basis for several other recommendations made in these guidelines. Finally, the use of the AGREE instrument is strongly recommended for future guideline architects.
REFERENCES

APPENDIX 1.

Search strategy for guidelines—example from Medline, 1966 to October week 2, 2007

(((((("Dentistry"[Mesh])) OR ((dental treatment))) OR ((oral surgery))) OR ((dental scaling))) AND (((((("Anticoagulants"[Mesh])) OR ((aspirin))) OR ((coumadin))) OR ((oral anticoagulant*))) OR ((clopidogrel))) AND (((((("Guidelines"[Mesh])) OR ((recommendation*))) OR ((standard*))) OR ((algorithm*))) OR ((expert consensus))).

Search strategy
1. guideline* or practice guideline (148,721)
2. recommendation* (80,582)
3. standard* of care (169,479)
4. practice standard* OR professional standard (3,461)
5. algorithm OR clinical algorithm* (99,648)
6. practice algorithm (4,734)
7. clinical guideline* (3,161)
8. expert* consensus (4,074)
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (453,686)
10. anticoagulant* (159,302)
11. aspirin (40,461)
12. coumadin (10,573)
13. coumarin* (10,982)
14. warfarin (13,390)
15. clopidogrel (2,951)
16. oral anticoagulant* (3,223)
17. ticlopidine (3,255)
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (200,244)
19. dentistry (280,115)
20. dental treatment* (4,140)
21. dental surgery (37,932)
22. dental extraction* (989)
23. dental scaling (2,450)
24. dentoalveolar procedure* (7)
25. 19 or 20 or 21 or 22 or 23 or 24 (281,153)
26. 9 and 18 and 25 (76)
27. limit 26 to human (73)
APPENDIX 2.

Review of the conclusions from 4 guidelines on patients using antithrombotic drugs (aspirin, clopidogrel, heparin, oral anticoagulants) undergoing dental surgery.

Risk of bleeding
There is no evidence on risk of bleeding during and after invasive dental procedures in patients on low-molecular-weight-heparin (LMWH)\(^\text{17}\).

The risk of bleeding in patients on oral anticoagulation (OAC) with stable international normalized ratio (INR) (2-4) is very small\(^\text{16}\).

Risk of bleeding after dental surgery in patients without OAC is approximately 1\%\(^\text{16}\).

Risk of bleeding after dental surgery in patients on OAC was 9\%, 3.5\% serious, i.e., not controlled by local measures\(^\text{16}\).

Major bleeding in patients with INR <4 undergoing dental surgery is approximately 0.2\%; no deaths occurred\(^\text{16}\).

Patients taking antiplatelet medication (APM) will have prolonged bleeding time, but this may not be clinically relevant\(^\text{18}\).

Bleeding risk of combination aspirin and dipyridamole is similar to aspirin alone\(^\text{18}\).

There is insufficient evidence to comment on the risk of bleeding when aspirin is combined with clopidogrel\(^\text{18}\).

Patients on APM have a prolonged bleeding time, but this may not be clinically relevant\(^\text{18}\).

The incidence of postoperative bleeding not controlled by local measures varies from 0\% to 3.8\%\(^\text{19}\).

Continuing warfarin during dental surgical procedures may increase risk of postoperative bleeding requiring intervention\(^\text{19}\).

Stopping warfarin does not eliminate the risk of postoperative bleeding\(^\text{19}\).

Serious bleeding can occur in non-anticoagulated patients\(^\text{19}\).

Risk of thrombosis
Discontinuation of warfarin before a dental procedure increases the risk of thromboembolic events\(^\text{17}\).
There is no evidence on the risk of thromboembolism as result of stopping LMWH temporarily\textsuperscript{17}.
The risk of thrombosis may be increased in patients in whom OAC is temporarily interrupted\textsuperscript{16}.
Risk of thrombosis when OAC is temporarily stopped is approximately 1%, but potentially fatal\textsuperscript{16}.
Stopping APM increases the risk of stroke\textsuperscript{18}.
Stopping APM increases the risk of myocardial infarction\textsuperscript{18}.
Patients stopping APM before surgical procedures are more at risk of permanent disability or death\textsuperscript{18}.
Stopping dual-therapy aspirin/clopidogrel increased the risk of thromboembolic events\textsuperscript{18}.
Cessation of APM seems to be associated with stroke and myocardial infarction approximately 10 days after stopping\textsuperscript{18}.
Stopping aspirin before surgical procedures may increase risk of thromboembolic events by 0.005%\textsuperscript{18}.
Interruption of APM seems to induce a rebound effect\textsuperscript{18}.
Stopping warfarin increases the risk of thromboembolic events\textsuperscript{19}.
Patients with a target INR between 3.0 and 4.0 are at a high risk of thromboembolism, and stopping OAC or reducing their INR exposes them to an increased risk of life-threatening thrombosis\textsuperscript{19}.

