Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs

Guidance Development Methodology

August 2015
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1. Overview of the SDCEP Guidance Development Process

The development of *Management of Dental Patients Taking Anticoagulant or Antiplatelet Drugs* followed SDCEP’s guidance development process as outlined below:

- Topic proposal and selection;
- GDG selection;
- Scoping including horizon scanning literature review and baseline research on stakeholder attitudes to the topic and proposed guidance;
- Agreement on scope and key clinical questions;
- Preparation of draft guidance for consultation including:
  - Systematic literature review,
  - Evidence appraisal, synthesis and summary,
  - Considered judgements,
  - Formulating recommendations,
  - Grading recommendations;
- Open consultation and peer review;
- Review of consultation feedback and revision of the guidance and other related products;
- Final draft sign off;
- Design for publication and print;
- Dissemination and Implementation.

For further details of the standard process see the SDCEP Guidance Development Process Manual available at [www.sdcep.org.uk/how-we-work/sdcep-guidance-development-process/](http://www.sdcep.org.uk/how-we-work/sdcep-guidance-development-process/). Consistent with SDCEP’s standard guidance development methodology the development of *Management of Dental Patients Taking Anticoagulant or Antiplatelet Drugs* aimed to be transparent, systematic and to adhere as far as possible to international standards set out by the AGREE (Appraisal of Guidelines Research and Evaluation) Collaboration ([www.agreetrust.org](http://www.agreetrust.org)).

Specific details of the methodology used for the development of the *Management of Dental Patients Taking Anticoagulant or Antiplatelet Drugs* guidance are presented either in the full guidance ([www.sdcep.org.uk/published-guidance/anticoagulants-and-antiplatelets/](http://www.sdcep.org.uk/published-guidance/anticoagulants-and-antiplatelets/)) or in the following sections of this methods document.

For further details, queries or requests for unpublished information, please contact SDCEP using the details provided on the front page of this document.
2. The Guidance Development Group

The following Guidance Development Group (GDG), comprising individuals from a range of branches of the dental and medical professions and a patient representative, was convened to develop and write this guidance.

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garry Sime (Chair)</td>
<td>Senior Dental Officer and Specialist in Special Care Dentistry, NHS Tayside</td>
</tr>
<tr>
<td>Carol Armstrong</td>
<td>Dental Tutor Therapist, UHISOHs, NHS Dumfries &amp; Galloway</td>
</tr>
<tr>
<td>Dean Barker</td>
<td>Consultant in Restorative Dentistry/Honorary Clinical Senior Lecturer, University of Aberdeen Dental School and Hospital</td>
</tr>
<tr>
<td>Adrian Brady</td>
<td>Consultant Cardiologist, NHS Greater Glasgow &amp; Clyde; Associate Professor, University of Glasgow</td>
</tr>
<tr>
<td>Patricia Green</td>
<td>Patient Representative and Anticoagulation Europe (ACE) Local Patient Contact, Aviemore</td>
</tr>
<tr>
<td>Steven Johnston</td>
<td>Salaried Dental Officer, Public Dental Service, NHS Orkney</td>
</tr>
<tr>
<td>Douglas Kennedy</td>
<td>Consultant in Oral &amp; Maxillofacial Surgery, NHS Tayside</td>
</tr>
<tr>
<td>Clare Marney</td>
<td>Consultant in Oral Medicine, Dundee Dental Hospital and School</td>
</tr>
<tr>
<td>Steve McGlynn</td>
<td>Specialist Principal Pharmacist (Cardiology), NHS Greater Glasgow &amp; Clyde; Honorary Senior Teaching Fellow, University of Strathclyde</td>
</tr>
<tr>
<td>Namita Nayyer</td>
<td>Specialist Trainee in Oral Surgery, Dundee Dental Hospital and School</td>
</tr>
<tr>
<td>Avril Neilson</td>
<td>Consultant in Oral Surgery, Dundee Dental Hospital and School</td>
</tr>
<tr>
<td>Gillian Nevin</td>
<td>General Dental Practitioner, Coupar Angus; Assistant Director of Postgraduate GDP Education, Dundee Dental Education Centre</td>
</tr>
<tr>
<td>Christine Randall</td>
<td>Senior Medicines Information Pharmacist and UKMi Representative, North West Medicines Information Centre, Liverpool</td>
</tr>
<tr>
<td>Simon Randfield</td>
<td>General Practitioner, NHS Forth Valley</td>
</tr>
<tr>
<td>Petrina Sweeney</td>
<td>Senior Lecturer/Honorary Consultant in Special Care Dentistry, University of Glasgow Dental School</td>
</tr>
<tr>
<td>Campbell Tait</td>
<td>Consultant Haematologist, NHS Greater Glasgow &amp; Clyde</td>
</tr>
<tr>
<td>Liz Theaker</td>
<td>Consultant in Oral Medicine, Dundee Dental Hospital and School</td>
</tr>
<tr>
<td>John Wall</td>
<td>General Dental Practitioner, Perth</td>
</tr>
</tbody>
</table>

Scheduled meetings of the full GDG or of subgroups took place as part of the guidance development process. The minutes of these meetings are available from SDCEP on request.
3. Scoping Research

A preliminary evidence search was carried out to identify existing policies, guidelines, systematic reviews and other material relevant to the proposed topic. This information was summarised in a provisional scope proposal which was considered by the GDG prior to agreeing on the general scope (Appendix 1).

Additional research to inform the scope and content of the guidance was carried out by SDCEP research collaborators TRiaDS (Translation Research in a Dental Setting), following their framework for translating guidance recommendations into practice (Clarkson et al., 2010). The views of general dental practitioners on current practice, attitudes to the management of patients taking anticoagulants or antiplatelet drugs and preferred content of this guidance were obtained via telephone interviews. Patient experiences and views were obtained via a questionnaire posted on charity websites and distributed through local anticoagulation clinics (see www.triads.org.uk for further information).

4. Key Clinical Questions

Key clinical questions relevant to the scope of the guidance were drafted by the SDCEP Programme Development Team (PDT) along with the GDG chair. These were further discussed and agreed by the wider GDG.

1. Should warfarin or other vitamin K antagonists be continued or interrupted for dental treatment? (To include warfarin, acenocoumarol and phenindione)
2. Should antiplatelet drugs be continued or interrupted for dental treatment? (To include aspirin, clopidogrel, dipyridamole, prasugrel, ticagrelor and combined therapies)
3. Should the NOACs be continued or interrupted for dental treatment? (To include apixaban, dabigatran and rivaroxaban)
4. Should the injectable anticoagulants be continued or interrupted for dental treatment? (To include dalteparin, enoxaparin and tinzaparin)
5. Should other measures be used for dental treatment on patients taking anticoagulants or antiplatelet drugs?

These key clinical questions informed the strategy for the systematic evidence searches.

5. Literature Search

The guiding principle for developing guidance within SDCEP is to first source existing guidelines, policy documents, legislation or other recommendations. Similarly, relevant systematic reviews are also initially identified. These documents are appraised for their
quality of development, evidence base and applicability to the remit of the guidance under development. In the absence of these documents or when supplementary information is required, other published literature and unpublished work may be sought.

For this guidance, a comprehensive search of MEDLINE, EMBASE and CINAHL was conducted on the 6th October 2014 and of the Cochrane Database of Systematic Reviews and the Cochrane Database of Abstracts of Reviews of Effects on the 10th October 2014. No date limits were applied. Each database was queried using 3 groups of search terms: ‘anticoagulant’ terms with ‘dental treatment’ terms, ‘anticoagulant’ terms with ‘surgical’ terms and ‘anticoagulant’ terms with ‘risk’ terms. The second and third searches were broader than the first and designed to retrieve any indirect non-dental evidence relating to other surgical and non-surgical bleeding risks. The 3 searches retrieved 520, 7260 and 14967 records, respectively.

These literature searches were performed by Anne Littlewood, Trials Search Co-ordinator, Cochrane Oral Health Group. The details of the searches can be found in Appendix 2. Potentially eligible articles were identified separately by two reviewers from the list of titles and abstracts retrieved by the dental specific search. An article was considered potentially eligible if it met all of the following criteria:

1. The article was a systematic review or a guideline. An article would be included as a systematic review, if it included a methods section, a search of 1 or more electronic databases and a table of included studies.

2. The article referred to (i) anticoagulants or antiplatelet drugs and (ii) bleeding or thromboembolic risk in the context of dental treatment.

Where insufficient evidence relevant to dental treatments was obtained, the search results from the broader ‘surgical’ and ‘risk’ searches were queried using individual drug names.

Copies of all potentially eligible articles in full were retrieved. Additional manual searching of guideline repositories and other resources, and follow up of citations from relevant articles found through the systematic searching was also carried out. Other sources of evidence identified by GDG members were also considered, taking relevance and methodological quality into account.

6. Evidence Appraisal and Synthesis

Eligible articles relevant for each of the key clinical questions were identified. Precedence was given to the most recent articles, where of suitable quality, published in English. A reviewer assessed the full text of each article and extracted the information applicable to the clinical question. Additional appraisals in the form of critical commentaries on systematic reviews provided by the Centre for Reviews and Dissemination (CRD) at the University of York (www.crd.york.ac.uk) were also available for some of the articles. The evidence appraisal form for each of the relevant articles can be found in Appendix 3.
For the development of this guidance SDCEP used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess and rate the quality of evidence (www.gradeworkinggroup.org). The GRADE framework is a widely accepted system for grading both the evidence and the recommendations, and is used internationally by other guideline producers.

After systematic consideration of a number of criteria, a GRADE ‘quality of evidence’ rating was assigned to the evidence relevant to each clinical question. GRADE evidence ratings are defined by the GRADE working group as:

<table>
<thead>
<tr>
<th>Quality Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High quality</td>
<td>Further research is unlikely to change our confidence in the estimate of the effect (e.g. risk of bleeding)</td>
</tr>
<tr>
<td>Moderate quality</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the effect</td>
</tr>
<tr>
<td>Low quality</td>
<td>Further research is very likely to have an important impact on our confidence in the evidence and is likely to change the estimate of the effect.</td>
</tr>
<tr>
<td>Very low quality</td>
<td>Any estimate of effect from the evidence is very uncertain</td>
</tr>
</tbody>
</table>

The GRADEpro software was used for assigning evidence quality levels and the results are recorded in the evidence appraisal forms in Appendix 3. Copies of the GRADEpro output tables are available on request.

For guidelines, the AGREE II instrument was used in addition to GRADE to assess the methodological quality of the retrieved articles (www.agreetrust.org). The AGREE II instrument is a simple and validated assessment tool that provides an overall quality score for each guideline and an indication of how reliable the guideline might be. These assigned scores are recorded in the evidence appraisal forms in Appendix 3. The output forms produced by the AGREE II tool used for assessing guidelines are available on request.

7. Considered Judgements and Development of Recommendations

The synthesised evidence for each clinical question was summarised and distributed to members of the GDG prior to meetings of the group to inform and facilitate the development of the recommendations for the guidance. Where authoritative evidence was unavailable, the GDG was asked to make recommendations based on current best practice and expert opinion, reached by consensus.

The process for development of recommendations followed the GRADE approach, with considered judgements based on the quality of evidence, the balance of risks and benefits, the values and preferences of the patients, and the practicalities of the treatment. The relative importance of each of these criteria for a given recommendation was decided by the GDG.
According to GRADE the strength of recommendations should be defined as:

<table>
<thead>
<tr>
<th>Strength</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong for</td>
<td>benefits outweigh risks of the intervention</td>
</tr>
<tr>
<td>Strong against</td>
<td>risks outweigh benefits of the intervention</td>
</tr>
<tr>
<td>Weak for/or weak against</td>
<td>most informed people would choose this recommendation but a substantial number would not (risks and benefits finely balanced)</td>
</tr>
</tbody>
</table>

Note: It is possible to have a strong recommendation where the evidence is weak, but other considerations such as patient preference or cost make the decision to make a strong recommendation clear.

The evidence summaries, GDG consideration of the criteria and the resulting outcomes for each key recommendation are recorded in the Considered Judgement Forms (one for each key clinical question) which can be found in Appendix 4. Some of the recommendations were subject to further review and revisions by the group during the course of the guidance development process.

The GRADE approach allows for different words, numbers or symbols to be used to express the strength of the recommendations. The PDT and GDG agreed to directly state the recommendation strength (strong or conditional) and the quality of evidence rating (high, moderate, low or very low quality) along with each recommendation, for clarity. This approach was the preferred choice to avoid confusion over the meaning of symbols or numbers or misinterpretation of the wording used in the recommendations. Brief justifications for each recommendation were also included in the guidance text.

### 8. Consultation

A four week external consultation process on the draft guidance was initiated on February 10th 2015. The consultation draft was made openly available through the SDCEP website and notification of this was sent to a wide range of individuals and organisations with a particular interest in this topic, in addition to professional bodies and charities representing patient groups. All dentists, dental therapists and dental hygienists in Scotland were notified that the consultation draft was available for comment. To encourage feedback from the end-users of the guidance, 50 random dentists were contacted directly to evaluate the guidance.

A consultation feedback form was provided to facilitate the process. All comments received were compiled, considered carefully by the GDG and the guidance amended accordingly prior to publication.

The compiled comments and GDG responses are available on request.
9. Updating guidance

A review of the context of this guidance (e.g. regulations, legislation, trends in working practices, evidence) will take place three years after publication and, if this has changed significantly, the guidance will be updated accordingly.

10. Conflict of Interest

All contributors to SDCEP, including members of the GDG, are required to complete an SDCEP Declaration of Interests form to disclose relevant interests including financial conflicts of interest, such as receipt of fees for consulting with industry, and intellectual conflicts of interest, such as publication of original data bearing directly on a recommendation. These forms are held by SDCEP, updated yearly and are available on request. At the beginning of each group meeting during guidance development, participants are asked to confirm whether there are any changes to their Declaration of Interests.

Any declared interests which could constitute a conflict of interest are considered by the group to decide whether and how the extent of the individual’s participation in the guidance development should be limited (e.g. exclusion from certain decisions or stages, or complete withdrawal).

For the Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs guidance project the following potential conflicts of interest and management decisions were recorded:

10.1 Consideration of Potential Conflicts of Interest

<table>
<thead>
<tr>
<th>Guidance project</th>
<th>Anticoagulants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of Disclosures</td>
<td>All of the GDG members completed and returned the Declaration of Interests form. The Clinical Chair of the group had no declared interests. Only 2 out of the 18 external group members disclosed interests relevant to the guidance which could potentially cause, or be perceived to cause, conflicts of interest.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GDG member 1 – Campbell Tait</th>
<th></th>
</tr>
</thead>
</table>
| Details of interest(s) relevant to guidance | 1. Lecture fees from Boehringer Ingelheim Ltd and Bayer for giving lectures (primarily to GP groups or occasionally hospital doctors) on the topic of the novel anticoagulants.  
2. Consultancy fees from Boehringer Ingelheim Ltd and Bristol-Myers Squibb/Pfizer for attending advisory board meetings relating to their NOACs |
10

11. Equality Impact Assessment for the Guidance

The possibility of inequalities associated with the guidance was considered at various stages during guidance development. Potential issues were identified through discussions with guidance development group members, from interviews with practitioners, from the responses to the patient questionnaire and from feedback from the external consultation. Issues identified and actions taken were recorded in an EQIA checklist which is available on request.
Appendix 1 – Scope

Full title:

Management of Patients taking Anticoagulant and Antiplatelet Drugs requiring Dental Treatment

Why the guidance is needed

A number of primary and secondary care dental practitioners have raised the issue of anticoagulants in dentistry, particularly in terms of clarifying guidance for the treatment of patients taking the newer classes of anticoagulants and antiplatelet drugs (novel oral anticoagulants, NOACs, apixaban, rivaroxaban and dabigatran; novel oral antiplatelets, NOAPs, prasugrel and ticagrelor). Concerns have been expressed about a lack of knowledge and confidence around best practice for treating patients, particularly those taking NOACs, and possible uncertainty about when to refer to secondary care. Appropriate management of dental care for patients taking these and other anticoagulants and antiplatelet medications is clearly a safety issue in terms of risk of bleeding complications. NDAC agree that a national approach to guidance would be useful.

The newer anticoagulant treatments began to be approved in the UK for prescription for thromboembolic and cardiac conditions in 2008 and have since been advocated by NICE. Although warfarin is still widely prescribed, the use of NOACs is increasing. Recent NICE guidance has made new recommendations for the use of apixaban, rivaroxaban and dabigatran for stroke prevention in patients with atrial fibrillation (www.nice.org.uk/guidance/cg180). These recommendations are likely to further increase the prescribing of NOACs and the prevalence of patients who are taking them and presenting for dental treatment.

There are a number of existing documents available which provide guidance for the treatment of dental patients taking the well known anticoagulants and antiplatelet treatments, such as warfarin, other vitamin K antagonists, aspirin and clopidogrel (Perry et al., 2007; Randall, 2007, Randall, 2010). The use of INR monitoring for patient clotting time prior to invasive dental treatment is well established. INR testing is not appropriate for patients taking NOACs (Favaloro et al., 2012) although these patients still present a risk of bleeding complications, therefore risk assessment for their treatment has to rely on other considerations.

Several groups of dental professionals have recently developed their own local guidelines highlighting the need for accessible, consistent guidance (Brewer, 2012; Sime, 2013; Devennie, 2014; Scott et al., 2014). Up to date national guidance providing evidence-based (where available) and best practice guidance on the management of dental patients taking anticoagulants could provide clarity on the new treatments and the potential for
standardisation of care of patients on all of the various anticoagulation therapies in all regions.

**What the guidance aims to do**

The guidance aims to:

- Encourage a consistent approach to the management of dental treatment for patients who are taking antiplatelet and anticoagulant drugs, including the novel oral anticoagulants and antiplatelets.
- Provide a resource of information, relevant to dental treatment, on the new and emerging anticoagulant treatments.
- Provide evidence and/or consensus of opinion based recommendations for the clinical management of dental patients taking anticoagulants.
- Empower dentists to treat patients in primary care.
- Inform decision making for referral to secondary care.
- Improve communication of relevant information between the medical and dental practitioner and the patient.
- Improve patient safety.

**What the guidance will include**

Information on the following antiplatelet and anticoagulant medications including:

- Vitamin K antagonists (warfarin, acenocoumarol, phenindione).
- The new oral anticoagulants (rivaroxaban, apixaban, dabigatran).
- Antiplatelet drugs (aspirin, clopidogrel, dipyridamole, prasugrel and ticagrelor).
- Parenteral anticoagulants seen in outpatient settings (dalteparin, enoxaparin, tinzaparin).
- Drugs likely to be approved for use in the UK in the next year (vorapaxar, edoxaban).
- List of trade names for the drugs above (including those used in countries other than Scotland) and indications for use.

Patient and treatment bleeding risk assessment:

- Patient history – antithrombotic medication and indication for, INR record if appropriate, previous bleeding history, other medications, medical conditions and risk factors.
- Bleeding risk associated with different dental procedures (including implants).

Treatment planning:

- Whether and when to request blood test(s) (e.g. INR) and current best practice on levels suitable for treatments.
- When to delay treatment e.g. for patients on short term anticoagulation.
• Consensus/evidence for timing treatment between doses of drugs.
• Whether anticoagulant regime should be altered prior to dental treatment (current guidance on this is contradictory).
• Common sense advice on timing of treatment early in day/week.
• When to liaise with the prescribing physician.
• Referring patients on anticoagulants for treatment in secondary dental and medical care.

Minimising bleeding:
• Local anaesthetic delivery route
• Limiting initial treatments until bleeding assessed e.g. single extractions, limited area of scaling.
• Local haemostatic measures

Post-treatment guidance:
• Interactions between anticoagulants/antiplatelets and drugs which dentists can prescribe.
• Post-treatment patient advice.
• Emergency procedures.

What the guidance will **not** include

• Patients with inherited and other bleeding disorders
• Patients on acute anticoagulation therapy administered in secondary medical care (i.e. fibrinolytics and antithrombotics administered intravenously)
• Details of how to treat a referred patient in secondary medical care

What the guidance is based on

When available and of suitable quality, the guidance will be based on existing guidelines, guidance and policy statements. To supplement this information, systematic reviews and primary research evidence will be reviewed to inform recommendations. Where necessary, recommendations may be based on expert opinion, using consensus development techniques as appropriate (Pope and Mays, 2006).

The questions we will endeavour to address through a systematic search of research evidence are:

i. Do any of the anticoagulants or antiplatelets (or combinations of) cause a greater risk of bleeding complications after dental or other invasive treatments?

ii. Should the patient’s anticoagulation or antiplatelet treatment regime be interrupted or modified for dental treatments that are likely to cause bleeding?
iii. Should the timing of dental treatment relative to the patient’s medication schedule be taken into consideration (e.g. delaying dental treatment)?

iv. What other factors (e.g. physical and medical conditions, other medications) affect the patient’s risk of bleeding complications?

v. Are there additional measures that should be used to minimise intra- or post-treatment bleeding?

**Target groups**

- The guidance will be applicable to patients who are currently taking anticoagulant or antiplatelet medications (as described above), of all ages in all population groups, who present for outpatient dental treatment.

**Target users**

- The guidance will primarily be directed at dentists, hygienists and therapists in primary care dental practice, including the general dental service and public dental service.
- The guidance will also be of relevance to the secondary care dental service, those involved in dental education and undergraduate trainees.
- The guidance may contain specific patient information and advice for general medical practitioners, nurses and pharmacists dealing with patients taking anticoagulants, relating to their dental care.

**Format and usage**

The guidance may be best presented as:

- A complete document with detail about risk assessment, treatment planning, referrals and precautionary measures.
- A short summary with main recommendations including treatment management for regular use in the surgery (e.g. could be a flowchart)
- Patient information, if appropriate, e.g. a patient information leaflet that GPs, pharmacists and dentists can distribute and/or a poster for display in surgery waiting rooms.

**Equality Issues**

Initial scoping discussions suggested that the risk of inequality (for patients) arising from the guidance would be very low, as any consequences for dental treatment would reflect the anticoagulant taken rather than be specific to any protected characteristic or other groups.
Further assessment of the potential equality impact of the guidance will take place during guidance development.
Appendix 2 – Evidence Searches

SDCEP Anticoagulants in dental treatment
Contact: Michele West

Summary of Searches: October 2014
Searches carried out by Anne Littlewood, Cochrane Oral Health Group

<table>
<thead>
<tr>
<th>Database</th>
<th>Date of search</th>
<th>Reviews: Dental</th>
<th>Guidelines: Dental</th>
<th>Reviews: Risk</th>
<th>Guidelines: Risk</th>
<th>Reviews: Surgical</th>
<th>Guidelines: Surgical</th>
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</thead>
<tbody>
<tr>
<td>Cochrane Database of Systematic Reviews</td>
<td>6 October 2014</td>
<td>180</td>
<td>N/A</td>
<td>971</td>
<td>N/A</td>
<td>757</td>
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<tr>
<td>DARE</td>
<td>6 October 2014</td>
<td>26</td>
<td>N/A</td>
<td>1,101</td>
<td>N/A</td>
<td>359</td>
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<td>MEDLINE via OVID</td>
<td>10 October 2014</td>
<td>64</td>
<td>36</td>
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<td>EMBASE via OVID</td>
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<td>164</td>
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<td>5,691</td>
<td>2,603</td>
<td>3,168</td>
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<td>CINAHL via EBSCO</td>
<td>10 October 2014</td>
<td>19</td>
<td>30</td>
<td>890</td>
<td>1,395</td>
<td>220</td>
<td>395</td>
</tr>
</tbody>
</table>
**TOTALS:**

- **DENTAL + ANTICOAGULANTS – SYSTEMATIC REVIEWS:** 334
- **DENTAL + ANTICOAGULANTS – GUIDELINES:** 186
- **SURGERY + ANTICOAGULANTS – SYSTEMATIC REVIEWS:** 3,788
- **SURGERY + ANTICOAGULANTS – GUIDELINES:** 3,472
- **RISK FACTORS + ANTICOAGULANTS – SYSTEMATIC REVIEWS:** 8,030
- **RISK FACTORS + ANTICOAGULANTS – GUIDELINES:** 6,946

**AL Refs:**

- Cochrane Library: SDCEP Anticoagulants and dental treatment
- MEDLINE: SDCEP MEDLINE Anticoagulants
- EMBASE: SDCEP EMBASE Anticoagulants
- CINAHL: SDCEP Anticoagulants

**COCHRANE DATABASE OF SYSTEMATIC REVIEWS (CDSR) AND DATABASE OF ABSTRACTS OF REVIEWS OF EFFECTS (DARE) SEARCH STRATEGY**

1. [mh Dentistry]
2. (dental* or dentist*)
3. ((oral or periodont*) near/5 surg*)
4. (pulpotom* or pulpect* or endodont* or "pulp cap*" or apicoectom* or apicectom* or gingivec* or gingivoplast*)
5. ((dental or tooth or teeth or molar*) near/5 (fill* or restor* or extract* or remov* or "cavity prep*" or caries or carious or decay* or scal* or polish* or "root plan*"))
6. ("root canal" and (therap* or treat*))
7. (tooth near/3 replant*)
8. ((dental or oral) near/2 implant*)
9. ((dental or teeth or tooth) near/2 (anesthes* or anaesthes* or "nerve block"))
10. "root surface instrumentation"
11. (crown* or bridge* or prosthodontic*)
12. ((oral or mouth or dental) near/5 biops*)
13. (or #1-#12)
14. MeSH descriptor: [Specialties, Surgical] explode all trees
15. (surgery or surgical or preoperative or pre-operative or postoperative or post-operative or perioperative or peri-operative or intraoperative or intra-operative or postsurgical or post-surgical or periprocedural or peri-procedural or operat*)
16. (invasive and procedure)
17. (Zawilska et al.-#16)
18. [mh Anticoagulants]
19. [mh "Fibrinolytic agents"]
20. [mh "Heparin, low-molecular weight"]
21. MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees
22. [mh ^warfarin]
23. [mh ^dicumarol]
24. [mh ^acenocoumarol]
#25 [mh ^phenindione]
#26 [mh ^aspirin]
#27 [mh ^dipyridamole]
#28 (anticoagula* or anti-coagula*)
#29 "indirect thrombin inhibitor**"
#30 (fibrinolytic next (agent* or drug*))
#31 (antithrombic next (agent* or drug*))
#32 (thrombolytic next (agent* or drug*))
#33 (antiplatelet* or anti-platelet*)
#34 (platelet* near/2 inhibitor*)
#35 (platelet* next (antagonist* or aggregant*))
#36 ("low molecular weight heparin" or dalteparin or enoxaparin* or nadroparin* or fragmin* or Kabi-2165 or tedelparin or FR-860 or clexane or EMT-966 or EMT-967 or lovenox or PK-10169 or CY-216 or fraxiparin*)
#37 (NOAC or "thrombin inhibitor**" or "Factor Xa inhibitor**" or "vitamin K inhibitor**")
#38 (warfarin or aldocumar or coumadin* or marevan or tedicumar or warfant or jantoven or uniwarfarin)
#39 (dicumarol or dicoumarin or dicoumarol or bishydroxycoumain or coumarin)
#40 (acenocoumarol or acenocoumarin or nicoumalone or sinkumar or sinthrom or sintrom or syncumar or synthrom)
#41 (phenindione or dindevan or fenilin or phenylindanedione or phenyline or pindione)
#42 (dabigatran or pradax* or prazaxa)
#43 (rivaroxaban or xarelto)
#44 (apixaban or elegis or edoxaban or lixiana)
#45 (aspirin* or "acetylsalicylic acid" or acetylsal or acylpyrin or aloxiprimum or colfarit or dispir or easprin or ecotrin or endosprin or magneycyl or micristin or polopir* or solpin or solupsan or sorprin)
#46 (clopidogrel or iscover or plavix)
#47 (dipyridamole or dipyrimadole or antistenocardin or cerebrovase or cleridium or curantil or curantyl or dipyramidole or kurantil or miosen or novo-dipiradol or persantin* or "asasanat retard")
#48 (prasugrel or efient or effient or prasita)
#49 (ticagrelor or brilinta or brilique or possia)
#50 (tinzaparin or innohep)
#51 (fondaparinux or arixtra or quixidar)
#52 (vorapaxar or zontivity)
#53 (or #18–#52)
#54 [mh ^"Risk factors"])  
#55 [mh ^Stroke]
#56 [mh "Embolism and Thrombosis"]
#57 [mh Hemorrhage]
#58 (risk* or "adverse event**" or "adverse effect**" or complication* or bleed* or haemosta* or hemosta* or comorbid* or thrombus or thromboembolism or thrombosis or embolism or thrombotic or stroke* or apoplex*)
#59 (or #54–#58)
#60 #53 and #13
#61 #53 and #17
MEDLINE via OVID SEARCH STRATEGY

1. exp DENTISTRY/
2. (dental$ or dentist$).ti,ab.
3. ((oral or periodont$) adj5 surg$).ti,ab.
4. (pulpotom$ or pulpect$ or endodont$ or "pulp cap$" or apicoectom$ or apicectom$ or gingivectom$ or gingivoplast$).ti,ab.
5. ((dental or tooth or teeth or molar$) adj5 (fill$ or restor$ or extract$ or remov$ or "cavity prep$" or caries or carious or decay$ or scal$ or polish$ or "root plan$")).ti,ab.
6. (root canal and (therap$ or treat$)).ti,ab.
7. (tooth adj3 replant$).ti,ab.
8. ((dental or oral) adj2 implant$).ti,ab.
9. ((dental or teeth or tooth) adj2 (anesthes$ or anaesthes$ or "nerve block$"))_.ti,ab.
10. "root surface instrumentation".ti,ab.
11. (crown$ or bridge$ or prosthodontic$).ti,ab.
12. ((oral or mouth or dental) adj5 biops$).ti,ab.
13. or/1-12
14. exp Specialties, Surgical/
15. (surgery or surgical or preoperative or pre-operative or postoperative or post-operative or perioperative or peri-operative or intraoperative or intra-operative or postsurgical or post-surgical or periprocedural or peri-procedural or operat$).ti,ab.
17. or/14-16
18. exp Anticoagulants/
19. Fibrinolytic agents/
20. Platelet aggregation inhibitor/
21. exp Heparin, Low-Molecular-Weight/
22. Warfarin/
23. Dicumarol/
24. Acenocoumarol/
25. Phenindione/
26. Aspirin/
27. Dipyridamole/
28. (anticoagula$ or anti-coagula$).ti,ab.
29. "indirect thrombin inhibitor$".mp.
30. (fibrinolytic adj (agent$ or drug$)).ti,ab.
31. (antithrombic adj (agent$ or drug$)).ti,ab.
32. (thrombolytic adj (agent$ or drug$)).ti,ab.
33. (antiplatelet$ or anti-platelet$).ti,ab.
34. (platelet$ adj2 inhibitor$).ti,ab.
35. (platelet$ adj (antagonist$ or aggregant$)).ti,ab.
36. ("low molecular weight heparin" or dalteparin or enoxaparin$ or nadroparin$ or fragmin$ or Kabi-2165 or tedelparin or FR-860 or clexane or EMT-966 or EMT-967 or lovenox or PK-10169 or CY-216 or fraxiparin$).ti,ab.
37. (NOAC or "thrombin inhibitor$" or "Factor Xa inhibitor$" or "vitamin K inhibitor$").ti,ab.
38. (warfarin or aldocumar or coumadin$ or marevan or tedicumar or warfant or jantoven or uniwarfarin).ti,ab.
39. (dicumarol or dicoumarin or dicoumarol or bishydroxycoumain or coumarin).ti,ab.
40. (acenocoumarol or acenocoumarin or nicoumalone or sinkumar or synthrome or sintrom or syncumar or synthrom).ti,ab.
41. (phenindione or dindevan or fenilin or phenylindanedione or phenyline or pindione).ti,ab.
42. (dabigatran or pradax$ or prazaxa).ti,ab.
43. (rivaroxaban or xarelto).ti,ab.
44. (apixaban or eliquis or edoxaban or lixiana).ti,ab.
45. (aspirin$ or "acetylsalicylic acid" or acetyals or acylypyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecl or micristin or polopir$ or solprin or solupsan or zorprin).ti,ab.
46. (clopidogrel or iscover or plavix).ti,ab.
47. (dipyridamole or dipyrimadole or antistenocardin or cerebrovase or clerkidium or curantil or curantyl or dipyramidole or kurantil or miosen or novo-dipiradol or persantin$ or "asasantin retard").ti,ab.
48. (prasugrel or efient or effient or prasita).ti,ab.
49. (ticagrelor or brilinta or brilique or possia).ti,ab.
50. (tinzaparin or innohep).ti,ab.
51. (fondaparinux or arixtra or quixidar).ti,ab.
52. (vorapaxar or zontivity).ti,ab.
53. or/18-52
54. Risk factors/
55. Stroke/
56. exp Hemorrhage/
57. exp "Embolism and Thrombosis"/
58. (risk$ or "adverse event$" or "adverse effect$" or complication$ or bleed$ or haemosta$ or hemosta$ or comorbid$ or thrombus or thromboembolism or thrombosis or embolism or thrombotic or stroke$ or apoplex$).ti,ab.
59. or/54-58
60. 53 and 13
61. 53 and 17
62. 53 and 59
63. Meta-Analysis as Topic/
64. meta analy$.tw.
65. metaanaly$.tw.
66. Meta-Analysis/
67. (systematic adj (review$1 or overview$1)).tw.
68. exp Review Literature as Topic/
69. or/63-68
Appendix 2 – Evidence Searches

70. cochrane.ab.
71. embase.ab.
72. (psychlit or psyclit).ab.
73. (psychinfo or psycinfo).ab.
74. (cinahl or cinhal).ab.
75. science citation index.ab.
76. bids.ab.
77. cancerlit.ab.
78. or/70-77
79. reference list$.ab.
80. bibliograph$.ab.
81. hand-search$.ab.
82. relevant journals.ab.
83. manual search$.ab.
84. or/79-83
85. selection criteria.ab.
86. data extraction.ab.
87. 85 or 86
88. Review/
89. 87 and 88
90. Comment/
91. Letter/
92. Editorial/
93. animal/
94. human/
95. 93 not (93 and 94)
96. or/90-92,95
97. 69 or 78 or 84 or 89
98. 97 not 96
99. guideline.pt.
100. practice guideline.pt.
101. guideline$.ti.
102. or/99-101
103. 60 and 102
104. 60 and 98
105. 61 and 102
106. 61 and 98
107. 62 and 102
108. 62 and 98

EMBASE via Ovid Search Strategy

1. exp DENTISTRY/
2. (dental$ or dentist$).ti,ab.
3. ((oral or periodont$) adj5 surg$).ti,ab.
4. (pulpotom$ or pulpect$ or endodont$ or "pulp cap$" or apicoectom$ or apicectom$ or gingivectom$ or gingivoplast$).ti,ab.

21
5. \((\text{dental or tooth or teeth or molar$}) \text{ adj5 (fill$ or restor$ or extract$ or remov$ or "cavity prep$" or caries or carious or decay$ or scal$ or polish$ or "root plan$"))}\).ti,ab.

6. \((\text{root canal and (therap$ or treat$))}\).ti,ab.

7. \((\text{tooth adj3 replant$)}\).ti,ab.

8. \((\text{dental or oral) adj2 implant$)}\).ti,ab.

9. \((\text{dental or teeth or tooth) adj2 (anesthes$ or anaesthes$ or "nerve block$")}\).ti,ab.

10. "\text{root surface instrumentation}".ti,ab.

11. \((\text{crown$ or bridge$ or prosthodontic$)}\).ti,ab.

12. \((\text{oral or mouth or dental) adj5 biops$)}\).ti,ab.

13. or/1-12

14. \exp \text{Surgery/}

15. \((\text{surgery or surgical or preoperative or pre-operative or postoperative or post-operative or perioperative or peri-operative or intraoperative or intra-operative or postsurgical or post-surgical or periprocedural or peri-procedural or operat$)}\).ti,ab.

16. \((\text{invasive and procedure})\).ti,ab.

17. or/14-16

18. \exp \text{Anticoagulant agent/ae}

19. \text{Fibrinolytic agent/ae}

20. \exp \text{Antithrombocytic agent/ae}

21. \text{Low molecular weight hepain/ae}

22. \text{Warfarin/ae}

23. \text{Dicumarol/ae}

24. \text{Aacenocoumarol/ae}

25. or/18-24

26. \exp \text{Anticoagulant agent/}

27. \text{Fibrinolytic agent/}

28. \exp \text{Antithrombocytic agent/}

29. \text{Low molecular weight hepain/}

30. \text{Warfarin/}

31. \text{Dicumarol/}

32. \text{Aacenocoumarol/}

33. or/26-32

34. \((\text{anticoagula$ or anti-coagula$)}\).ti,ab.

35. "\text{indirect thrombin inhibitor$}".mp.

36. \((\text{fibrinolytic adj (agent$ or drug$))}\).ti,ab.

37. \((\text{antithrombic adj (agent$ or drug$))}\).ti,ab.

38. \((\text{thrombolytic adj (agent$ or drug$))}\).ti,ab.

39. \((\text{antiplatelet$ or anti-platelet$)}\).ti,ab.

40. \((\text{platelet$ adj2 inhibitor$)}\).ti,ab.

41. \((\text{platelet$ adj (antagonist$ or aggregant$))}\).ti,ab.

42. "\text{"low molecular weight heparin" or dalteparin or enoxaparin$ or nadroparin$ or fragmin$ or Kabi-2165 or tedelparin or FR-860 or clexane or EMT-966 or EMT-967 or lovenox or PK-10169 or CY-216 or fraxiparin$)}\).ti,ab.
43. (NOAC or "thrombin inhibitor$" or "Factor Xa inhibitor$" or "vitamin K inhibitor$").ti,ab.
44. (warfarin or aldocumar or coumadin$ or marevan or tedicumar or warfant or jantoven or uniwarfarin).ti,ab.
45. (dicumarol or dicoumarin or dicoumarol or bishydroxycoumain or coumarin).ti,ab.
46. (acenocoumarol or acenocoumarin or nicoumalone or sinkumar or synthrome or sintrom or syncumar or synthrom).ti,ab.
47. (phenindione or dindevan or fenilin or phenylindanedione or phenyline or pindione).ti,ab.
48. (dabigatran or pradax$ or prazaxa).ti,ab.
49. (rivaroxaban or xarelto).ti,ab.
50. (apixaban or elquis or edoxaban or lixiana).ti,ab.
51. (aspirin$ or "acetylsalicylic acid" or acetysal or aclypyrin or aloxiprimium or colfarit or dispril or easprin or ecotrin or endosprin or magneycl or micristin or polopir$ or solprin or solupsan or zorprin).ti,ab.
52. (clopidogrel or iscover or plavix).ti,ab.
53. (dipyridamole or dipyrimadole or antistenocardin or cerebrovase or cleridium or curantil or curantyl or dipyramidole or kurantil or miosen or novo-dipiradol or persantin$ or "asasantin retard").ti,ab.
54. (prasugrel or efient or effient or prasita).ti,ab.
55. (ticagrelor or brilinta or brilique or possia).ti,ab.
56. (tinzaparin or innohep).ti,ab.
57. (fondaparinux or arixtra or quixidar).ti,ab.
58. (vorapaxar or zontivity).ti,ab.
59. or/34-58
60. 25 or 59
61. 33 or 59
62. Risk factor/
63. Cerebrovascular accident/
64. Bleeding/
65. exp Thromboembolism/
66. (risk$ or "adverse event$" or "adverse effect$" or complication$ or bleed$ or haemosta$ or hemosta$ or comorbid$ or thrombus or thromboembolism or thrombosis or embolism or thrombotic or stroke$ or apoplex$ or hemorrhage$ or haemorrhage$).ti,ab.
67. or/62-66
68. 13 and 61
69. 17 and 60
70. 67 and 60
71. exp Meta Analysis/
72. ((meta adj analy$) or metaanalys$).tw.
73. (systematic adj (review$1 or overview$1)).tw.
74. or/71-73
75. cancerlit.ab.
76. cochrane.ab.
77. embase.ab.
78. (psychlit or psyclit).ab.
79. (psychinfo or psycinfo).ab.
80. (cinahl or cinhal).ab.
81. science citation index.ab.
82. bids.ab.
83. or/75-82
84. reference lists.ab.
85. bibliograph$.ab.
86. hand-search$.ab.
87. manual search$.ab.
88. relevant journals.ab.
89. or/84-88
90. data extraction.ab.
91. selection criteria.ab.
92. 90 or 91
93. review.pt.
94. 92 and 93
95. letter.pt.
96. editorial.pt.
97. animal/
98. human/
99. 97 not (97 and 98)
100. or/95-96,99
101. 74 or 83 or 89 or 94
102. 101 not 100
103. Practice guideline/
104. guideline$.ti.
105. 103 or 104
106. 68 and 102
107. 68 and 105
108. 69 and 102
109. 69 and 105
110. 70 and 102
111. 70 and 105

CINAHL via EBSCO Search Strategy

S80 S59 AND S74
S79 S59 AND S71
S78 S58 AND S74
S77 S58 AND S71
S76 S57 AND S74
S75 S71 AND S57
S74 S72 or S73
S73 TI guideline*
S72 (MH "Practice Guidelines")
S71 S65 NOT S70
Appendix 2 – Evidence Searches

S70  S66 or S67 or S68 or S69
S69  (MH "Animals")
S68  PT editorial
S67  PT letter
S66  PT commentary
S65  S60 or S61 or S62 or S63 or S64
S64  (systematic N1 (review or overview))
S63  (MH "Literature Review+")
S62  metaanalys*
S61  "meta analys*"
S60  (MH "Meta Analysis")
S59  S50 and S56
S58  S17 and S50
S57  S13 AND S50
S56  S51 or S52 or S53 or S54 or S55
S55  (risk* or “adverse event**” or “adverse effect**” or complication* or bleed* or haemosta* or hemosta* or comorbid* or thrombus or thromboembolism or thrombosis or embolism or thrombotic or stroke* or apoplex*)
S54  (MH "Hemorrhage+")
S53  (MH "Embolism and Thrombosis (Non-Cinahl)+")
S52  (MH "Stroke")
S51  (MH "Risk Factors")
S50  S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49
S49  (vorapaxar or zontivity)
S48  (fondaparinux or arixtra or quixidar)
S47  (tinzaparin or innohep)
S46  (ticagrelor or brilinta or brilique or prasia)
S45  (prasugrel or effient or effient or prasia)
S44  (dipyridamole or dipyrimadole or antistenocardin or cerebrovase or cerelidium or curantil or curantyl or dipyramidole or kurantil or miosen or novo-dipiradol or persantin* or "asasantin retard")
S43  (clopidogrel or iscover or plavix)
S42  (aspirin* or "acetylsalicylic acid" or acetylsal or acylpyrin or alopixurum or colfarit or dispril or easprin or ecotrin or endosprin or magneyel or micristin or polopir* or solprin or solupsan or zorprin)
S41  (apixaban or eliquis or edoxaban or lixiana)
S40  (rivaroxaban or xarelto)
S39  (dabigatran or pradax* or prazaxa)
S38  (phenindione or dindevan or fenilin or phenylindanedione or phenyline or pindione)
S37  (acenocoumarol or acenocoumarin or nicoumalone or sinkumar or sinthrom or sintrum or syncumar or synthrom)
S36  (dicumarol or dicoumarin or dicoumarol or bishydroxycoumain or coumarin)
S35  (warfarin or aldoumar or coumaidin* or marevan or tedicumar or warfant or jantoven or uniwarfarin)
S34  (NOAC or "thrombin inhibitor*" or "Factor Xa inhibitor**" or "vitamin K inhibitor**")
Appendix 2 – Evidence Searches