**Balance between bleeding risk and thrombosis risk**
Bleeding complications after dental surgery carry less risk than thromboembolic complications\textsuperscript{18}.
Risk of thromboembolic events after withdrawal of warfarin outweighs the risk of oral bleeding\textsuperscript{19}.
Bleeding complications do not carry the same risks as thromboembolic complications\textsuperscript{19}.
Patients whose INR results are within the acceptable therapeutic range are more at risk of permanent disability or death if they have their warfarin stopped before a surgical procedure than if they continue it\textsuperscript{19}.
Prevention of re-bleeding

A 2-day regimen of postoperative 4.8% tranexamic acid mouthwashes (TAM) is as effective as a 5-day regimen after simple oral surgery procedures\textsuperscript{17}.

TAM is effective in preventing postoperative bleeds after oral surgery in patients on warfarin with INR between 2.5 and 4.8\textsuperscript{17}.

Bleeding risk is minimized by oxidized cellulose in socket\textsuperscript{16}.

Bleeding risk is minimized by 5\% TAM for 2 days 4 times daily\textsuperscript{16}.

Bleeding risk is minimized by collagen sponge in socket\textsuperscript{16}.

Bleeding risk is minimized by sutures\textsuperscript{16}.

TAM in primary dental care is expensive\textsuperscript{19}.

TAM is difficult to obtain\textsuperscript{19}.

TAM is no more effective than other local hemostatic measures\textsuperscript{19}.

TAM used alone reduces postoperative bleeding\textsuperscript{19}.

TAM used with local hemostatic measures and suturing provides little additional bleeding reduction\textsuperscript{19}.

Treatment of postoperative bleeding

Bleeding after a simple dental extraction can be controlled with local hemostatic measures\textsuperscript{17}.

Most cases of postoperative bleeding are easily treated with local measures, such as:

- Packing with hemostatic dressing.
- Suturing.
- Pressure appliance\textsuperscript{19}.

Patients on mono-APM who bleed after surgery can be controlled using local hemostatic measures\textsuperscript{18}.

Bleeding time tests

Sixty-eight percent of patients on OAC are outside their target range when measured by portable INR monitors\textsuperscript{17}.

Bleeding time test is not useful to assess oral bleeding after invasive dental procedures in patients taking APM\textsuperscript{17}.

There is no correlation between bleeding time test results and the rate of surgical bleeding complications\textsuperscript{18}.
Dentistry and antithrombotics: critical appraisal of guidelines

Analgesics

Non-steroidal anti-inflammatory drugs (NSAIDs) and other platelet aggregation inhibitors effect hemostasis after routine dental procedures\(^1\). NSAIDs may increase bleeding time, but not to exceed normal limits\(^2\). Paracetamol (acetaminophen) is safe in patients taking APM\(^2\). Aspirin in analgesic doses and NSAIDs are less safe as analgesics\(^2\). Occasional doses of paracetamol do not affect the anticoagulant effect of warfarin\(^3\). Prolonged regular use of paracetamol may enhance the anticoagulant effect of warfarin\(^3\). Concurrent use of aspirin increases the likelihood of bleeding by 3-5 times, increases the bleeding time, and may damage stomach lining\(^3\). NSAIDs irritate the stomach lining, which can result in gastrointestinal bleeding which will be more severe in anticoagulated patients\(^3\).

Antibiotics

Antibiotics and antifungals affect hemostasis after routine dental procedures\(^1\). A single dose of prophylactic antibiotics will not impair the ability to achieve adequate hemostasis\(^1\). Clindamycin does not interact with warfarin when given as a single dose for endocarditis prophylaxis\(^3\). There is a single case report of an interaction between warfarin and a course of clindamycin\(^3\). A single 3 g dose of amoxicillin given for endocarditis prophylaxis has not been shown to produce a clinically relevant interaction with warfarin\(^3\). Metronidazole interacts with warfarin\(^3\). Erythromycin interacts with warfarin unpredictably and only affects certain individuals\(^3\).
Extent of surgical procedures

Minor surgical procedures are:

- Simple extraction of less than 3 teeth.
- Gingival surgery.
- Crown and bridge work.
- Dental scaling.
- Surgical removal of teeth.

Miscellaneous

Published reviews of the available literature advise that oral anticoagulants should not be stopped before dental surgery.

Published trial data suggests that minor dental surgical procedures can be safely carried out on patients with INR <4.0.

The consensus from reviews on the management of dental patients taking warfarin is that minor dental surgical procedures should be carried out without alteration to the patient’s warfarin therapy if the INR is within the therapeutic range (INR 2.0-4.0).

Dentists from general and community dental practices have reported no problems in carrying out minor dental surgical procedures on patients with an INR within the therapeutic range.