S33 ("low molecular weight heparin" or dalteparin or enoxaparin* or nadroparin* or fragmin* or Kabi-2165 or tedelparin or FR-860 or clexane or EMT-966 or EMT-967 or lovenox or PK-10169 or CY-216 or fraxiparin*)
S32 (platelet* n1 (antagonist* or aggregant*))
S31 (platelet* n2 inhibitor*)
S30 (antiplatelet* or anti-platelet*)
S29 (thrombolytic n1 (agent* or drug*))
S28 (antithrombic n1 (agent* or drug*))
S27 (fibrinolytic n1 (agent* or drug*))
S26 "indirect thrombin inhibitor*"
S25 (anticoagula* or anti-coagula*)
S24 (MH "Dipyridamole")
S23 (MH "Aspirin")
S22 (MH "Warfarin")
S21 (MH "Platelet Aggregation Inhibitors+")
S20 (MH "Heparin, Low-Molecular-Weight")
S19 (MH "Fibrinolytic Agents")
S18 (MH "Anticoagulants+")
S17 S14 or S15 or S16
S16 (invasive and procedure)
S15 (surgery or surgical or preoperative or pre-operative or postoperative or post-operative or perioperative or peri-operative or intraoperative or intra-operative or postsurgical or post-surgical or periprocedural or peri-procedural or operat*)
S14 (MH "Specialties, Surgical+")
S13 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
S12 ((oral or mouth or dental) N5 biops*)
S11 (crown* or bridge* or prosthodontic*)
S10 "root surface instrumentation"
S9 ((dental or teeth or tooth) N2 (anesthes* or anaesthes* or "nerve block"))
S8 ((dental or oral) N2 implant*)
S7 (tooth N3 replant*)
S6 ("root canal" and (therap* or treat*))
S5 ((dental or tooth or teeth or molar*) N5 (fill* or restor* or extract* or remov* or "cavity prep*" or caries or carious or decay* or scal* or polish* or "root plan*"))
S4 (pulpotom* or pulpect* or endodont* or "pulp cap*" or apicoectom* or apicectom* or gingivectom* or gingivoplast*)
S3 ((oral or periodont*) N5 surg*)
S2 (dental* or dentist*)
S1 (MH "Dentistry+")

Document prepared by:

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School of Dentistry
The University of Manchester
Coupland III Building
# Appendix 3 – Evidence Appraisal Forms

**Systematic Review SR1: Nematullah et al., 2009**

<table>
<thead>
<tr>
<th>Systematic Review:</th>
<th>Ref. No.: SR1</th>
<th>Reviewer(s): MW_021014</th>
</tr>
</thead>
</table>

**Aim of study:** is there a clearly focussed question?

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

<table>
<thead>
<tr>
<th>Patient/Problem: (target patients and actual participant characteristics)</th>
<th>Intervention or risk factors:</th>
<th>Comparison:</th>
<th>Outcomes: note which are critical/important (from patient perspective) for the guidance recommendation*</th>
</tr>
</thead>
</table>
| patient undergoing dental surgery                                         | continuing warfarin or acenocoumarol | discontinuing or reducing dose of warfarin or acenocoumarol | 1. major bleeding* (not in meta analysis; defined as significant blood loss requiring transfusion, reoperation, anticoagulation reversal or which was fatal)  
2. non-major bleeding* (clinically significant non-major bleeding was defined as non-major bleeding which resulted in a visit to medical facility or an unplanned intervention or procedure such as suturing)  
3. minor bleeding* (defined as bleeding not meeting above criteria)  
4. thromboembolic events* (not in meta analysis)  
5. all cause mortality* (not in meta analysis) |

**Study Type:**

<table>
<thead>
<tr>
<th>Appropriate study types?</th>
<th>Appropriate search terms?</th>
<th>yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Appropriate databases?</td>
<td>yes</td>
</tr>
<tr>
<td>Correct components to address question?</td>
<td>Unpublished studies?</td>
<td>yes</td>
</tr>
<tr>
<td>Yes</td>
<td>Follow up of citations?</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>Personal contact with experts?</td>
<td>yes</td>
</tr>
</tbody>
</table>

**Search Strategy:**

<table>
<thead>
<tr>
<th>Study selection:</th>
<th>No. of selectors: 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Studies including patients on warfarin requiring dental procedure, with thromboembolism (TE) or post-op bleeding as outcomes</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Studies without treatment (i.e. usual warfarin therapy) and control (i.e. interruption or reduction) arms</td>
</tr>
</tbody>
</table>
### Study no.s:
4 or 5 depending on outcome

### Nb search limited to studies in English

### Non-RCT studies

#### Risk of bias/systematic error (study limitations that could cause systematic error): consider risk of bias for each important outcome

| Randomisation: is it reported and appropriate? | Blinding: consider whether blinding of patients or assessors would be important for outcomes considered | Other limitations: e.g. attrition bias (incomplete accounting of patients and outcome events), reporting bias (selective outcome reporting), surrogate outcomes(?)
1/5 described patient withdrawals
1/5 described blinding

<table>
<thead>
<tr>
<th>Inconsistency: Refers to unexplained heterogeneity in results.</th>
<th>Imprecision (random error):</th>
<th>Indirectness: consider implications for both systematic review and guidance</th>
<th>Publication bias:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is heterogeneity analysis reported?</td>
<td>Confidence intervals reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chi² and I² values reported; no significant heterogeneity between studies for either outcome based on RR, but 1 study had much higher bleeding rates for treatment and control |
CIs are sufficiently narrow to have confidence in (lack of) effect. |
Mostly extractions, so may not be applicable to other dental procedures. |
4/5 studies carried out in hospital setting. |
Locations of populations in individual studies not stated. Co-interventions varied between studies. Some used tranexamic acid. |
e.g. when intervention is new and not many studies available—may be biased for positive results |
Limited to English language |

### Meta analysis: no meta analysis, because of significant variation between studies in type of invasive procedure, outcomes and interventions

#### No. of data extractors: 3

#### Overall results (for each outcome):

<table>
<thead>
<tr>
<th>Are results for individual studies shown?</th>
<th>Was it reasonable to combine study results?</th>
<th>Was an appropriate method used?</th>
<th>Are reasons for variation in results discussed?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are results for individual studies shown?</td>
<td>Possibly not (see comments box)</td>
<td>DerSimonian and Laird’s random effects model of pooling</td>
<td></td>
</tr>
<tr>
<td>Would confounders affect overall result?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nd</td>
<td></td>
<td></td>
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<tr>
<td>nd</td>
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</tr>
</tbody>
</table>

1. nd
2. RR (random)=0.71, 95% CI 0.39-1.28, p=0.25, I²=0%
3. RR (random)=1.19, 95% CI 0.9-1.58, p=0.22, I²=0%
4. nd

<table>
<thead>
<tr>
<th>Is the effect substantial?</th>
<th>Is there dose-response data?</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

---

1. This is only relevant for observational studies (automatically start at low quality) for which none of the quality criteria need to be downgraded, and allows for the possibility of upgrading. Not relevant for RCTs where quality starts at high.
### Adverse events:

<table>
<thead>
<tr>
<th>Outcome (bleeding) is an adverse effect</th>
</tr>
</thead>
</table>

### Benefit/harm/cost considerations?

No data presented of effect on risk of embolism comparing treatment and control (although 1% risk for patients altering therapy estimated in other studies).

Authors noted that thromboembolic events are potentially more serious than bleeding.

### Values/preferences considerations?

Not discussed

### Reviewer’s comments:

Include summary of main findings

Review reports that there is no significant difference in bleeding outcomes for patients continuing versus interrupting warfarin.

Doubtful whether these studies should have been pooled: co-interventions such as haemostatic measures varied between studies; INRs varied; 1 study uses acenocoumarol rather than warfarin; in 2 studies treatment was reduced not stopped, which would tend to underestimate effect; the study which was most heavily weighted in the meta analysis used acenocoumarol, only reduced dose (not stopped), used heparin bridging and had much higher bleeding rates (albeit similar RR) - would tend to underestimate overall effect of interrupting anticoagulation.

### GRADE evidence quality rating:

**Rating and brief explanation**

**Low quality**

This is due to potential bias (poor randomization/allocation concealment and poor reporting of dropouts/withdrawals) in 3 of the 5 studies, and variation in the control treatments and co-interventions, which may make the studies unsuitable for meta analysis.
Systematic Review SR2: Napenas et al., 2013

Appendix 3 – Evidence Appraisal Forms

Systematic Review SR2: Napenas et al., 2013


Aim of study: is there a clearly focussed question?
To assess the risk of oral bleeding complications after dental procedures in patients on antiplatelet therapy.

Patient/Problem: (target patients and actual participant characteristics)
Patients having an invasive dental procedure i.e. extraction, alveoplasty, apicoectomy, implant, torus removal, biopsies, flap surgery, perio surgery, deep scaling, root planing and periodontal probing.

Intervention or risk factors:
Aspirin alone or with α-tocopherol, clopoidigrel, diprymidole etc, also warfarin

Comparison:
Placebo, no antiplatelets or interrupted anti-platelets, depending on study

Outcomes: note which are critical/important (from patient perspective) for the guidance recommendation*
1. intra-operative bleeding*
2. immediate post-operative bleeding (<60min)*
3. late post-operative bleeding (>60min)*

Different outcomes were measured in different studies

Study Type:
Appropriate study types? RCTs, cohort studies, case control studies (prospective or retrospective)
Correct components to address question?
Yes, studies relevant to antithrombotic therapy and dental practice
Study no.s: 3 RCTs, 9 prospective cohort, 3 retrospective cohort (2 of the RCTs assessed bleeding on periodontal probing and were not included in bleeding outcomes above)

Search Strategy:
Appropriate search terms? Not stated
Appropriate databases? Medline, Embase, National Guideline Clearing House only
Unpublished studies? Not stated
Follow up of citations? Yes
Personal contact with experts? Yes

Study selection:
Inclusion criteria:
1 group of patients on at least 1 antiplatelet and measurement of bleeding outcomes after invasive dental treatment
Exclusion criteria:
Case reports, reviews, guidelines, expert opinion, repeat publications of same work excluded

Ref. No.: SR2
Reviewer(s): MW_271014
### Risk of bias/systematic error (study limitations that could cause systematic error): consider risk of bias for each important outcome

<table>
<thead>
<tr>
<th>Randomisation: is it reported and appropriate?</th>
<th>Blinding: consider whether blinding of patients or assessors would be important for outcomes considered</th>
<th>Other limitations: e.g. attrition bias (incomplete accounting of patients and outcome events), reporting bias (selective outcome reporting), surrogate outcomes?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reported</td>
<td>The 3 RCTs were double blinded</td>
<td>Studies were small e.g. RCTs had 17, 37 or 37 patients in treatment arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient numbers do not add up in one study.</td>
</tr>
</tbody>
</table>

### Inconsistency: Refers to unexplained heterogeneity in results.

<table>
<thead>
<tr>
<th>Is heterogeneity analysis reported?</th>
</tr>
</thead>
<tbody>
<tr>
<td>No analysis</td>
</tr>
</tbody>
</table>

### Imprecision (random error):

<table>
<thead>
<tr>
<th>Imprecision (random error):</th>
</tr>
</thead>
<tbody>
<tr>
<td>No indicator of error to judge precision</td>
</tr>
</tbody>
</table>

### Indirectness: consider implications for both systematic review and guidance

<table>
<thead>
<tr>
<th>Indirectness: consider implications for both systematic review and guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patient demographics will have to consult original studies.</td>
</tr>
<tr>
<td>Some of the antiplatelets are not used in Scotland (e.g. vasodilator cilostazol not recommended for intermittent claudication in NHS Scotland)</td>
</tr>
</tbody>
</table>

### Publication bias:

<table>
<thead>
<tr>
<th>Publication bias:</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. when intervention is new and not many studies available– may be biased for positive results</td>
</tr>
<tr>
<td>2/15 studies included were published by the review author</td>
</tr>
</tbody>
</table>

### Meta analysis: no meta analysis, because of significant variation between studies in type of invasive procedure, outcomes and interventions

<table>
<thead>
<tr>
<th>Meta analysis: no meta analysis, because of significant variation between studies in type of invasive procedure, outcomes and interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of data extractors: not stated</td>
</tr>
</tbody>
</table>

### Overall results (for each outcome):

<table>
<thead>
<tr>
<th>Overall results (for each outcome):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. intra-operative bleeding: 1.9% (3/151) occurrence of excessive bleeding (&gt;30ml) for antiplatelets (aspirin; aspirin and clopolidgril; aspirin, clopolidgril and cilostazol) compared to control (1%, 1/100) from 2 cohort studies</td>
</tr>
<tr>
<td>2. immediate post-operative bleeding (&lt;60min): 66.7% (22/33) occurrence for aspirin and clopolidgril, 2.6% (2/78) for aspirin or clopolidgril, 0.4% (2/532) for control in 1 study; 40% (4/10) for aspirin and clopolidgril, 6% (1/17) for aspirin, (no control group) in 2nd study. 2 other studies reported 0% (0/51) for aspirin and 0.6% (1/155) for single/dual antiplatelet</td>
</tr>
<tr>
<td>3. late post-operative bleeding (&gt;60min): for 1st study above, 0%</td>
</tr>
</tbody>
</table>

---

2 This is only relevant for observational studies (automatically start at low quality) for which none of the quality criteria need to be downgraded, and allows for the possibility of upgrading. Not relevant for RCTs where quality starts at high.
incidences of patient reported bleeding; for 2nd study above, 0% incidences requiring management; 5 other studies also found 0% patient reported bleeding; 1 study reported 1.4% (2/141) for single/dual antiplatelets, 4.1% (9/219) for warfarin and 8.2% (6/73) for combined.

Is the effect substantial? Yes Only for immediate post-operative bleeding in some studies

Is there dose-response data? No

<table>
<thead>
<tr>
<th>Adverse events:</th>
<th>Benefit/harm/cost considerations?</th>
<th>Values/preferences considerations?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome (bleeding) is an adverse effect</td>
<td>Risk of acute coronary events which could result in death, if antiplatelet therapy discontinued, were considered</td>
<td>Not discussed</td>
</tr>
</tbody>
</table>

Reviewer’s comments:

Include summary of main findings

No significant difference in occurrence of excessive intra-operative blood loss between patients on single or dual antiplatelet drugs and controls

Apparent increase in occurrence of immediate post-operative bleeding for dual antiplatelet therapy compared to single or control (no difference between single and control)

7 studies reported no late post-operative bleeding for patients on single or dual anti-platelet therapy (0/346)

Authors conclude that there is no indication to alter or discontinue antiplatelet therapy before invasive dental procedures, although management of patients on dual therapy warrants added consideration.

The authors make the point that while high quality RCTs for the effect of antiplatelet drugs on bleeding after dental procedures are lacking, it is very unlikely that any new RCTs will be carried out in future because of ethical issues of randomising patients for the intervention who have no indication for antiplatelet use, or whose anticoagulation therapy should be individually tailored.
### Systematic Review SR3: O’Dell et al., 2012

**Systematic Review:**

**Aim of study:** is there a clearly focussed question?

The aim of this article was to provide a systematic review of recently published clinical data on the direct thrombin inhibitors and factor Xa inhibitors in the management of atrial fibrillation.

<table>
<thead>
<tr>
<th>Patient/Problem: (target patients and actual participant characteristics)</th>
<th>Intervention or risk factors:</th>
<th>Comparison:</th>
<th>Outcomes: note which are critical/important (from patient perspective) for the guidance recommendation*</th>
</tr>
</thead>
</table>
| Patients with atrial fibrillation | Treatment with dabigatran, rivaroxaban or apixaban | Treatment with warfarin | 1. stroke and systemic embolism  
2. major bleeding*  
3. intracranial bleeding  
* bleeding accompanied by a decrease in the hemoglobin level of at least 2 g per deciliter or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death. |

<table>
<thead>
<tr>
<th>Study Type:</th>
<th>Search Strategy:</th>
<th>Study selection:</th>
</tr>
</thead>
</table>
| Appropriate study types?  
3 randomised phase III clinical trials (ARISTOTLE, RELY, ROCKET)  
Correct components to address question?  
Yes, studies relevant to assessing the efficacy and safety of the NOACs  
Study no.s: 3 | Appropriate search terms? Individual NOACs  
Appropriate databases? ClinicalTrials.gov registry  
Unpublished studies? Meeting abstracts  
Follow up of citations? Yes  
Personal contact with experts? Not stated | Inclusion criteria:  
Limited to clinical trials that included patients with AF  
Completed trials with warfarin as a comparator  
Exclusion criteria:  
Ongoing studies |

**Risk of bias/systematic error (study limitations that could cause systematic error): consider risk of bias for each important outcome**

| Randomisation: is it reported and appropriate? | Blinding: consider whether blinding of patients or assessors would be important for Other limitations: e.g. attrition bias (incomplete accounting of patients and outcome events), reporting bias (selective outcome reporting), surrogate outcomes(?) |
|---|---|---|
### Appendix 3 – Evidence Appraisal Forms

#### Systematic Review SR3: O’Dell et al., 2012

<table>
<thead>
<tr>
<th>All 3 studies were randomised</th>
<th>outcomes considered</th>
<th>The data are based on limited Phase III studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 trials were double blind, double dummy, 1 was open label</td>
<td>There was suboptimal warfarin management in the rivaroxaban trial – tended to be subtherapeutic which may lead to underestimation of the bleeding rates in patients on warfarin – however this would tend to favour warfarin over rivaroxaban for lower bleeding risk.</td>
<td></td>
</tr>
<tr>
<td>(Note that in each group, ~30–40% of patients were also taking aspirin)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inconsistency: Refers to unexplained heterogeneity in results.</th>
<th>Imprecision (random error):</th>
<th>Indirectness: consider implications for both systematic review and guidance</th>
<th>Publication bias:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confidence intervals indicated for risk of stroke, but not for bleeding. P-values shown.</td>
<td>The data should be considered indirect as the bleeding outcome only includes major bleeding events and not minor events and does not identify bleeding as a result of surgical procedures (dental or otherwise). The comparator also contributes to indirectness since it is warfarin rather than interruption or discontinuation of the NOAC. In addition, there were strict inclusion and exclusion criteria for trials, such that the results may not be generally applicable to the wider population.</td>
<td>e.g. when intervention is new and not many studies available - may be biased for positive results</td>
<td></td>
</tr>
</tbody>
</table>

#### Meta analysis: no meta analysis carried out

<table>
<thead>
<tr>
<th>Overall results (for each outcome):</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. major bleeding events:</td>
</tr>
<tr>
<td>RELY: Dabigatran 150 mg: 3.11% (P = 0.31); dabigatran 110 mg: 2.71% (P =0.003); warfarin: 3.36%</td>
</tr>
<tr>
<td>ROCKET: Rivaroxaban: 3.6% (P =0.58); warfarin: 3.4%</td>
</tr>
<tr>
<td>ARISTOTLE: Apixaban: 2.13% (P &lt;0.001); warfarin: 3.09%</td>
</tr>
<tr>
<td>Only considered this outcome since it may include periprocedural bleeding (intracranial and gastrointestinal bleeding are likely to be spontaneous rather than as a result of surgery)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Are results for individual studies shown?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was it reasonable to combine study results?</td>
<td>No, because each compared a different NOAC to warfarin</td>
</tr>
<tr>
<td>Was an appropriate method used?</td>
<td>n/a</td>
</tr>
<tr>
<td>Are reasons for variation in results discussed?</td>
<td>Each result was for a different drug</td>
</tr>
<tr>
<td>Would confounders affect overall result?</td>
<td>n/a</td>
</tr>
</tbody>
</table>

3 This is only relevant for observational studies (automatically start at low quality) for which none of the quality criteria need to be downgraded, and allows for the possibility of upgrading. Not relevant for RCTs where quality starts at high.
### Adverse events:

<table>
<thead>
<tr>
<th>Outcome (bleeding) is an adverse effect</th>
<th>Benefit/harm/cost considerations?</th>
<th>Values/preferences considerations?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors note lack of reversal agents for NOACs, also the higher cost compared to warfarin (although this is not relevant for the guidance).</td>
<td>Not discussed</td>
<td></td>
</tr>
</tbody>
</table>

### Reviewer’s comments:

**Include summary of main findings**

The incidences of major bleeding events for dabigatran, rivaroxaban and apixaban are not significantly higher than for warfarin. For dabigatran 110mg and apixaban, the incidences are significantly lower.

Note that this systematic review only considers data from the 3 trials which studied the NOACs compared to warfarin and did not include the other trials which compare the NOACs to antiplatelets such as aspirin or enoxaparin.

**GRADE evidence quality rating:**

**Very low quality** (for bleeding outcome relevant to the guidance) because of risk of bias of trial results and because evidence has serious indirectness in that bleeding risk is compared to warfarin rather than interrupted/discontinued NOAC or no treatment, and refers to major bleeding, not specifically to postoperative bleeding.
Systematic Review SR4: Patatanian and Fugate, 2006

<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Ref. No.:</strong></td>
<td>SR4 Reviewer(s): MW_131114</td>
</tr>
</tbody>
</table>

**Aim of study:** is there a clearly focussed question?
To evaluate the efficacy and safety of local-acting haemostatic agents to prevent bleeding in patients taking oral anticoagulants (OA) and undergoing dental extraction.

<table>
<thead>
<tr>
<th><strong>Patient/Problem:</strong> (target patients and actual participant characteristics)</th>
<th><strong>Intervention or risk factors:</strong></th>
<th><strong>Comparison:</strong></th>
<th><strong>Outcomes:</strong> note which are critical/important (from patient perspective) for the guidance recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving continued anticoagulation and undergoing dental extractions or various oral surgeries including dental extraction.</td>
<td>Tranexamic acid (TXA) or epsilon aminocaproic acid</td>
<td>Placebo mouthwash, interrupted OA, haemostatic mouthwash for a different duration, and gelatin sponge sutures or autologous fibrin glue, depending on study.</td>
<td>1. incidence of bleeding requiring treatment* 2. thromboembolic risk* Unclear whether outcomes were specified before study selection.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Study Type:</strong></th>
<th><strong>Search Strategy:</strong></th>
<th><strong>Study selection:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate study types?</td>
<td>Appropriate search terms?</td>
<td>Inclusion criteria: Clinical trials were included if they evaluated hemostatic mouthwashes in patients receiving continued anticoagulation and undergoing dental extractions or various oral surgeries including dental extraction.</td>
</tr>
<tr>
<td>Prospective studies</td>
<td>Yes, anticoagulation, warfarin, hemostatic mouthwashes, epsilon aminocaproic acid, tranexamic acid, dental extraction, and oral surgery</td>
<td>Exclusion criteria: Non-english language articles</td>
</tr>
<tr>
<td><strong>Correct components to address question?</strong></td>
<td><strong>Appropriate databases?</strong> Medline, IPA, Embase</td>
<td></td>
</tr>
<tr>
<td>Yes, studies all involved haemostatic mouthwash and dental extractions</td>
<td><strong>Unpublished studies?</strong> Not stated</td>
<td></td>
</tr>
<tr>
<td><strong>Study no.s:</strong> 8 prospective studies of which 6 were randomized</td>
<td><strong>Follow up of citations?</strong> Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Personal contact with experts?</strong> Not stated</td>
<td><strong>No. of selectors: not stated</strong></td>
<td></td>
</tr>
</tbody>
</table>
### Risk of bias/systematic error (study limitations that could cause systematic error): consider risk of bias for each important outcome

<table>
<thead>
<tr>
<th>Randomisation: is it reported and appropriate?</th>
<th>Blinding: consider whether blinding of patients or assessors would be important for outcomes considered</th>
<th>Other limitations: e.g. attrition bias (incomplete accounting of patients and outcome events), reporting bias (selective outcome reporting), surrogate outcomes?</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 trials included randomisation, method not reported</td>
<td>The 3 trials where placebo mouthwash was used by the control group were double blinded.</td>
<td>Studies were small e.g. a total of 65 TXA versus 67 placebo treated individuals from the 2 double blinded trials for patients with uninterrupted anticoagulation; 50 per group for TXA versus fibrin glue compared to gelatin sponge and sutures alone.</td>
</tr>
</tbody>
</table>

### Inconsistency: Refers to unexplained heterogeneity in results.

<table>
<thead>
<tr>
<th>Imprecision (random error):</th>
<th>Indirectness: consider implications for both systematic review and guidance</th>
<th>Publication bias:</th>
</tr>
</thead>
<tbody>
<tr>
<td>No indicator of error to judge precision</td>
<td>Patients were aged from 19-93, where indicated, and from Italy, Israel, Sweden, Denmark, Spain or Australia. All taking warfarin or other VKAs, different indications for anticoagulation. No substantial indirectness identified.</td>
<td>E.g. when intervention is new and not many studies available - may be biased for positive results. Restriction to publications in English could result in missing articles.</td>
</tr>
</tbody>
</table>

### Meta analysis: no meta analysis, because of variation between studies in interventions and comparators

<table>
<thead>
<tr>
<th>Overall results (for each outcome):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are results for individual studies shown?</td>
</tr>
<tr>
<td>Was it reasonable to combine study results?</td>
</tr>
<tr>
<td>Was an appropriate method used?</td>
</tr>
<tr>
<td>Are reasons for variation in results discussed?</td>
</tr>
</tbody>
</table>

1. Incidence of bleeding requiring treatment:
Two RCT’s found a statistically significant reduction in post-operative bleeding incidences comparing TXA versus placebo mouthwash for patients on continued OA (suturing for most patients, no haemostatic dressing); 1.5% (1/65) vs 27% (18/67). One non-randomised, non-blinded CT found no significant difference in post-operative bleeding with TXA or fibrin glue, both in addition to gelatin sponge and sutures, compared with gelatin sponge and sutures alone (for patients continuing OA); 6/50 and 4/50 vs 3/50. A smaller RCT also found no significant difference between TXA and fibrin glue (both interventions in patients on continued OA with sutures and haemostatic dressings); 0/26 vs 2/23.

2. Thromboembolic risk: no incidences reported in any of the studies.

Is the effect substantial? Yes, for TXA vs placebo, with sutures but in absence of haemostatic dressing.
### Adverse events:
- Outcome (bleeding) is an adverse effect

### Benefit/harm/cost considerations?
- Possibility of increased thromboembolic risk due to TXA considered. Rare even with systemic TXA treatment and theoretically less likely for local treatment. Other adverse effects are considered.

### Values/preferences considerations?
- Not discussed

### Reviewer’s comments:
Include summary of main findings
Various small trials are considered in this SR that vary in interventions and comparators making it difficult to assess overall effect of haemostatic mouthwash across all studies e.g. some studies compare uninterrupted versus interrupted OA in addition to TXA comparisons. In addition the studies vary in their methodological quality making a single GRADE evidence quality rating difficult. The studies are described in the SR in narrative form without meta analysis.

In this appraisal, the studies comparing (i) TXA vs placebo (continued OA plus sutures) and (ii) those comparing TXA or fibrin glue vs no treatment (continued OA plus haemostatic dressing and sutures) are considered as 2 separate groups:
- (i) results indicate that TXA reduces bleeding complications compared to placebo mouthwash (when no other haemostatic dressing)
- (ii) results indicate that there is no significant effect of TXA or fibrin glue compared to no treatment (when carried out in addition to haemostatic dressing and sutures).

### GRADE evidence quality rating:
- **Rating and brief explanation**
  - **Moderate quality** for effect of TXA vs placebo on patients taking continued OA because of robust study design.
  - **Low quality** for effect of TXA vs fibrin glue or no treatment because the evidence comes from fairly small controlled trials which lack blinding and/or randomisation.
### Guideline G2: Douketis et al., 2012

**Title:**
Perioperative Management of Antithrombotic Therapy

**Source:**
Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

**Ref. No.:** G2

**Reviewer(s):** MW_281014

**Authors/organisation:** James D. Douketis, MD, Alex C. Spyropoulos, Frederick A. Spencer, Michael Mayr, Amir K. Jaffer, Mark H. Eckman, Andrew S. Dunn, and Regina Kunz, American College of Chest Physicians

**Date of publication/revision:** 2012

**Original version:** 2008

**Source:** CHEST 2012; 141(2)(Suppl):e326S–e350S


<table>
<thead>
<tr>
<th>Aim(s) of guidance:</th>
</tr>
</thead>
<tbody>
<tr>
<td>To address the management of patients who are receiving anticoagulant or antiplatelet therapy and require an elective surgery or procedure.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Key recommendations: relevant to SDCEP guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In patients who require a minor dental procedure, we suggest continuing VKAs with coadministration of an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure instead of alternative strategies (Grade 2C – weak, low to very low quality evidence).</td>
</tr>
<tr>
<td>2. In patients who are receiving ASA (aspirin) for the secondary prevention of cardiovascular disease and are having minor dental or dermatologic procedures or cataract surgery, we suggest continuing ASA around the time of the procedure instead of stopping ASA 7 to 10 days before the procedure (Grade 2C).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Geographical setting for guidance:</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Healthcare setting for guidance:</th>
</tr>
</thead>
<tbody>
<tr>
<td>users and patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is guidance currently used?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not stated</td>
</tr>
</tbody>
</table>

**Basis for recommendations:** e.g. published evidence, expert opinion etc.

If evidence based, review evidence in sections below

Evidence based recommendations.

**VKAs:**
Evidence for VKAs was assessed from 3 RCTs and a number of observational studies and the outcomes of thromboembolic events, major, moderate and minor bleeding considered. The evidence suggested that 2 approaches for perioperative management, VKA continuation with a pro-haemostatic agent or partial (2-3d) interruption, were associated with a low risk of bleeding.

**Antiplatelets:**
In patients having dental procedures, several small studies (<100 patients) comprising randomized trials (3) and cohort studies (3) suggested no increase in major bleeding with ASA continuation. Only one 43-patient retrospective cohort study assessed the safety of dental procedures in patients (29) receiving combined ASA and clopidogrel and found no bleeding episodes with continuation of dual antiplatelet therapy.
The evidence is not recorded in more detail in this form since it has already been thoroughly appraised by the guideline authors using GRADE criteria and rated as low quality. See methods and supplementary information accompanying the guideline for Summary of Findings Tables.

<table>
<thead>
<tr>
<th>Description of evidence questions for recommendations (if applicable):</th>
<th>this has been carried out by authors of guideline – see above</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient/Problem:</strong> (target patients and actual participant characteristics)</td>
<td><strong>Intervention or risk factors:</strong></td>
</tr>
<tr>
<td><strong>Comparison:</strong></td>
<td><strong>Outcomes:</strong> note which are critical/important (from patient perspective) for the guidance recommendation*</td>
</tr>
<tr>
<td><strong>Details of evidence search:</strong> study types, search strategy, study selection, no. of selectors</td>
<td><strong>Study limitations:</strong> risk of bias, limitations, inconsistency, imprecision, indirectness</td>
</tr>
<tr>
<td><strong>Meta analysis:</strong></td>
<td><strong>Evidence:</strong> for each outcome or recommendation as applicable</td>
</tr>
<tr>
<td><strong>Benefit/harm/cost considerations?</strong></td>
<td><strong>Values/preferences considerations?</strong></td>
</tr>
<tr>
<td>Authors cite a study suggesting that continuation of VKA therapy is less expensive than VKA interruption with bridging, for patients undergoing minor dental procedures. State that perioperative antithrombotic management is based on risk assessment for thromboembolism and bleeding, and recommended approaches aim to simplify patient management and minimize adverse clinical outcomes.</td>
<td>Potential influence of different patient values considered, but no evidence for the values.</td>
</tr>
<tr>
<td><strong>Overall quality of guidance (AGREE II) and explanation:</strong></td>
<td><strong>Rating of recommendations:</strong> Should the recommendations made be considered for SDCEP guidance?</td>
</tr>
<tr>
<td>Overall quality 6/7 (see AGREE_15665 appraisal) High quality guidelines</td>
<td>The evidence was appraised for quality using GRADE methods and the recommendations stated clearly with wording reflective of GRADE strength of recommendation. The recommendations relevant to dental procedures (see above) were both graded 2C which refers to a weak recommendation, based on low or very low quality evidence.</td>
</tr>
<tr>
<td><strong>Reviewer’s comments:</strong></td>
<td></td>
</tr>
<tr>
<td>The guideline for patients taking VKAs offers 2 options; continuing VKA with oral prohaemostatic agent or stopping VKA 2-3 days before surgery. For antiplatelets, the suggestion is to continue with aspirin. Although these are developed by the American College of Chest Physicians, there is no obvious reason why they would not be generally applicable to the Scottish population.</td>
<td></td>
</tr>
</tbody>
</table>
Guideline G3: Armstrong et al., 2013

**Title:**
– see full guideline at http://www.neurology.org/content/80/22/2065/suppl/DC2

**Ref. No.:** G3 AGREE_15777
**Reviewer(s):** MW_041114

**Authors/organisation:**

**Date of publication/revision:** 2013  
**Original version:** n/a  
**Source:** [www.neurology.org](http://www.neurology.org)  
http://www.neurology.org/content/80/22/2065

**Aim(s) of guidance:**
To assess evidence regarding periprocedural management of antithrombotic drugs in patients with ischemic cerebrovascular disease.

**Key recommendations:** relevant to SDCEP guidance

It is axiomatic that clinicians managing antithrombotic medications periprocedurally routinely weigh bleeding risks from drug continuation against thromboembolic risks from discontinuation in each patient. Neurologists should counsel that temporarily discontinuing aspirin is probably associated with increased stroke risk (Level B). Neurologists should counsel that periprocedural thromboembolic risks associated with different strategies for patients receiving chronic anticoagulation (AC) are unknown (Level U) but is probably higher if AC is stopped for ≥7 days (Level B).

1. Given minimal *clinically important bleeding risks, stroke patients undergoing dental procedures should routinely continue aspirin (Level A).*
2. Given minimal *clinically important increased bleeding risks, stroke patients requiring warfarin therapy should routinely continue warfarin when undergoing dental procedures (Level A)*

*Clinically important bleeding (moderate or severe) was defined as follows:
Severe or life-threatening bleeding: Intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention.
Moderate bleeding: Bleeding that requires blood transfusion but does not result in hemodynamic compromise.
Mild bleeding: Bleeding that does not meet moderate or severe criteria.
<table>
<thead>
<tr>
<th>Geographical setting for guidance:</th>
<th>Healthcare setting for guidance:</th>
<th>Is guidance currently used?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidelines developed by American Society but include studies published in British Journals.</td>
<td>Not stated</td>
<td>Don’t know</td>
</tr>
</tbody>
</table>

**Basis for recommendations:** e.g. published evidence, expert opinion etc.

*If evidence based, review evidence in sections below*

Systematic review of evidence from primary studies including RCTs and observational studies. Evidence rated according to scheme described in Reviewer’s comments section below.

Data from some studies pooled, otherwise studies described.

Recommendations (see ratings below) derived on the basis of evidence level.

Authors note: It is axiomatic that clinicians managing antithrombotic medications periprocedurally weigh bleeding risks from drug continuation against TE risks from discontinuation at the individual patient level, although high-quality evidence on which to base this decision is often unavailable. In addition, even when evidence is insufficient to exclude a difference in bleeding or shows a small increase in clinically important bleeding with antithrombotic agents, physicians may reasonably judge that the risks and morbidity of TE events exceed those associated with bleeding.

**Description of evidence questions for recommendations (if applicable):**

- **Patient/Problem:** (target patients and actual participant characteristics)
  Patients taking oral antithrombotic agents for primary or secondary cardiovascular disease or stroke prevention (including atrial fibrillation)

- **Intervention or risk factors:**
  Continuing anticoagulants or antiplatelet agents

- **Comparison:**
  Discontinuing anticoagulants or antiplatelet agents (may include reducing e.g. to meet lower target INR).

- **Outcomes:** note which are critical/important (from patient perspective) for the guidance recommendation*
  1. thromboembolic risk of temporarily discontinuing antiplatelet therapy*
  2. thromboembolic risk of temporarily discontinuing anticoagulant therapy*
  3. perioperative (dental) bleeding risk of continuing antiplatelet agents*
  4. perioperative (dental) bleeding risk of continuing anticoagulant agents*

Different outcomes were measured in different studies.
**Details of evidence search:** search strategy, study selection, study types

<table>
<thead>
<tr>
<th>Study limitations: risk of bias, limitations, inconsistency, imprecision, indirectness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias and other limitations are not explicitly considered for each study.</td>
</tr>
<tr>
<td>Only includes data for warfarin continuation for a maximum mean INR of 2.7</td>
</tr>
<tr>
<td>No heterogeneity analysis, but studies analysed have consistent results</td>
</tr>
<tr>
<td>CIs for RDs (arithmetic risk difference) calculated by Wilson’s method</td>
</tr>
<tr>
<td>For patient demographics will have to consult original studies. Some of the studies were published in British journals.</td>
</tr>
<tr>
<td>Most of the data for antiplatelets refers to aspirin (1 study included clopidogrel). No other antiplatelets covered. Similarly, evidence for anticoagulants mostly on warfarin (1 study included acenocoumarol). May not be able to extrapolate conclusions to other VKAs and antiplatelet drugs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study types included were RCTs, cohort studies, case control studies (prospective or retrospective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: Articles were included if they studied patients taking oral antithrombotic agents for primary or secondary cardiovascular disease or stroke prevention (including articles relating to atrial fibrillation), studied at least 20 subjects, included a comparison group, assessed risks of continuing or discontinuing an agent, and clearly described interventions and outcome measures. Both cardiac and stroke patients were included because risks overlap and many studies do not distinguish between the two groups. Non–English-language articles were included for which translations could be obtained.</td>
</tr>
<tr>
<td>Exclusion criteria: Case reports, review papers, and articles studying coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, pacemaker/defibrillator placement, and cerebrovascular procedures such as carotid endarterectomy were excluded because of confounding issues (e.g., procedure-related stroke) and because this guideline focuses on antithrombotic questions posed to treating neurologists.</td>
</tr>
</tbody>
</table>

**Meta analysis:**

<table>
<thead>
<tr>
<th>Evidence: for each outcome or recommendation as applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>No meta analysis performed, because of variation in study type and outcome measures.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence: for each outcome or recommendation as applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Aspirin discontinuation is probably associated with increased stroke or TIA risk (one Class I study (2010 RCT), two Class II studies (2005 case control, 2011 retrospective cohort)). Estimated stroke risk varies with the duration of aspirin discontinuation: RR was 1.97 for 2 weeks, OR was 3.4 for 4 weeks, and RR was 1.40 for 5 months (one Class II study each). The RCT (2010) found that MACE (major adverse cardiac events) and stroke/TIA (transient ischaemic attacks) occurred in 2.7% (3/109) of the aspirin group and in 9% (10/111) of the placebo group (p=0.049, RD 6.3%, 95% CI 0% to 13.3%).</td>
</tr>
<tr>
<td>2. No studies meeting inclusion criteria compared TE risks in subjects continuing warfarin with those discontinuing warfarin (with or without periprocedural heparin bridging). Studies lacked the statistical precision needed for conclusions to be drawn (one Class I study, three Class II studies with various methodologies). The TE event risk of warfarin discontinuation is probably higher if AC is stopped for ≥7 days (one Class I study).</td>
</tr>
<tr>
<td>3. It is highly probable that aspirin does not increase minor bleeding in patients undergoing dental surgery (two Class I studies, one Class II study). However, the studies’ degree of statistical precision fails to exclude an increased bleeding risk of up to 8.3%. It is possible that dual</td>
</tr>
</tbody>
</table>
### Appendix 3 – Evidence Appraisal Forms

**Guideline G3: Armstrong et al., 2013**

<table>
<thead>
<tr>
<th>Benefit/harm/cost considerations?</th>
<th>Values/preferences considerations?</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP therapy has no increased bleeding risk over clopidogrel therapy alone (one Class II study); no bleeding events occurred in either group, but a bleeding risk of up to 11.7% cannot be excluded.</td>
<td>INR values for which this data applies are stated (maximum mean=2.7)</td>
</tr>
<tr>
<td>4. It is highly probable that warfarin does not increase clinically important bleeding risks with dental extractions (four Class I studies, each with ~50 patients/treatment arm). All 4 studies showed a RD of 0% i.e. no difference in clinically important bleeding comparing anticoagulant continuation versus discontinuation for dental treatment. 1 of the studies included patients taking acenocoumarol (2007)</td>
<td>RD= arithmetic Risk Difference</td>
</tr>
<tr>
<td>Cost considerations not mentioned.</td>
<td>RD= arithmetic Risk Difference</td>
</tr>
<tr>
<td>Balance of risk of thromboembolism versus significant bleeding is the major focus of the guideline.</td>
<td>Importance of considering patient preferences noted - In a study comparing preferences of patients with AF with those of physicians, patients were willing to experience a mean of 17.4 excess-bleeding events with warfarin and 14.7 excess-bleeding events with aspirin to prevent a stroke. Devereaux et al (2001) BMJ.</td>
</tr>
</tbody>
</table>

### Overall quality of guidance (AGREE II) and explanation:

<table>
<thead>
<tr>
<th>Rating of recommendations: Should the recommendations made be considered for SDCEP guidance?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall quality = 5/7 (see AGREE_15777)</td>
</tr>
<tr>
<td>Although the authors do not use GRADE, the recommendations are based on the evidence and appropriate wording used to indicate the strength of recommendation, in addition to a rating for each.</td>
</tr>
<tr>
<td>The recommendations relevant to dental procedures (see above) are graded Level A, which is the highest level (requires at least 2 consistent highest quality studies).</td>
</tr>
</tbody>
</table>

**Reviewer’s comments:**

These are high quality guidelines based on a systematic review and appraisal of evidence. The recommendations to not interrupt aspirin or warfarin are rated at the highest level (i.e. ‘should routinely continue medication’).

Although these are developed by the American Academy of Neurologists, there is no obvious reason why they would not be generally applicable to the Scottish population.

**Note.** The authors state that the experience with aspirin and warfarin cannot be confidently extrapolated to other antithrombotic medications i.e. it could be considered too indirect to apply these recommendations to, for example, other VKAs or other antiplatelets.

The authors make different recommendations for different surgical procedures, suggesting that it may be considered too indirect to apply recommendations from other surgical procedures to dental treatments.
Classification of Evidence for Prognostic Studies

Class I: A cohort study of a broad spectrum of persons at risk for developing the outcome (e.g., target disease, work status). The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class II: A case control study of a broad spectrum of persons with the condition compared to a broad spectrum of controls or a cohort study of a broad spectrum of persons at risk for the outcome (e.g., target disease, work status) where the data was collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class III: A case control study or a cohort study where either the persons with the condition or the controls are of a narrow spectrum where the data was collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who did not determine the presence of the risk factor. Study results allow calculation of measures of a prognostic accuracy.

Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

Classification of Recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an “A” recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).
### Guideline G4: Randall 2007

<table>
<thead>
<tr>
<th>Title:</th>
<th>Surgical Management of the Primary Care Dental patient on Warfarin (2007)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref. No.:</td>
<td>G4 AGREE_15805</td>
</tr>
<tr>
<td>Reviewer(s):</td>
<td>MW_051114</td>
</tr>
<tr>
<td>Authors/organisation:</td>
<td>C. Randall, North West Medicines Information Centre, UK Medicines Information</td>
</tr>
<tr>
<td>Date of publication/revision:</td>
<td>2007</td>
</tr>
<tr>
<td>Original version:</td>
<td>2001</td>
</tr>
</tbody>
</table>

#### Aim(s) of guidance:
To provide evidence based recommendations for the management of patients taking warfarin who require dental procedures (although aim not explicitly stated).

#### Key recommendations: relevant to SDCEP guidance
1. Warfarin does not need to be stopped before primary care dental surgical procedures
2. Tranexamic acid mouthwash should not be used routinely in primary dental care

#### Geographical setting for guidance: users and patients | Healthcare setting for guidance: Primary care dental practice | Is guidance currently used? |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

#### Basis for recommendations: e.g. published evidence, expert opinion etc.
*If evidence based, review evidence in sections below*

Review of evidence from primary studies (listed in a table) including RCTs and observational studies.

No ratings given for evidence quality.

Data from some studies pooled, otherwise studies described.

Recommendations are derived from summaries of evidence. The strength of the recommendations is suggested by the wording used, but not explicitly defined.
### Description of evidence questions for recommendations (if applicable):

<table>
<thead>
<tr>
<th>Patient/Problem: (target patients and actual participant characteristics)</th>
<th>Intervention or risk factors:</th>
<th>Comparison:</th>
<th>Outcomes: note which are critical/important (from patient perspective) for the guidance recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients taking warfarin requiring dental surgery</td>
<td>1. Continuing warfarin 2. Use of tranexamic acid with or without local haemostatic measures</td>
<td>1. Discontinuing warfarin (may include reducing e.g. to meet lower target INR). 2. Placebo mouthwash or local haemostatic measures alone</td>
<td>1.1 risk of thromboembolic event if warfarin discontinued* 1.2 incidence of postoperative bleeding if warfarin continued* 2.1 incidence of postoperative bleeding with tranexamic acid 2.2 incidence of postoperative bleeding with placebo mouthwash</td>
</tr>
</tbody>
</table>

### Details of evidence search: search strategy, study selection, study types

<table>
<thead>
<tr>
<th>Study limitations: risk of bias, limitations, inconsistency, imprecision, indirectness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search strategy not described</td>
</tr>
<tr>
<td>Study types included were RCTs, cohort studies, case control studies (prospective or retrospective)</td>
</tr>
<tr>
<td>Study selection criteria not described</td>
</tr>
</tbody>
</table>

### Study limitations: risk of bias, limitations, inconsistency, imprecision, indirectness

- Risk of bias and other limitations are not explicitly considered for each study.
- Not all studies have a comparison mentioned e.g. difficult to estimate base TE rate for patients continuing on warfarin preoperatively.
- No heterogeneity analysis, but studies analysed generally have consistent results.
- No indication of statistical precision of data.
- For patient demographics will have to consult original studies. Some of the studies were published in British journals.
- Evidence for anticoagulants mostly on warfarin (2 studies included acenocoumarol).

### Meta analysis: Evidence: for each outcome or recommendation as applicable

<table>
<thead>
<tr>
<th>No formal meta analysis performed, because of variation in study type and outcome measures, but some pooling of data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the studies assessing bleeding risk, the dental procedures, haemostatic measures</td>
</tr>
<tr>
<td>1.1 Stopping warfarin for two days increases the risk of thromboembolic events. This risk is difficult to estimate (because of differences in study designs) but is probably between 0.02% and 1%. This risk will depend on the individual’s baseline risk for TE (affected by indication for warfarin i.e. higher for mechanical heart valve, acute MI, lower for AF without stroke etc), on the period of anticoagulant interruption and the follow up period used for outcome measures. There is no clear indication of risk of TE for patients continuing on warfarin (although estimated at 0.4% (1/237) compared to 0.6% (6/996) for stopping</td>
</tr>
<tr>
<td>1.2 Incidence of postoperative bleeding if warfarin continued</td>
</tr>
<tr>
<td>2.1 Incidence of postoperative bleeding with tranexamic acid</td>
</tr>
<tr>
<td>2.2 Incidence of postoperative bleeding with placebo mouthwash</td>
</tr>
</tbody>
</table>

---

Guideline G4: Randall, 2007
This evidence would probably rate as **low to very low quality** using GRADE criteria, based on the types of studies (observational), lack of control group in some of the studies and variability in study design (e.g. period of drug interruption and period of follow up).

1.2 Continuing warfarin during dental surgical procedures will increase the risk of postoperative bleeding requiring intervention. Stopping warfarin is no guarantee that the risk of postoperative bleeding requiring intervention will be eliminated as serious bleeding can occur in non-anticoagulated patients. Most cases of postoperative bleeding can be managed by pressure or repacking and resuturing the socket.

The incidence of postoperative bleeding not controlled by local measures varies from 0% to 3.8%.

The guideline presents a table of studies, describing haemostatic measures and postoperative bleeding events for patients continuing their anticoagulant for dental procedures. Data from 18 studies (including 10 RCTs) was pooled to give an estimate of 9.5% (139/1463) delayed postoperative bleeds, of which 3.8% (56/1463) were serious (required intervention e.g. repacking and resuturing). The INR levels of the patients to which these estimates apply ranged from 1.2 to 5.2.

Data pooled from 2 controlled studies estimated the incidence of serious bleeding events in control patients (who had never taken anticoagulants) to be 1.2% (3/260). 178/1463 patients (from 2 studies) were taking acenocoumarol rather than warfarin.

The evidence is likely to rate as **low quality** according to GRADE, because although a significant number of the studies were RCTs, not all studies had the same comparator and some provided indirect evidence using no anticoagulant ever taken as a surrogate control for interrupted anticoagulant.

2.1 When used alone with no local haemostatic dressing, tranexamic acid mouthwash reduces serious postoperative bleeding compared to placebo mouthwash (1.6%, 1/63 versus 18.5%, 12/65 from 2 studies).

When used in combination with local haemostatic measures and suturing, tranexamic acid mouthwash provides little additional reduction in postoperative bleeding.

Pooling the results from 5 studies where tranexamic acid mouthwash was used, delayed postoperative bleeding requiring treatment occurred in 3.6% of patients. These rates compare to a serious postoperative bleeding rate of 5.4% when results were pooled from studies where local haemostatic measures and suturing were used without tranexamic acid.

<table>
<thead>
<tr>
<th>Benefit/harm/resource considerations?</th>
<th>Values/preferences considerations?</th>
</tr>
</thead>
<tbody>
<tr>
<td>The balance of the risk and potential outcomes of a thromboembolism versus the risk of significant bleeding is a major focus of the guideline. Practical issues associated with the use of tranexamic acid in primary care are</td>
<td>Not discussed</td>
</tr>
</tbody>
</table>

---

Guideline G4: Randall, 2007
Discussing (prescribing and cost).

<table>
<thead>
<tr>
<th>Overall quality of guidance (AGREE II) and explanation:</th>
<th>Rating of recommendations: Should the recommendations made be considered for SDCEP guidance?</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGREE rating 5/7 (see AGREE_15805 appraisal)</td>
<td>Although the GRADE framework is not used, the recommendations are clearly based on the evidence and the strength of each recommendation is implied from the wording used (no ratings assigned for quality of evidence or strength of recommendations). The evidence is likely to rate as low quality according to GRADE, because although a significant number of the studies were RCTs, not all studies had the same comparator and some provided indirect evidence using no anticoagulant ever taken as a surrogate control for interrupted anticoagulant.</td>
</tr>
<tr>
<td>Clear recommendations based on careful review of the evidence available at the time of development. The evidence quality and recommendations are not formally graded.</td>
<td></td>
</tr>
</tbody>
</table>

Reviewer’s comments:

The evidence for whether or not to discontinue anticoagulants before dental surgery are indirect, since bleeding incidences are only reported for patients continuing on anticoagulants (compared to those never having taken anticoagulants) rather than comparing continuing versus discontinuing medication.
**Guideline G5: Randall 2010**

<table>
<thead>
<tr>
<th>Title:</th>
<th>Surgical Management of the Primary Care Dental patient on Antiplatelet Medication.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref. No.:</td>
<td>G5 AGREE_15893 Reviewer(s): MW_071114</td>
</tr>
<tr>
<td>Authors/organisation:</td>
<td>C. Randall, North West Medicines Information Centre, UK Medicines Information</td>
</tr>
</tbody>
</table>

**Aim(s) of guidance:**
To provide evidence based recommendations for the management of patients taking antiplatelet medications who require dental procedures (although aim not stated).

**Key recommendations:** relevant to SDCEP guidance

Dental procedures carried out routinely in primary care can be performed with minimal risk without stopping or altering mono or dual antiplatelet therapy.

<table>
<thead>
<tr>
<th>Geographical setting for guidance:</th>
<th>Healthcare setting for guidance:</th>
<th>Is guidance currently used?</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>users and patients</td>
<td>Primary care dental practice</td>
</tr>
</tbody>
</table>

**Basis for recommendations:** e.g. published evidence, expert opinion etc.

*If evidence based, review evidence in sections below*

Review of evidence from primary studies including an RCT and observational studies.

No ratings given for evidence quality.

The evidence was described, but not pooled.

Treatment advice points based on the evidence are provided in the summary. The main recommendation is derived from summaries of the evidence. The strength of the recommendation is suggested by the wording used, but not explicitly defined.
### Description of evidence questions for recommendations (if applicable):

<table>
<thead>
<tr>
<th>Patient/Problem: (target patients and actual participant characteristics)</th>
<th>Intervention or risk factors:</th>
<th>Comparison:</th>
<th>Outcomes: note which are critical/important (from patient perspective) for the guidance recommendation*</th>
</tr>
</thead>
</table>
| Patients on mono or dual antiplatelet therapy requiring dental surgery | Continuing mono or dual antiplatelet therapy | Discontinuing mono or dual antiplatelet therapy | 1. risk of thromboembolic event if mono or dual antiplatelet therapy discontinued*  
2. incidence of postoperative bleeding if mono or dual antiplatelet therapy continued*  
Different outcomes were measured in different studies |

### Details of evidence search: search strategy, study selection, study types

| Search strategy not described | Risk of bias and other limitations are not explicitly considered for each study. |
| Study types included were RCTs, cohort studies, case control studies (prospective or retrospective) | Not all studies have a comparison mentioned |
| Study selection criteria not described | No heterogeneity analysis, but studies analysed generally have consistent results |
|  | No indication of statistical precision of data |
|  | For patient demographics will have to consult original studies. Some of the studies were published in British journals. |
|  | Evidence for antiplatelets mostly on aspirin (some studies included clopidogrel or prasugrel). |

### Study limitations: risk of bias, limitations, inconsistency, imprecision, indirectness

### Meta analysis: Evidence: for each outcome or recommendation as applicable

| No formal meta analysis performed, because of variation in study type and outcome measures and control groups. | 1. Stroke and myocardial infarction have been associated with cessation of antiplatelet medication approximately 10 days before the event (observational cohort and case control studies). Stopping aspirin prior to surgical procedures may increase the risk of TE events by 0.005% (estimate from 1 study). Major adverse cardiac events are associated with stopping or interrupting clopidogrel or clopidogrel/aspirin therapy in patients with coronary artery stents. Most of this evidence comes from studies where patients admitted to hospital for acute cardiac syndrome or strokes were assessed for whether their antiplatelet therapy had been discontinued prior to the event.  
This evidence would probably rate as low quality using GRADE criteria, based on the types of studies (observational) and lack of control groups in some of the studies. Evidence from newer studies is considered in Armstrong et al (2013). |
|  | 2. Patients taking antiplatelet medications have a prolonged bleeding time but this may not be clinically relevant. Postoperative bleeding |

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Appendix 3 – Evidence Appraisal Forms

Guideline G5: Randall, 2010
after dental procedures can be controlled using local haemostatic measures in patients taking antiplatelet monotherapy. There is little evidence available on the bleeding risk if patients take dual therapy with aspirin and clopidogrel but retrospective study data suggest that this risk is similar to that seen with single antiplatelet therapy (Napenas et al, 2013 includes more studies).

In 1 study, for patients continuing on clopidogrel/aspirin or prasugrel/aspirin dual therapy for dental procedures, similar incidences of minimal bleeding events were reported (3.8%, 1/26 or 2.9%, 1/34, respectively). No other studies provided evidence on bleeding risks for continuing on prasugrel dual therapy for dental procedures.

We did not rate this evidence for the outcome of bleeding, because this evidence was included in Napenas et al (2013), which we GRADE rated as **low quality**.

### Benefit/harm/resource considerations?

The balance of the risk and potential outcomes of a thromboembolism versus the risk of significant bleeding is a major focus of the guideline.

### Values/preferences considerations?

Not discussed

### Overall quality of guidance (AGREE II) and explanation:

**Rating of recommendations:** *Should the recommendations made be considered for SDCEP guidance?*

AGREEII rating: 4/7

These are clear guidelines based on carefully reviewed evidence. The lower AGREE rating is a consequence of the guideline not meeting all of AGREE’s criteria for guideline development methodology.

Although the GRADE framework is not used, the summary statements are clearly based on the evidence and the strength of the recommendation is implied from the wording used (no ratings assigned for quality of evidence or strength of recommendations).

### Reviewer’s comments:

The evidence is in favour of continuing aspirin monotherapy, or clopidogrel monotherapy or dual therapy, because of an association of TE with discontinuing therapy, and a lack of documented cases of clinically significant bleeding after dental procedures in patients taking mono or dual antiplatelet therapy.
Appendix 4 – Considered Judgement Forms
Qu 1 Interrupting warfarin for dental treatment

Considered Judgement for Recommendations

Key question 1: Should warfarin or other vitamin K antagonists be continued or interrupted for dental treatment? (To include warfarin, acenocoumarol and phenindione)

Evidence Appraisal ref:
G4, SR1, G2, G3,

1. Summary of evidence

**Summary of evidence**

*Summarise the evidence for the effects of the intervention on the important outcomes e.g. what effect does continuing antiplatelet treatment have on the risk of bleeding? Ideally evidence will be from systematic reviews or guidelines.*

(a) Surgical Management of the Primary Care Dental patient on Warfarin. North West Medicines Information Centre (Randall, 2007) G4

*This guideline is included here for comparison with newer articles, since it is considered to be an authoritative source of recommendations that are widely accepted in current practice.*

This guideline (AGREEII rating 5/7) makes clear recommendations based on careful review of the evidence available at the time of development. The key recommendation is:

**Patients requiring dental surgical procedures in primary care and who have an INR below 4.0 should continue warfarin therapy without dose adjustment.**

- The guideline reports that stopping warfarin for two days increases the risk of thromboembolic (TE) events and states that this risk is difficult to estimate (because of differences in study designs) but is probably between 0.02% and 1%. There is no clear indication of risk of TE for patients continuing on warfarin (although estimated at 0.4% (1/237) compared to 0.6% (6/996) for stopping warfarin, in 1 systematic review cited).
- Evidence reviewed supports the conclusion that continuing warfarin during dental surgical procedures will increase the risk of postoperative bleeding requiring intervention. Data from 18 studies (including 10 RCTs) was pooled to give an estimate of 9.5% (139/1463) delayed postoperative bleeds, of which 3.8% (56/1463) were serious (required intervention e.g. repacking and resuturing, or transfusion in extreme cases). Most cases of postoperative bleeding were managed by pressure or repacking and resuturing the socket. The INR levels of the patients to which these estimates apply ranged from 1.2 to 5.2.
- Data pooled from 2 studies estimated the incidence of serious bleeding events in control patients (who had never taken anticoagulants) to be 1.2% (3/260).
- 178 of the 1463 patients (from 2 of the studies) were taking acenocoumarol rather than warfarin and had a lower rate of serious bleeding incidences that those taking warfarin.

The evidence and recommendations in this guidance were not graded.

(b) Dental surgery for patients on anticoagulant therapy with warfarin: A systematic review and meta-analysis (Nematullah et al., 2009) SR1

The aim of this systematic review was to evaluate the effect of continuing warfarin therapy on the bleeding risk of patients undergoing elective dental surgical procedures.
- 5 randomised controlled trials (RCTs) assessing patients continuing on their anticoagulant...
therapy, compared with control patients where anticoagulant medication was interrupted or modified, were included. The review concluded that 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.

- The relative risk (RR; the risk of bleeding when continuing anticoagulant divided by the risk when discontinuing or modifying anticoagulant) was estimated at 0.71 for clinically significant non-major bleeding and at 1.19 for minor bleeding.

Major bleeding (not included in meta analysis) was defined as significant blood loss requiring transfusion, reoperation, anticoagulation reversal or which was fatal; clinically significant non-major bleeding was defined as non-major bleeding which resulted in a visit to medical facility or an unplanned intervention or procedure such as suturing; minor bleeding was defined as bleeding not meeting any of the above criteria.

- Patients were taking acenocoumarol rather than warfarin in 1 of the studies.

We have rated the quality of the evidence included in this systematic review as low for all bleeding outcomes, according to the GRADE framework.

(c) Perioperative Management of Antithrombotic Therapy (Douketis et al., 2012) G2

These are high quality guidelines (AGREEII rating 6/7) which provide evidence based recommendations for clinicians to address the management of patients who are receiving anticoagulant or antiplatelet therapy and require an elective surgery or procedure. The relevant key recommendation is:

**In patients who require a minor dental procedure, we suggest continuing VKAs with co-administration of an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure instead of alternative strategies** (Grade 2C - weak recommendation, low to very low quality evidence by GRADE rating).

- Considering data from 3 RCTs, the relative risk for moderate bleeding when continuing warfarin prior to dental treatment (compared with interrupting warfarin) was estimated at 0.68, suggesting that continuing warfarin does not increase the risk of clinically significant post-operative bleeding, which is in close agreement with (b). As in (b), the relative risk of minor bleeding was increased (RR=1.76) when warfarin was continued.

- None of these studies included patients taking VKAs other than warfarin.

- The different studies assessing the bleeding risk involved different bleeding management strategies, including continuing anticoagulants with coadministration of prohaemostatic interventions such as the antifibrinolytic agent, tranexamic acid. Analysis of these studies suggests that continuing VKAs with a prohemostatic agent is associated with a low (<5%) risk for clinically relevant non-major bleeding.


These high quality guidelines (AGREEII rating 5/7) include recommendations relevant to patients requiring dental treatment and recommend that:

**Given minimal clinically important increased bleeding* risks, stroke patients requiring warfarin therapy should routinely continue warfarin when undergoing dental procedures** (Level A)

Level A = established as effective, ineffective or harmful for the given condition in the specified population (Level A rating requires at least two consistent Class I studies).

*Clinically important bleeding (moderate or severe) was defined as follows:
Severe or life-threatening bleeding: Intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention.
### Moderate bleeding: Bleeding that requires blood transfusion but does not result in hemodynamic compromise.

### Mild bleeding: Bleeding that does not meet moderate or severe criteria.

- Regarding the risk of thromboembolism if anticoagulant therapy is interrupted; the studies considered lacked the statistical precision needed for conclusions to be drawn (one Class I study, three Class II studies with various methodologies). The TE event risk of warfarin discontinuation is probably higher if AC is stopped for ≥7 days (one Class I study).
- The guideline concludes that it is highly probable that warfarin does not increase clinically important bleeding risks with dental extractions (four Class I studies, each with ~50 patients/treatment arm). All 4 studies showed a RD (risk difference; the arithmetic difference in risks between the groups) of 0%, that is, no difference in the incidence of clinically important bleeding comparing anticoagulant continuation versus discontinuation for dental treatment.
- 1 of the studies included patients taking acenocoumarol.

## 2. Quality and quantity of evidence

*Comment here on the quality and quantity of the evidence available for this question. The quality of evidence reflects the extent to which confidence in the estimate of the effect is adequate to support a particular recommendation. Note where evidence is lacking.*

- All 4 articles considered the same body of evidence to various extents (4 RCTs and ~15 observational studies). Some only considered RCTs, others included observational studies with or without control groups in their analysis. Douketis et al (2012) identified 2 new observational studies, although these did not change the conclusions.
- The key studies were appraised in Douketis et al (2012) using GRADE and rated as low quality for all outcomes (thromboembolic events, major, moderate and minor bleeding) because of lack of direct controls in many of the studies, risk of bias and small study sizes. The recommendation made by this group is rated as Level 2C, which is defined as a weak recommendation based on uncertainty in the evidence. This uncertainty, in which patient management is best, is reflected in their recommendation, which suggests the options of continuing VKAs or discontinuing for 2-3 days prior to dental treatment (there is low quality evidence from several studies supporting each of the options). This recommendation has been downgraded from their earlier 2008 guidelines (previously Level 1B), as a consequence of the more stringent GRADE criteria now applied, rather than as a result of new evidence. Suitable INR levels for which the recommended options apply were not stated.
- The recommendation made by Douketis et al (2012) also suggest the use of an oral prohaemostatic agent (tranexamic acid) if warfarin is continued perioperatively. This is because several of the studies considered included this as a cointervention with warfarin, and again reflects uncertainty in the treatment options because of evidence assigned a low quality rating. Evidence for whether the use of tranexamic acid should be recommended is discussed in the Considered Judgement – Qu 5 additional measures to minimise bleeding form in this appendix.
- Armstrong et al (2013) rate their recommendation to 'routinely continue warfarin’ at Level A, the highest level in the scheme that they use, even though they consider some of the same studies. The evidence rating scheme used by Armstrong et al (2013) appears to be less stringent than GRADE.
- None of the studies was able to determine an estimate for the risk of a thromboembolic event for patients discontinuing warfarin, because of a lack of data and variation in study design and interventions. Longer follow up periods may have been required to obtain a record of TE events. Randall (2007) suggested that it may be between 0.02 and 1%, but this may well vary depending on the medical condition for which the patient is being
Appendix 4 – Considered Judgement Forms

Qu 1 Interrupting **warfarin** for dental treatment

- Most of the studies included extractions or root canal treatment as the dental procedure. Only 2 studies included implant placement, and only in a small number of cases, therefore there is insufficient evidence on which to base a recommendation specific for implants regarding continuing or discontinuing VKA therapy.
- Most of the evidence comes from studies of patients taking warfarin, although 1 or 2 of the studies analysed in the articles included patients taking acenocoumarol. No evidence was found for phenindione. The lack of data on these other VKAs most likely reflects the limited usage of these compared to warfarin and thus it seems unlikely that new high quality studies will emerge.

**Acenocoumarol:**
According to the SPC sheet: Patients on Sinthrome, who undergo surgical or invasive procedures require close surveillance of their coagulation status. Under certain conditions, e.g. when the operation site is limited and accessible to permit effective use of local procedures for haemostasis, dental and minor surgical procedures may be performed during continued anticoagulation, without undue risk of haemorrhage. The decision to discontinue Sinthrome, even for a short period of time, should carefully consider individual risks and benefits. The introduction of bridging anticoagulant treatment, e.g. with heparin should be based on careful assessment of the expected risks of thromboembolism and bleeding ([www.medicines.org.uk/emc/medicine/129](http://www.medicines.org.uk/emc/medicine/129)).

**Phenindione:**
The SPC sheet for phenindione states: **Dindevan need not be stopped before routine dental surgery e.g. tooth extraction** ([www.medicines.org.uk/emc/medicine/23547](http://www.medicines.org.uk/emc/medicine/23547)).

3. **Consistency**
*Comment here on the degree of consistency demonstrated by the available evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence.*

**Risk of thromboembolism when discontinuing warfarin:**
- All 4 articles agree that there is insufficient evidence to estimate the increase in risk of a thromboembolic event if anticoagulation is disrupted.

**Risk of bleeding when continuing warfarin:**
- Randall (2007) suggests that continuing warfarin during dental surgical procedures **will increase the risk of postoperative bleeding requiring intervention.** The conclusion from the analysis in Nematullah et al (2009) is that 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.** Data from these 2 articles gives similar estimates of the risk of clinically significant bleeding at 3.8% and 5.4%, respectively. The discrepancy in their conclusions is due to differences in their estimate of bleeding risk for the control patients (1.2% and 9%, respectively). The control patients contributing to the estimate in Randall (2007) had never taken anticoagulants, while those included in the estimate in Nematullah et al (2009) had discontinued or modified their anticoagulant dose.
- The 2 other articles agree from their analysis that continuing warfarin **does not increase the risk of clinically significant post-operative bleeding.** Irrespective of whether the articles found that continuing warfarin increased the bleeding risk for dental treatment or not, all 4 studies recommended continuing warfarin as a treatment option. Douketis et al (2012) suggested stopping for 2-3 days as an alternative management
Appendix 4 – Considered Judgement Forms

Qu 1 Interrupting warfarin for dental treatment

option, as discussed above.

Other non-appraised, evidence-based guidelines:

- Aframian and colleagues (Aframian et al., 2007) recommend that for patients with an INR below or equal to 3.5 warfarin therapy need not be modified or discontinued for simple dental extractions.
- British Society of Haematology guidelines (Perry et al., 2007) recommend that oral anticoagulants should not be discontinued in the majority of patients requiring outpatient dental surgery including dental extraction.
- SIGN 129 Antithrombotics: indications and management (SIGN, 2013)
  These national clinical guidelines briefly review the same body of evidence and recommend that vitamin K antagonists should not be discontinued in patients undergoing outpatient dental surgery, including dental extraction. (Level A)
  In addition they suggest that the INR should be checked preoperatively to ensure it is in the target range and that the use of topical haemostatic measures such as sutures and collagen sponges, and tranexamic acid as a mouthwash, should be considered. (Recommended best practice)

4. Subgroup considerations

Comment here on any subgroup considerations e.g. should recommendations for patients at high or low risk be considered separately?

The recommendations are likely to be restricted to patients whose INR is controlled and <4. Evidence suggests that minor dental surgical procedures can be carried out safely on this patient group. It is generally considered that patients with an unstable INR, or an INR>4 have a higher risk of significant bleeding, and so should be considered separately. This is consistent with guidelines from the British Society of Haematology (Perry et al., 2007) and others.

5. Balance of effects

Comment here on the desirable and undesirable effects of the intervention and how substantial the effects are. Indicate whether the overall balance of effects favours the intervention or comparison.

Recommendations for perioperative VKA management should be based on the assessment of risk for thromboembolic events (associated with interrupting or adjusting anticoagulant medication) versus risk of clinically significant bleeding (associated with continuing usual anticoagulant medication). Even though the risk of a bleeding incident associated with continuing the VKA may be higher or uncertain, it was considered reasonable to judge that the risk outcomes and morbidity associated with TE events exceed those associated with bleeding.

6. Generalisability and applicability

Comment here on how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline.

No reasons were identified to suggest why the results from the evidence above would not be generalisable to the population addressed by the guidance.

7. Values and preferences

How much do people value the main outcomes? Uncertainty and variability in how much those affected value the outcomes of interest can be a reason not to make a strong recommendation and might affect the direction of a recommendation.

Indirect evidence suggests that patients would place a higher value on avoiding a
thromboembolism, than avoiding a bleeding complication following a dental procedure, considering the potential outcomes of each. In a study comparing preferences of patients with atrial fibrillation with those of physicians, patients were willing to accept a mean of 17.4 excess-bleeding events for the prevention of 1.8 strokes (per 100 patients over 2 years) with warfarin (Devereaux et al., 2001). A more recent systematic review, while acknowledging significant variation in studies, suggests that there is a preference for major bleeds over stroke or myocardial infarction (MacLean et al., 2012).

Note, however, that the available evidence considers spontaneous and non-procedural bleeding events rather than specifically measuring patient preference when considering bleeding associated with dental procedures.

<table>
<thead>
<tr>
<th>8. Acceptability</th>
</tr>
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<tbody>
<tr>
<td>Is intervention (e.g. continuing or interrupting medication) acceptable to patients, caregivers and providers?</td>
</tr>
<tr>
<td>No reasons noted why intervention would not be acceptable.</td>
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<tr>
<th>9. Feasibility</th>
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<tbody>
<tr>
<td>Comment on cost effectiveness, resource implications and implementation considerations here, if applicable.</td>
</tr>
<tr>
<td>The alternative treatment option of interrupting VKA medication could require consultation with prescribing clinician which may delay dental treatment and impose a burden on patient, dentist and clinician.</td>
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<tr>
<th>10. Other factors</th>
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<tbody>
<tr>
<td>Indicate here any other factors that were taken into account when assessing the evidence base.</td>
</tr>
<tr>
<td>There is significant clinical experience which indicates that treating patients (with an appropriate INR), without interrupting warfarin, rarely leads to significant bleeding complications.</td>
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</table>

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<tr>
<th>11. Recommendation for guidance</th>
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<tbody>
<tr>
<td>Summarise the group’s judgements for the recommendation e.g. which criteria were most influential for the decision. Record any dissenting opinion within the group and how a consensus was reached, if applicable. State the recommendation for the guidance, clearly indicating the strength, using GRADE appropriate wording.</td>
</tr>
<tr>
<td>Proposed recommendation:</td>
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<tr>
<td>Patients should continue taking warfarin or the other vitamin K antagonists for dental treatment.</td>
</tr>
<tr>
<td>This is based on the available evidence (considered to be low quality, by GRADE standards) and extensive clinical experience. The majority of the group would make a strong recommendation (13 for strong, 4 for weak). Those favouring a strong recommendation put more weight on the potential seriousness of a thromboembolic event, if warfarin was interrupted, on the body of clinical experience indicating that continuing on warfarin rarely causes bleeding complications, and on patient preference which evidence suggests is in favour of accepting the chance of bleeding over stroke.</td>
</tr>
<tr>
<td>Further points:</td>
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<tr>
<td>For patients taking warfarin, or the other vitamin K antagonists, and who require dental treatment which involves a significant risk of bleeding:</td>
</tr>
<tr>
<td>◦ The INR should be checked within 72 hours of the procedure, for a well controlled patient, otherwise within 24 hours.</td>
</tr>
<tr>
<td>◦ For dental treatment in primary care, the patient should have a controlled INR, which</td>
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</table>
should be no higher than 4.

- If the patient’s INR is not controlled, or is above 4, the dentist should consult with the patient’s medical practitioner.

### 12. Additional Information

*Include any further information that is relevant to the recommendation.*

Two new systematic reviews with relevance for this clinical question were published after the initial considered judgement was made. The first compared the risk of bleeding complications associated with minor oral surgical procedures for patients who were on continued versus modified VKA therapy (16 studies) and concluded that there was no significant difference in bleeding events between the 2 treatment options (Kammerer et al., 2015). The second considered all relevant studies carried out since the 1950’s and estimated the incidence of bleeding complications requiring more than local measures (31/5431 patients; 0.6%; from 83 studies) versus the incidence of embolic complications (22/2673 patients; 0.8%; from 64 studies). Significantly, while there were no recorded fatalities from bleeding complications for patients continuing their medication, 6 patients whose anticoagulant was interrupted for dental treatment died of embolic complications (Wahl et al., 2015).

There were no new significant primary studies identified in either of these reviews so the evidence for bleeding outcomes and thromboembolic risk should still be rated as low quality. The results from these 2 systematic reviews are consistent with that already considered therefore the recommendation to treat dental patients without interrupting their warfarin therapy is unaffected by this evidence.
Qu 2 Interrupting antiplatelets for dental treatment

Considered Judgement for Recommendations

<table>
<thead>
<tr>
<th>Key question 2: Should antiplatelet medication be continued or interrupted for dental treatment? (To include aspirin, clopidogrel, dipyridamole, prasugrel, ticagrelor and combined therapies)</th>
<th>Evidence Appraisal</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>refs:</td>
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<tr>
<td></td>
<td>G5, G2, SR2, G3</td>
</tr>
</tbody>
</table>

1. Summary of evidence

Summarise the evidence for the effects of the intervention on the important outcomes e.g. what effect does continuing antiplatelet treatment have on the risk of bleeding? Ideally evidence will be from systematic reviews or guidelines.

(a) Surgical Management of the Primary Care Dental patient on Antiplatelet Medication. North West Medicines Information Centre (Randall, 2010) G5

This guideline is included for comparison with the newer articles since it is considered to be an authoritative source of recommendations that are widely accepted in current practice.

This guideline (AGREEII rating 4/7) makes evidence based statements to inform the management of patients taking mono and dual antiplatelet therapies. The key recommendation is:

**Dental procedures carried out routinely in primary care can be performed with minimal risk without stopping or altering mono or dual antiplatelet therapy.**

**Risk of thromboembolic events:**

- The guideline reports that stroke and myocardial infarction have been associated with cessation of antiplatelet medication approximately 10 days before the event (observational cohort and case control studies).
- Stopping aspirin prior to surgical procedures may increase the risk of TE events by 0.005% (estimate from 1 study).
- Major adverse cardiac events are associated with stopping or interrupting clopidogrel or clopidogrel/aspirin therapy in patients with coronary artery stents.

This evidence would probably rate as low quality using GRADE criteria, based on the types of studies (observational) and lack of control groups in some of the studies. Evidence from newer studies is considered in Armstrong et al (2013).

**Risk of bleeding:**

- Patients taking antiplatelet medications have a prolonged bleeding time but this may not be clinically relevant. Postoperative bleeding after dental procedures can be controlled using local haemostatic measures in patients taking antiplatelet monotherapy. There is little evidence available on the bleeding risk if patients take dual therapy with aspirin and clopidogrel but retrospective study data suggest that this risk is similar to that seen with single antiplatelet therapy (Napenas et al., 2013 includes more studies).
- In 1 trial, for patients on clopidogrel/aspirin or prasugrel/aspirin dual therapy, similar incidences of minimal bleeding events after dental procedures were reported by this guideline (3.8%, 1/26 or 2.9%, 1/34, respectively). No other studies provided evidence on bleeding risks for continuing prasugrel dual therapy for dental procedures.

We did not rate the evidence for the outcome of bleeding, because this evidence is included in Napenas et al (2013), which we judged to be low quality, according to GRADE.
The evidence and recommendations in this guidance were not graded by the guideline author.

(b) Perioperative Management of Antithrombotic Therapy (Douketis et al., 2012) G2

These are high quality guidelines (AGREEII rating 6/7) that provide evidence based recommendations for clinicians to address the management of patients who are receiving anticoagulant or antiplatelet therapy and require an elective surgery or procedure. The key recommendation is:

**In patients who are receiving ASA (acetylsalicylic acid; aspirin) for the secondary prevention of cardiovascular disease and are having minor dental or dermatologic procedures or cataract surgery, we suggest continuing ASA around the time of the procedure instead of stopping ASA 7 to 10 days before the procedure.** (Grade 2C - weak recommendation; low to very low quality evidence by GRADE rating)

- In patients having dental procedures, several small studies (<100 patients) comprising randomized trials (3) and cohort studies (3) suggested no increase in major bleeding with ASA continuation. Only one 43-patient retrospective cohort study assessed the safety of dental procedures in 29 patients receiving combined ASA and clopidogrel and found no bleeding episodes with continuation of dual antiplatelet therapy.
- No recommendations were made for dental patients taking clopoidigrel since none of the studies included patients taking clopoidigrel alone. 3 cohort studies assessing perioperative continuation of clopoidigrel for non-cardiac surgery suggested increased bleeding rates with continuation, although this is indirect evidence since the procedures were non-dental.
- This guideline did not provide estimates for the risk of TE events associated with discontinuing antiplatelet medication.

(c) Review of postoperative bleeding risk in dental patients on antiplatelet therapy (Napenas et al., 2013). SR2

This systematic review aimed to assess the risk of oral bleeding complications after dental procedures in patients on antiplatelet therapy. Evidence is reported from 3 RCTs, 9 prospective cohort and 3 retrospective cohort studies (including 5 of the 6 studies assessed by Douketis et al., 2012). No meta analysis (statistical combining) of the data was conducted due to significant variation between studies in the antiplatelets, dental treatments and bleeding measures. The main findings were:

- No significant difference in occurrence of excessive intra-operative blood loss between patients on single or dual antiplatelet drugs and controls.
  (1.9% (3/151) occurrence of excessive intra-operative bleeding (>30ml) for antiplatelets (aspirin or aspirin with clopoidigrel or aspirin with both clopoidigrel and cilostazol) compared to control (1%, 1/100) from 2 cohort studies).
- An apparent increase in the occurrence of immediate post-operative bleeding for dual antiplatelet therapy compared to single therapy or control (no difference between single and control).
  (66.7% (22/33) occurrence of bleeding <60 min after dental treatment for aspirin with clopoidigrel, 2.6% (2/78) for aspirin or clopoidigrel, 0.4% (2/532) for control in 1 study; 40% (4/10) for aspirin with clopoidigrel, 6% (1/17) for aspirin, (no control group) in 2nd study. 2 other studies reported 0% (0/51) for aspirin and 0.6% (1/155) for single or dual antiplatelet therapy).
- Most studies reported no late post-operative bleeding for patients on single or dual antiplatelet therapy.
  (for 1st study directly above, 0% incidences of patient reported late post-operative bleeding
Considered Judgement Forms
Qu 2 Interrupting antiplatelets for dental treatment

(>60 min after dental treatment); for 2nd study above, 0% incidences requiring management; 5 other studies also found 0% patient reported late bleeding (total for 7 studies, 0/346); 1 study reported 1.4% (2/141) for single or dual antiplatelet therapy.

There was no analysis of thromboembolic events associated with continuing or discontinuing antiplatelet medications.

The authors concluded that there is no indication to alter or discontinue antiplatelet therapy before invasive dental procedures, although management of patients on dual therapy warrants added consideration.


These high quality guidelines (AGREEII rating 5/7) include recommendations relevant to patients requiring dental treatment and recommend that:

**Given minimal clinically important bleeding* risks, stroke patients undergoing dental procedures should routinely continue aspirin** (Level A)

*Clinically important bleeding (moderate or severe) was defined as follows:

Severe or life-threatening bleeding: Intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention.

Moderate bleeding: Bleeding that requires blood transfusion but does not result in hemodynamic compromise.

(Mild bleeding: Bleeding that does not meet moderate or severe criteria).

**Risk of bleeding:**

- Assessment of the evidence for bleeding found that it is highly probable that aspirin does not increase minor bleeding in patients undergoing dental surgery (two Class I studies, two Class II studies). However, the studies’ degree of statistical precision fails to exclude an increased bleeding risk of up to 8.3%. It is possible that dual antiplatelet therapy has no increased bleeding risk over clopidogrel therapy alone (one Class II study); no bleeding events occurred in either group, but a bleeding risk of up to 11.7% cannot be excluded.
- The two class II studies included patients taking clopidogrel alone or with aspirin.

**Risk of thromboembolic events:**

- Regarding the risk of thromboembolism, the guideline finds that aspirin discontinuation is probably associated with increased risk of stroke or TIA (transient ischaemic attack) (Level B - probably effective, ineffective or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.))
- The estimated stroke risk varies with the duration of aspirin discontinuation: RR was 1.97 for 2 weeks, OR was 3.4 for 4 weeks, and RR was 1.40 for 5 months (Class II studies). The RCT (2010) found that MACE (major adverse cardiac events) and stroke/TIA occurred in 2.7% (3/109) of the aspirin group and in 9% (10/111) of the placebo group. This RCT was not included in Randall (2010).

2. Quality and quantity of evidence

Comment here on the quality and quantity of the evidence available for this question. The quality of evidence reflects the extent to which confidence in the estimate of the effect is adequate to support a particular recommendation. Note where evidence is lacking.

**Aspirin monotherapy:**

- None of the 4 articles found a significant increase in clinically significant perioperative bleeding in patients continuing on aspirin for dental procedures. The evidence came from >15 studies, which were mostly observational. Some of the same studies were included in each article.
- Douketis et al (2012) rated the evidence they considered as low to very low quality (GRADE).
We rated the evidence included in Napenas et al (2013) for the effect of the antiplatelet(s) on each of the bleeding outcomes as low quality, according to GRADE criteria. This is because the evidence comes mainly from observational studies, rather than RCTs and because the studies are small (few patients) and are limited in that they often lack control groups.

- Only Randall (2010) and Armstrong et al (2013) considered the risk of TE and both found that aspirin discontinuation is probably associated with an increased risk of stroke or TIA, although there is insufficient evidence for an accurate estimate of the actual risk increase.

**Clopidogrel monotherapy or aspirin/clopidogrel dual therapy:**

- While most evidence relates to patients taking aspirin, Randall (2010), Napenas et al (2013) and Armstrong et al (2013) included studies totalling >50 patients taking clopidogrel alone and >100 patients taking clopidogrel with aspirin. Although there was a higher incidence of immediate post-operative bleeding for patients on dual therapy, none of the patients experienced late post-operative bleeding, indicating that the haemostatic measures carried out were sufficient to manage any postoperative bleeding. These studies were all included within Napenas et al (2013), which was assigned a low quality evidence rating for all bleeding outcomes.
- Randall (2010) considered the risks of discontinuing clopidogrel and stated that patients with cardiac stents are at high risk of thromboembolic events and that the greatest risk for stent thrombosis is premature discontinuation of clopidogrel. It is not clear what the absolute risk is or what the quality of the evidence is for this statement.

**Dipyridamole:**

- None of the dental studies assessed recorded including patients taking dipyridamole.
- The SPC sheet for Persantin states that the addition of dipyridamole to acetylsalicylic acid (aspirin) does not increase the incidence of bleeding events, and that when dipyridamole was administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone (www.medicines.org.uk/emc/medicine/29640). However, these statements do not include post-procedural or operative bleeding.

**Prasugrel:**

- Randall (2010) included 1 study with patients continuing prasugrel/aspirin dual therapy, which found no increase in bleeding events following dental procedures, compared with patients on clopidogrel/aspirin dual therapy.
- The SPC provides the following advice: Patients should be advised to inform physicians and dentists that they are taking prasugrel before any surgery is scheduled, and before any new medicinal product is taken. If a patient is to undergo elective surgery, and an antiplatelet effect is not desired, Efient should be discontinued at least 7 days prior to surgery (www.medicines.org.uk/emc/medicine/21504).

**Ticagrelor:**

- No evidence for the effect of ticagrelor on bleeding associated with dental treatments was found.
- The Scottish Medicines Consortium SPC advises that: As dual therapy with aspirin, ticagrelor demonstrated a significant reduction in ischaemic events compared with another antiplatelet drug without significantly increasing the incidence of study-defined major bleeding (www.medicines.org.uk/emc/medicine/23935). This did not include post-operative bleeding.
- If a patient is to undergo elective surgery and antiplatelet effect is not desired, Brilique should be discontinued 7 days prior to surgery.

**Additional non-appraised, evidence-based guideline/review:**

- In a non-systematic review (Wahl, 2014), the author pooled data from a variety of studies and provides an estimate of a 5% risk of a thrombotic complication for patients who had...
discontinued antiplatelet medication for dental treatment (17/324), although this includes 1 study where patients were selected because they had acute coronary syndrome and so may be an overestimate. In agreement with the studies above, this review recommends that antiplatelet medications should not be interrupted for dental surgery.

3. Consistency

Comment here on the degree of consistency demonstrated by the available evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence.

All 4 appraised articles provide evidence supporting a recommendation to not interrupt antiplatelet therapy for dental treatment.

4. Subgroup considerations

Comment here on any subgroup considerations e.g. should recommendations for patients at high or low risk be considered separately?

Since the bleeding risks associated with aspirin alone versus other single or dual antiplatelet therapies may be different, individual recommendations or caveats should be considered.

5. Balance of effects

Comment here on the desirable and undesirable effects of the intervention and how substantial the effects are. Indicate whether the overall balance of effects favours the intervention or comparison.

Recommendations for perioperative antiplatelet management should be based on risk assessment for thromboembolism (associated with stopping antiplatelet therapy) versus bleeding (associated with continuing antiplatelet therapy), with the aim of simplifying patient management and minimising adverse clinical outcomes. Although it is likely that the absolute risk of thromboembolism is less than the risk of bleeding complications, the outcome is potentially much more serious.

6. Generalisability and applicability

Comment here on how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline.

No reasons were identified to suggest why the results from the evidence above would not be generalisable to the population addressed by the guidance.

7. Values and preferences

How much do people value the main outcomes? Uncertainty and variability in how much those affected value the outcomes of interest can be a reason not to make a strong recommendation and might affect the direction of a recommendation.

Indirect evidence suggests that patients would place a higher value on avoiding a thromboembolism, than avoiding a bleeding complication following a dental procedure, considering the potential outcomes of each. In a study comparing preferences of patients with atrial fibrillation with those of physicians, patients were willing to accept a mean of 14.7 excess-bleeding events for the prevention of 1.3 strokes (per 100 patients over 2 years) with aspirin (Devereaux et al., 2001). A more recent systematic review, while acknowledging significant variation in studies, suggests that there is a preference for major bleeds over stroke or myocardial infarction (MacLean et al., 2012).

Note, however, that the available evidence considers spontaneous and non-procedural bleeding
8. Acceptability
*Is intervention (e.g. continuing on antiplatelet medication) acceptable to patients, caregivers and providers?*

No reasons noted why intervention would not be acceptable.

9. Feasibility
*Comment on cost effectiveness, resource implications and implementation considerations here, if applicable.*

The treatment option of interrupting antiplatelet medication may delay treatment and cause inconvenience for patient, dentist and prescribing clinician.

10. Other factors
*Indicate here any other factors that were taken into account when assessing the evidence base.*

It should be noted that for some patients, such as those taking dual antiplatelet drugs after coronary stent placement, the risk of a serious thromboembolic event occurring if the therapy is interrupted may be even higher than for patients with other indications.

11. Recommendation for guidance
*Summarise the group’s judgements for the recommendation e.g. which criteria were most influential for the decision. Record any dissenting opinion within the group and how a consensus was reached, if applicable.*

Proposed recommendation:
**Patients should continue taking their antiplatelet medication (single or dual) for dental treatment.**

This is based on the group’s considered judgement of the evidence and criteria above. As for warfarin, the group agreed on a strong recommendation, in spite of evidence graded as low quality, because of the importance the group assigned to the risks associated with interrupting therapy, to the considerable clinical experience associated with the recommended treatment management, and to patient preference.

The experience of the dental clinicians in the group was that for patients taking dual aspirin/clopidogrel therapy, bleeding after invasive procedures is often prolonged (up to an hour). The guidance should advise that more caution is taken with patients on dual therapies (aspirin/clopidogrel, aspirin/dipyridamole, aspirin/prasugrel or aspirin/ticagrelor) compared to aspirin monotherapy, and should recommend that:

- Initial treatments are limited to single extractions, or subgingival periodontal scaling on up to 3 teeth, to allow assessment of the patient’s bleeding.
- Local haemostatic measures and suturing should be carried out.
- Elective flap surgery for patients on short-term dual therapy should be deferred if possible or cardiologist consulted.
- For patients taking clopidogrel or clopidogrel/aspirin for a coronary artery stent, it is especially important that antiplatelet therapy is not stopped or interrupted because of the risk of major adverse cardiac events.
Qu 3 Interrupting NOACs for dental treatment

Considered Judgement for Recommendations

<table>
<thead>
<tr>
<th>Key question 3: Should NOACs be continued or interrupted for dental treatment?</th>
<th>Evidence Appraisal</th>
</tr>
</thead>
<tbody>
<tr>
<td>To include apixaban, dabigatran and rivaroxaban (also possibly edoxaban)</td>
<td>refs: SR3</td>
</tr>
</tbody>
</table>

1. Summary of evidence

*Summarise the evidence for the effects of the intervention on the important outcomes e.g. what effect does continuing antiplatelet treatment have on the risk of bleeding? Ideally evidence will be from systematic reviews or guidelines.*

(a) New Oral Anticoagulants for Atrial Fibrillation: A Review of Clinical Trials (O’Dell et al., 2012).

This article provides a systematic review of recently published clinical data on the direct thrombin inhibitors and factor Xa inhibitors in the management of atrial fibrillation. The potential relevance for the guidance is that the outcome of bleeding is reported for dabigatran, rivaroxaban and apixaban versus warfarin. Although there is no data directly comparing the NOACs with each other, evidence is presented from 3 large (~14000-18000 participants) randomised controlled clinical trials, each assessing one of the NOACs compared to warfarin. Incidences of major bleeding (per year) were:

- **RELY:** Dabigatran 150 mg: 3.11% (P = 0.31); dabigatran 110 mg: 2.71% (P = 0.003); warfarin: 3.36%
- **ROCKET:** Rivaroxaban: 3.6% (P = 0.58); warfarin: 3.4%
- **ARISTOTLE:** Apixaban: 2.13% (P < 0.001); warfarin: 3.09%

* major bleeding was bleeding accompanied by a decrease in the hemoglobin level of at least 2 g per deciliter or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death.

The incidences of major bleeding events for dabigatran, rivaroxaban and apixaban were not significantly higher than for warfarin. For dabigatran 110mg and apixaban, the incidences were significantly lower.

This systematic review only considered data from the 3 trials which studied the efficacy and safety of apixaban, rivaroxaban and dabigatran compared to warfarin (ARISTOTLE, ROCKET and RELY respectively) for atrial fibrillation, and did not include other trials which compare these drugs to antiplatelets such as aspirin or enoxaparin. Systematic reviews of these other trials were not identified, but the data for bleeding rates from these trials are summarised in the table below.

(b) Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants (Dabigatran, Rivaroxaban, Apixaban) Versus Warfarin in Patients With Atrial Fibrillation (Miller et al., 2012).

This systematic review analyses data from the same 3 trials as in O’Dell et al (2012). The major bleeding rates for dabigatran, rivaroxaban and apixaban are presented as relative risks (RR; bleeding incidence for NOAC/bleeding incidence for warfarin) with the 2 doses of dabigatran combined:

- **RELY:** Dabigatran: RR = 0.94 (95%CI; 0.82-1.07)
- **ROCKET:** Rivaroxaban: RR = 1.03 (95%CI; 0.89-1.17)
- **ARISTOTLE:** Apixaban: RR = 0.7 (95%CI; 0.61-0.81)

This analysis supports the same conclusion as O’Dell et al (2012) that dabigatran and
rivaroxaban have comparable risks for major bleeding compared to warfarin, while apixaban demonstrates superiority for this outcome.

For comparison, a summary table of major bleeding rates from other clinical trials of the NOACs is shown:

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Comparison</th>
<th>Major bleeding (hazard ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVERROES Connolly et al (2011) NEJM; 364</td>
<td>Apixaban (versus aspirin) in patients with atrial fibrillation</td>
<td>1.13 (95% CI: 0.74–1.75; P=0.57)</td>
</tr>
</tbody>
</table>
| ADVANCE3 Lassen et al (2010) NEJM; 363 | Apixaban versus enoxaparin for thromboprophylaxis after hip replacement | *Apixaban: 0.8% (95% CI:0.5–1.3)  
*Enoxaparin: 0.7% (95% CI:0.4–1.1)  
P=0.54 |
| RECORD4 Turpie et al (2009) The Lancet; 373 | Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty | *Rivaroxaban: 0.7% (95% CI:0.3–1.2)  
*Enoxaparin: 0.3% (95% CI:0.1–0.7)  
P=0.1096 |
| RE-COVER Shulman et al (2009) NEJM; 361 | Dabigatran versus warfarin in the treatment of acute venous thromboembolism | 0.82 (95% CI:0.45-1.48) |
| EINSTEIN Bauersachs et al (2010) NEJM; 363 | Rivaroxaban (versus enoxaparin followed by a vitamin K antagonist) for symptomatic venous thromboembolism | 0.65 (95% CI: 0.33–1.30; P=0.21) |
| ENGAGE AF-TIMI 48 Giugliano et al (2013) NEJM; 369 | Edoxaban versus warfarin in patients with atrial fibrillation | High dose edoxaban: 0.80 (95% CI:0.71-0.91; P<0.001)  
Low dose edoxaban: 0.47 (95% CI:0.41-0.55; P<0.001) |

Hazard Ratio is a measure of how often a particular event happens in one group compared to how often it happens in another group, over time. Values <1 indicate that major bleeding occurred less often in NOAC treated patients than comparator treated patients.

* Indicates bleeding rate rather than hazard ratio

95%CI – 95% confidence interval

The P-value is an indicator of the statistical significance of result, usually values < 0.05 are classed as being statistically significant. If a P-value is >0.05, this would suggest that that risk of major bleeding with the NOAC is not statistically different from that of the comparator.

In summary, comparing the NOACs with VKAs, antiplatelets or LMWHs, the rates of major bleeding events are similar in some cases, and significantly lower for some treatments.

(c) Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin: Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) Randomized Trial (Healey et al., 2012).

Although this article is neither a systematic review nor a guideline, it is considered of possible relevance to the guidance because it reports on data pertaining to dabigatran and periprocedural bleeding (including from dental procedures) extracted from the RELY clinical trial:

- Data for patients in the RELY trial, who had undergone at least 1 surgery or invasive procedure, was analysed (4591 patients).
- There were no statistically significant differences in major bleeding risk between either dose of dabigatran and warfarin for major surgery (procedures taking >1hour): dabigatran 110 mg versus warfarin: relative risk, 0.78 [95% CI, 0.49–1.24; P=0.30]; dabigatran 150 mg versus warfarin: relative risk, 0.82 [95% CI, 0.53–1.29; P=0.40].
- There were no statistically significant differences in major bleeding risk between either dose of dabigatran and warfarin for minor surgery (procedures taking <1hour): dabigatran 110
mg versus warfarin: relative risk, 1.03 [95% CI, 0.39 –2.71; \( P=0.96 \)]; dabigatran 150 mg versus warfarin: relative risk, 1.75 [95% CI, 0.74–4.14; \( P=0.19 \)].

- There were also no statistically significant differences in bleeding rates between dabigatran (at either dose) and warfarin for different kinds of bleeding events including minor, major, fatal, those requiring reoperation or those requiring transfusion.
- \(~10\%\) of the patients in this analysis underwent dental procedures, although there was no separate analysis of this group.

It should be noted however, that under the conditions of the trial, patients on dabigatran interrupted the drug 49 hours on average before the procedure (compared to an average 114 hour interruption of warfarin), so the bleeding rates reported are not indicative of bleeding if patients were to continue on dabigatran through the procedure.

### 2. Quality and quantity of evidence

Comment here on the quality and quantity of the evidence available for this question. The quality of evidence reflects the extent to which confidence in the estimate of the effect is adequate to support a particular recommendation. Note where evidence is lacking.

- We did not find any direct evidence comparing the bleeding risk for continuing NOAC treatment compared to discontinuing/modifying the drugs (or compared to not taking the drugs at all) for dental (or surgical) procedures.
- The evidence provided above for major bleeding rates, comparing NOACs with VKAs, antiplatelet drugs or LMWHs can only be considered to be very low quality (for the bleeding outcome) according to GRADE. This is because the evidence has serious indirectness in that the bleeding risk refers to major bleeding, not specifically to periprocedural (general or dental) bleeding, and is compared for each NOAC to another treatment, rather than to discontinued/modified NOAC or no treatment. In addition, these clinical trials carry a possible risk of bias since they are pharmaceutical industry funded.
- Where the data for periprocedural bleeding associated with dabigatran was specifically analysed (Healey et al., 2012), it still suffers from indirectness in that it refers to all types of minor and major procedures (the data for dental procedures was not extracted) and the trial was designed to compare dabigatran (interrupted for 2 days) to warfarin (interrupted for 5 days). Continued dabigatran versus interrupted dabigatran would be the relevant comparison for the guidance.
- It is debatable whether this data could be extrapolated to suggest management approaches for NOACs for dental treatments, using the other antithrombotic drugs as comparisons.

**Additional sources of information:**

Advice from existing guidelines (not evidence-based) and product sheets are listed below for information. Some recommend carrying out dental procedures without interrupting the NOAC drug regime, some recommend timing the procedure relative to last dose (so that it takes place at the trough concentration of the NOAC) and some recommend temporarily interrupting drug intake (for a duration that may be dependent on kidney function):

(i) Dental Management of Patients Taking Anticoagulant Drugs Outside a General Hospital Setting: NHS Tayside Integrated Dental Service Local Guidance (Sime, 2013)

This guideline advises for apixaban, rivaroxaban and dabigatran to:

- For all extractions, scaling etc. **proceed without altering the drug regime.** Multiple extractions and surgical procedures are considered safe for patients continuing to take these anticoagulant drugs. When practical, however, the number of teeth to be extracted at a single visit should be limited to 3–4 teeth and it is advisable to assess the extent of bleeding...
after the extraction of the first tooth.
- For patients with a prosthetic valve or other device in place, consult the cardiologist for advice.
- For patients on short courses of anticoagulant, post orthopaedic surgery, delay any elective treatment until the patient is recovered. For emergency treatment in such patients, consult the orthopaedic surgery team before proceeding.
- Where a patient taking these drugs presents with a post operative haemorrhage, contact the Haematology Department for advice.

(ii) Dental Management of Patients Taking Anticoagulant Drugs Outside a General Hospital Setting: NHS Highland Integrated Dental Service Local Guidance (Devennie, 2014)

This guideline which is adapted from the Tayside guidelines above additionally advises:
- If the journey to a hospital with access to transfusion support is greater than 1 hour, discuss with OMFS and on call haematologist.
- Ensure that renal function (eGFR) has been tested within the month prior to dental treatment with significant risk of bleeding. The patient's GMP will check the patient's eGFR periodically, and will be able to carry out appropriate blood tests to ensure it is in the appropriate range.
- If eGFR is low and the patient may be at risk of enhanced anti-coagulation, elective treatment should be postponed. However if the patient is in pain and requires urgent treatment, a referral should be made by telephone to the nearest OMFS service.

(iii) Management of haemorrhage, surgery or other invasive procedures in patients receiving apixaban/rivaroxaban/dabigatran: NHS Greater Glasgow & Clyde Local Guidelines (Tait, 2013)
- While minor dental work (e.g. Prosthodontics, Conservation, Endodontics, Hygiene Phase Therapy & Orthodontics) may be undertaken without omitting any doses of anticoagulant, it is recommended that these procedures are undertaken at least 24h after the last dose of apixaban (18-24h for rivaroxaban, 12h for dabigatran). A local anaesthetic containing a vasoconstrictor should be used, unless contraindicated. Where possible use an infiltration or intra-ligamentary injection. If there is no alternative and an inferior alveolar nerve block is used, the injection should be administered slowly using an aspirating technique.
- For more invasive dental work (e.g. Extractions, Minor Oral Surgery, Periodontal Surgery & Biopsies), endoscopy, cataract surgery or joint injection it is recommended that this is delayed until 24-48h after the last dose of apixaban (24h for rivaroxaban or dabigatran). The next dose of anticoagulant should be deferred until 4h post procedure (or longer if haemostasis has not been achieved).
- If the patient has significant renal impairment (creatinine clearance [CrCl] <50 ml/min) apixaban may have to be omitted for 48h pre-procedure (>24h for rivaroxaban) and an assessment of anticoagulant status undertaken shortly pre-procedure. A prothrombin time (PT) within normal limits (less than or equal to 13s) will normally imply minimal residual apixaban or rivaroxaban effect.
- For dabigatran: If there is renal impairment (creatinine clearance [CrCl] <80 mVmin), dabigatran should be omitted for 36-48h pre-procedure and an assessment of anticoagulant status undertaken shortly pre-procedure. An APTT of less than or equal to 38s would imply minimal residual dabigatran effect.

(iv) Rivaroxaban: A Practical Guide, Belgian Society of Thrombosis and Haemostasis (Beauloye et al., 2012)
- Among minor interventions without significant bleeding risk we understand dental
Interventions such as extraction of 1 to 3 teeth, periodontal surgery, incision of an abscess or positioning of implants.

- Rivaroxaban interruption may not be required for superficial interventions. It is advised to respect a time window of at least 18 hours between the last intake of rivaroxaban and the scheduled procedure. An alternative recommendation could be to respect a time window of at least 24 hours between the last intake of rivaroxaban and the intervention.
- Tooth extractions should avoid the least possible trauma and the wounds need to be sutured. Rinsing the mouth gently with 10 ml of tranexamic acid 5%, 4 times a day for 5 days is recommended.
- The next intake of rivaroxaban should be delayed until hemostasis has been assured. Alternatively, one could wait to resume the intake of rivaroxaban until 24 hours after the intervention.

(v) Practical Guide Dabigatran, Belgian Society of Thrombosis and Haemostasis (Heidbuchel et al., 2013b)

- Dabigatran should not necessarily be discontinued for dental interventions like extraction of 1 to 3 teeth, periodontal surgery, incision of an abscess or positioning of implants. The procedure should ideally be performed 12 hours after last dosing, and precautions (as described above for rivaroxaban) taken.
- If the decision is to discontinue, dabigatran should be stopped 24h prior to tooth extraction or other dental procedure. It should be resumed as soon as haemostasis is achieved. For more extensive interventions, the patient should be referred to a maxillo-facial surgeon.

(vi) European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation (Heidbuchel et al., 2013)

- When the intervention does carry 'no clinically important bleeding risk' and/or when adequate local haemostasis is possible, like some dental procedures (extraction of 1 to 3 teeth, periodontal surgery, incision of abscess, implant positioning), the procedure can be performed at trough concentration of the NOAC (i.e. 12 or 24 h after the last intake, depending on bid or qd dosing) but should not be performed at peak concentration.
- It may be more practical to have the intervention scheduled 18–24 h after the last intake, and then restart 6 h later, i.e. with skipping one dose for bid NOAC.
- The patient can only leave the clinic when the bleeding has completely stopped, and be instructed about the normal postprocedural course and the measures to be taken in case of bleeding i.e. to contact the physician or dentist in case of bleeding that does not stop spontaneously. The physician or dentist (or an informed colleague) has to be accessible in such case.
- For dental procedures, the patient could rinse the mouth gently with 10 ml of tranexamic acid 5%, four times a day for 5 days.

(vii) NICE Clinical Knowledge Summary – Anticoagulation-oral (2014)

Defines bleeding risk of treatments:

- Treatments with 'no clinically important bleeding risk' include: Dental interventions such as extraction of 1 to 3 teeth, periodontal surgery, incision of abscess and implant positioning; Cataract or glaucoma interventions; Endoscopy without surgery; Minor surgery (e.g. abscess incision and small dermatologic excisions).
- Treatments with 'low bleeding risk' include: Endoscopy with biopsy; Prostate or bladder biopsy; Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single trans-septal puncture); Angiography;
Appendix 4 – Considered Judgement Forms

Qu 3 Interrupting NOACs for dental treatment

Pacemaker or implantable cardioverter defibrillator (ICD) implantation (unless complex anatomical setting, e.g. congenital heart disease).

- Treatments with 'high bleeding risk' include: Complex left-sided ablation (pulmonary vein isolation; VT ablation); Spinal or epidural anaesthesia; Lumbar diagnostic puncture; Thoracic surgery; Abdominal surgery; Major orthopaedic surgery; Liver biopsy; Transurethral prostate resection; Kidney biopsy.

Recommends that if the person needs to have surgery or any other invasive procedure, they may need to temporarily stop taking dabigatran, apixaban or rivaroxaban. For procedures associated with no clinically important bleeding risk (i.e. dental treatments as described above), the procedure can be performed as follows:

- Dabigatran: Just before the next dose is due, or approximately 18–24 hours after the last dose of was taken (dabigatran should be restarted 6 hours later). This means one dose of dabigatran may be missed.

- Apixaban: Just before the next dose is due or approximately 18–24 hours after the last dose of was taken (apixaban should be restarted 6 hours later). This means one dose of apixaban may be missed.

- Rivaroxaban: Just before the next dose is due or approximately 18–24 hours after the last dose of rivaroxaban was taken and rivaroxaban should be restarted 6 hours later.

For dental procedures, consider prescribing tranexamic acid 5% mouthwash; instruct the person to use 10 mL as a mouthwash four times a day for 5 days.

Extracts from The Summary of Product Characteristics (SPC) sheets:

**Apixaban:** (www.medicines.org.uk/emc/medicine/249880)

- Eliquis should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. This includes interventions for which the probability of clinically significant bleeding cannot be excluded or for which the risk of bleeding would be unacceptable.

- Eliquis should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. This includes interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled.

- Apixaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

**Rivaroxaban** (www.medicines.org.uk/emc/medicine/21265)

- If an invasive procedure or surgical intervention is required, Xarelto should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.

- Xarelto should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician.

**Dabigatran:** (www.medicines.org.uk/emc/medicine/20760)

- Surgical interventions may require the temporary discontinuation of dabigatran etexilate. Table 3 summarises discontinuation rules before invasive or surgical procedures.
Appendix 4 – Considered Judgement Forms

Qu 3 Interrupting NOACs for dental treatment

<table>
<thead>
<tr>
<th>Renal function (CrCL in mL/min)</th>
<th>Estimated half-life (hours)</th>
<th>Stop dabigatran before elective surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80</td>
<td>~ 13</td>
<td>2 days before</td>
</tr>
<tr>
<td>≥ 50&lt;80</td>
<td>~ 15</td>
<td>2-3 days before</td>
</tr>
<tr>
<td>≥ 30&lt;50</td>
<td>~ 18</td>
<td>4 days before</td>
</tr>
</tbody>
</table>

If an acute intervention is required, dabigatran etexilate should be temporarily discontinued. A surgery/intervention should be delayed if possible until at least 12 hours after the last dose.

3. Consistency

*Comment here on the degree of consistency demonstrated by the available evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence.*

Not applicable due to lack of evidence.

4. Subgroup considerations

*Comment here on any subgroup considerations e.g. should recommendations for patients at high or low risk be considered separately?*

The differences in half-life and dependency on renal function of each of the NOACs should be taken into account when considering possible subgroup recommendations.

5. Balance of effects

*Comment here on the desirable and undesirable effects of the intervention and how substantial the effects are. Indicate whether the overall balance of effects favours the intervention or comparison.*

Recommendations for perioperative NOAC management should be based on risk assessment for thromboembolism (associated with stopping therapy) versus bleeding (associated with continuing therapy). For the NOACs in particular there is a lack of evidence to support estimates of these risks. However, irrespective of the actual likelihood of a thromboembolic event compared to a bleeding complication, the outcome for a thromboembolic event is potentially much more serious.

The NOACs currently lack antidotes, which may affect the risk if excessive bleeding was to occur as a result of dental surgery (e.g. if the recommendation was to continue the NOACs perioperatively). However, the relatively short half-lives of the NOACs allow for anticoagulation levels to be lowered fairly quickly by withdrawing the drug.

6. Generalisability and applicability

*Comment here on how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline.*

The results from the evidence above may not be generalisable to bleeding risk associated with dental procedures.

7. Values and preferences

*How much do people value the main outcomes? Uncertainty and variability in how much those affected value the outcomes of interest can be a reason not to make a strong recommendation and might affect the direction of a recommendation.*
We did not identify any evidence specifically regarding patient preferences around bleeding versus thrombotic events for patients taking NOACs. It seems likely that patients would place a higher value on avoiding a thromboembolism, than avoiding a bleeding complication following a dental procedure, considering the potential outcomes of each. However, there is less certainty around whether most patients would choose to interrupt NOAC treatment or not, considering the lack of evidence and clinical experience to indicate the relative risks of bleeding versus a thromboembolic event for these drugs.

### 8. Acceptability

*Is intervention (e.g. continuing on antiplatelet medication) acceptable to patients, caregivers and providers?*

Either continuing or interrupting a patient’s NOAC treatment may not be acceptable to all patients, caregivers or providers.

### 9. Feasibility

*Comment on cost effectiveness, resource implications and implementation considerations here, if applicable.*

Interrupting anticoagulant medication may delay treatment and be less convenient for patient, dentist (and prescribing clinician, if contacted).

### 10. Other factors

*Indicate here any other factors that were taken into account when assessing the evidence base.*

The recommendations made in other guidelines that were based on expert opinion were noted.

### 11. Recommendation for guidance

*Summarise the group’s judgements for the recommendation e.g. which criteria were most influential for the decision. Record any dissenting opinion within the group and how a consensus was reached, if applicable.*

Proposed recommendation:

The group agreed on a recommendation to **suggest that dentists advise patients to interrupt their NOAC medication** by missing a single dose on the morning of their dental treatment.

The group agreed that there is a lack of direct evidence to favour either continuing or interrupting NOAC treatment for invasive dental treatments. The recommendation was based on taking into consideration the known characteristics of these drugs, such as their short half-lives and rapid onset of action, recommendations given by the drug manufacturers and other guidelines, the balance of likely effects of each option, and the expertise of the group members.

It was noted that, unlike the conventional anticoagulants and antiplatelet drugs, the short half-lives and rapid onset of action of the NOACs allow for relatively rapid modification of anticoagulation status, minimising the time period of therapeutically suboptimal anticoagulation and likely risk of a thromboembolic event.

The group felt that because of the lack of clinical evidence and experience with dental patients taking these drugs, and lack of reversal agents, a cautious approach was merited. It was agreed that this should be a **weak recommendation** because of the lack of evidence and the fine balance between the potential risks and benefits of the treatment options.
The following points should also be included in the recommendation:

- For patients on time-limited drug treatment (e.g. post-orthopaedic surgery, DVT treatment, ablation cardioversion) defer invasive dental procedures if possible. If medication is for an elective surgical procedure, consult with physician.
- Dentists should try to avoid carrying out procedures within 6 hours of the patient’s last dose of NOAC, while the drug will be at peak concentration. Invasive dental treatment should be carried out first thing in the morning to allow for monitoring, and treatment of unexpected bleeding issues (this practice advice would be feasible if the patient was advised to miss their dose of medication on the morning of treatment).
- Haemostatic packing and suturing should be carried out routinely.
- Patients should wait until haemostasis is achieved, or a minimum of 4 hours before restarting medication. Assuming bleeding has stopped, patients on a twice daily medication (apixaban or dabigatran) should take the next dose at the usual time; patients on a once daily schedule (rivaroxaban) may take their missed dose of medication 4 hours after treatment and then continue as normal the following day.
- For multiple extractions (up to 3), extract one tooth first and assess bleeding before continuing, similarly, limit scaling to up to 3 teeth initially.
- For more than 3 extractions, or extractions likely to result in large wounds (e.g. adjacent teeth) the dentist should consult with a medical practitioner to consider whether to discontinue for more than a single dose, particularly if the patient is taking dabigatran since dabigatran levels are more dependent on renal function. For all patients, if the dentist is unsure about any aspect of the patient’s treatment management, they should be encouraged to liaise with the medical practitioner.

12. Additional Information

Include any further information that is relevant to the recommendation.

Further considerations and revisions to recommendation

During further development of the draft guidance, after these initial considered judgements had taken place, the likely risk of post-operative bleeding complications associated with the various dental procedures was reassessed and revised. This re-categorisation of dental treatments was based on extensive clinical experience and expertise and identified a small group of treatments which while likely to cause some bleeding were judged to have a low risk of bleeding complications compared to the other dental surgical procedures. The fact that these treatments are defined as being of low bleeding complication risk was judged to change the balance of risk, with risk of thrombosis now outweighing the reassessed bleeding risk for those treatments.

The original recommendation was modified according to this rationale, so that now dentists carrying out these ‘lower risk’ treatments would not advise the patient to modify their medication. The initial recommendation was revised to be as follows:

Treat patients requiring dental treatment that is unlikely to cause bleeding or with a low risk of bleeding complications without interrupting their NOAC therapy.

Advise patients requiring dental treatment with a higher risk of bleeding complications to miss a single dose of apixaban, dabigatran or rivaroxaban on the morning of their dental treatment.

Both recommendations were rated as weak/conditional.
Qu 4 Interrupting injectable anticoagulants for dental treatment

Considered Judgement for Recommendations

Key question 4: Should injectable anticoagulants be continued or interrupted for dental treatment? (To include dalteparin, enoxaparin and tinzaparin)

Evidence Appraisal
refs: G3

1. Summary of evidence

Summarise the evidence for the effects of the intervention on the important outcomes e.g. what effect does continuing antiplatelet treatment have on the risk of bleeding? Ideally evidence will be from systematic reviews or guidelines.


These high quality guidelines (AGREEII rating 5/7) include recommendations relevant to patients requiring dental treatment. In addition to providing recommendations on whether patients should continue on warfarin or aspirin for dental treatment, these guidelines also considered the periprocedural bleeding risk associated with heparin bridging. 1 RCT (214 patients) compared bleeding events following dental extractions, where the patients received LMWH bridging versus continuing their oral anticoagulant, and found that any bleeding was minor and that there was no difference between the 2 groups.

2. Quality and quantity of evidence

Comment here on the quality and quantity of the evidence available for this question. The quality of evidence reflects the extent to which confidence in the estimate of the effect is adequate to support a particular recommendation. Note where evidence is lacking.

- Only 1 RCT was found (reported in the guideline of Armstrong et al, 2013), relating to the risk of bleeding for patients taking injectable LMWH and having dental treatment. The results suggested that the risk of bleeding is probably similar between LMWH bridging and oral anticoagulant continuation in dental procedures. This study assessed nadroparin calcium for bridging, rather than the LMWHs being considered here. It is also worth noting that periprocedural bridging is likely to involve therapeutic doses of LMWH whereas patients presenting for primary care dental care might be more likely to be taking lower prophylactic doses.
- This is likely to be insufficient evidence on which to base a recommendation.

Advice from existing guidelines and product sheets are listed below for information:

Dental Management of Patients Taking Anticoagulant Drugs Outside a General Hospital Setting: NHS Tayside Integrated Dental Service Local Guidance: (Sime, 2013)

This guideline advises:
- Low dose dalteparin (Fragmin; 5000units od), used for prophylaxis of Deep Vein Thrombosis, is equivalent to warfarin with target INR of 2-3 and could be managed as such.
- Due to the short half life, the fragmin could be omitted 24 hours prior to an elective
Appendix 4 – Considered Judgement Forms

Qu 4 Interrupting **injectable anticoagulants** for dental treatment

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**extraction if there are particular concerns regarding bleeding.**

- Higher therapeutic doses may cause bleeding problems and it would NOT be appropriate to proceed with extractions etc. whilst the patient is on such a treatment regime. Patient who require such a regime are almost certainly at high risk of a thrombotic event and there would be serious concerns regarding discontinuation of the fragmin regime. Where possible, dental work should be delayed.

- If dental treatment cannot be delayed, then the management of the patient must be discussed with the physician in charge of the anticoagulant treatment.

**Dental Management of Patients Taking Anticoagulant Drugs Outside a General Hospital Setting:**

**NHS Highland Integrated Dental Service Local Guidance** (Devennie, 2014)

This guideline which is adapted from the Tayside guidelines above advises:

- Low dose **enoxaparin** (Clexane; 40mg od), used for prophylaxis of Deep Vein Thrombosis, is equivalent to warfarin with target INR of 2-3 and could be managed as such.

- Due to the short half life, the enoxaparin could be omitted 24 hours prior to an elective extraction if there are particular concerns regarding bleeding.

Extracts from the drug SPC sheets refer to bleeding but are not necessarily specific to surgical bleeding and certainly not specific to dental, and as such can only be considered as indirect information:

**Dalteparin:** ([www.medicines.org.uk/emc/medicine/26896](http://www.medicines.org.uk/emc/medicine/26896))

- The SPC for Fragmin states that 'The risk of bleeding is depending on dose. Most bleedings are mild. Severe bleedings have been reported, some cases with fatal outcome.'

**Enoxaparin:** ([www.medicines.org.uk/emc/medicine/10054](http://www.medicines.org.uk/emc/medicine/10054))

- The SPC for Clexane states that 'In clinical studies, haemorrhages were the most commonly reported reaction. These included major haemorrhages, reported at most in 4.2% of the patients (surgical patients). Some of these cases have been fatal.'

- In surgical patients, haemorrhage complications were considered major: (1) if the haemorrhage caused a significant clinical event, or (2) if accompanied by an haemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial haemorrhages were always considered major.

- The SPC also states that no increased bleeding tendency is observed in the elderly within the prophylactic dosage ranges while elderly patients (especially patients aged 80 years and above) may be at an increased risk for bleeding complications within the therapeutic dosage ranges.

**Tinzaparin:** ([www.medicines.org.uk/emc/medicine/2623](http://www.medicines.org.uk/emc/medicine/2623))

- The SPC for Innohep states that 'Based on pooled study results, from a clinical trial programme where 3167 patients received Innohep, the overall bleeding risk was approximately 11% while the risk of major bleeding was approximately 0.5%.'

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**3. Consistency**

*Comment here on the degree of consistency demonstrated by the available evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence.*

Insufficient evidence to comment on consistency.

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**4. Subgroup considerations**

*Comment here on any subgroup considerations e.g. should recommendations for patients at high or low risk be considered separately?*

It may be appropriate to make separate recommendations for patients taking injectable
anticoagulants at prophylactic versus therapeutic doses and for different treatment periods.

**5. Balance of effects**  
Comment here on the desirable and undesirable effects of the intervention and how substantial the effects are. Indicate whether the overall balance of effects favours the intervention or comparison.

Recommendations for perioperative injectable anticoagulant management should, as for the oral anticoagulants, be based on risk assessment for thromboembolism versus bleeding. Although it may be that the risk of thromboembolism is less than the risk of bleeding complications, the outcome is potentially much more serious.

**6. Generalisability and applicability**  
Comment here on how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline.

The only evidence identified referred to the LMWH nadroparin, which is not licensed for use in the UK. It is not clear whether the bleeding risk suggested by this study can be generalized to the LMWHs currently in use in the UK.

**7. Values and preferences**  
How much do people value the main outcomes? Uncertainty and variability in how much those affected value the outcomes of interest can be a reason not to make a strong recommendation and might affect the direction of a recommendation.

It seems likely, as with other antithrombotics, that patients would place a higher value on avoiding a thromboembolism, than avoiding a bleeding complication following a dental procedure, considering the potential outcomes of each. The risks for bleeding and thromboembolism for patients taking LMWHs therapeutically versus prophylactically are likely to differ.

**8. Acceptability**  
Is intervention (e.g. continuing on antiplatelet medication) acceptable to patients, caregivers and providers?

Either continuing or interrupting a patient’s injectable anticoagulant treatment may not be acceptable to all patients, caregivers or providers.

**9. Feasibility**  
Comment on cost effectiveness, resource implications and implementation considerations here, if applicable.

Interrupting LMWH therapy may be less convenient for patient, dentist and prescribing clinician.

**10. Other factors**  
Indicate here any other factors that were taken into account when assessing the evidence base.

Patients presenting for dental treatment are likely to be taking prophylactic doses of LMWHs. However, it is conceivable that dental patients could be undergoing short-term peri procedural bridging therapy which involves higher therapeutic doses of LMWH. It may not be evident to the dentist which dose the patient is taking or for how long without contacting their general medical practitioner.
Appendix 4 – Considered Judgement Forms

Qu 4 Interrupting **injectable anticoagulants** for dental treatment

### 11. Recommendation for guidance

Summarise the group’s judgements for the recommendation e.g. which criteria were most influential for the decision. Record any dissenting opinion within the group and how a consensus was reached, if applicable.

State the recommendation for the guidance, clearly indicating the strength, using GRADE appropriate wording.

It was noted that, as for the NOACs, there is a lack of direct evidence regarding dental treatment on patients taking injectable anticoagulants. After discussion of the criteria above, the group agreed that a recommendation regarding the treatment management options of either continuing or interrupting treatment with injectable anticoagulants should not be made. Instead the guidance should advise that for patients taking injectable anticoagulants and requiring invasive dental treatment, the **dentist should consult with a medical practitioner**.

The basis for this decision is that patients taking these drugs are likely to have varied medical conditions and drug regimes, such that the dentist may need further information to make a reasonable judgement on treatment management. For example, the drug dosage could be once or twice a day and prophylactic or therapeutic. Patients taking the higher therapeutic doses are likely to have a higher bleeding risk, but may also have a higher risk of a thromboembolic event, making interrupting their anticoagulant inappropriate. For these patients the appropriate course of action would be to contact their general medical practitioner for more advice and to establish the length of drug treatment, so that delaying the dental procedures could be considered.

In addition, the number of patients taking LMWHs and presenting for dental treatment is likely to be small, so consulting for each one would not confer a substantial burden on dental and medical practitioners.
Qu 5 Additional measures to minimise bleeding

### Considered Judgement for Recommendations

#### Key question 5: Should other measures be used for dental treatment on patients taking anticoagulants or antiplatelet drugs?

#### Evidence Appraisal

**refs:**

SR4, G4

1. **Summary of evidence**

_Summarise the evidence for the effects of the intervention on the important outcomes e.g. what effect does continuing antiplatelet treatment have on the risk of bleeding? Ideally evidence will be from systematic reviews or guidelines._

(a) Hemostatic mouthwashes in anticoagulated patients undergoing dental extraction. (Patatanian and Fugate, 2006) SR4

The aim of this systematic review was to evaluate the efficacy and safety of local acting hemostatic agents in patients who are undergoing dental extraction(s) and are taking oral anticoagulants.

- 8 small studies (585 patients in total) were considered in which the indications for anticoagulation, the target INR ranges, the dental treatments and the anticoagulation and bleeding management strategies varied.
- 2 RCTs which directly compared tranexamic acid mouthwash with placebo in patients on uninterrupted anticoagulant both found a significant decrease in bleeding incidences.
- 1 trial compared 3 groups of patients, 1 treated with tranexamic acid, gelatin sponges and sutures, 1 with fibrin glue, gelatin sponges and sutures, 1 with just gelatin sponges and sutures. There was no statistically significant difference in bleeding rate between the 3 groups.
- The authors concluded that patients receiving uninterrupted anticoagulant and using hemostatic mouthwashes had no greater and, in some cases, lesser bleeding incidence compared with various other treatment groups (including interrupted or uninterrupted anticoagulant, autologous fibrin glue with uninterrupted anticoagulant, and reduced anticoagulant with heparin bridge). No severe adverse effects were reported.

(b) Surgical Management of the Primary Care Dental patient on Warfarin. North West Medicines Information Centre (Randall, 2007) G4

These guidelines (AGREEII rating 5/7) make clear recommendations based on careful review of the evidence available at the time of development. The key recommendation for the clinical question addressed in this considered judgement is:

**Tranexamic acid mouthwash should not be used routinely in primary dental care**

- Tranexamic acid was assessed in 9 studies, either as the only haemostatic agent compared to no treatment or placebo, or in addition to other measures.
- Pooling of data from 5 of the studies where tranexamic acid mouthwash was used, indicated a rate of delayed postoperative bleeding requiring treatment of 3.6% compared to a serious postoperative bleeding rate of 5.4% when results were pooled from studies where local haemostatic measures and suturing were used without tranexamic acid (although it is not
clear what the statistical significance of the pooled data is).

- The guideline concludes that when used alone with no local haemostatic dressing, tranexamic acid mouthwash reduces postoperative bleeding compared to placebo mouthwash, but when used in combination with local haemostatic measures and suturing, tranexamic acid mouthwash provides little additional reduction in postoperative bleeding.

(c) Topical application of tranexamic acid for the reduction of bleeding (Ker et al., 2013)
This Cochrane Review assessed the effects of the topical administration of tranexamic acid in the control of bleeding.

- 29 RCTs involving 2612 participants were assessed. 28 trials involved patients undergoing surgery, 4 of these trials were for dental procedures, and 1 trial involved patients with epistaxis (nosebleed). Tranexamic acid reduced blood loss by 29% (pooled ratio 0.71, 95% CI: 0.69-0.72; P < 0.0001).
- The effect on the risk of thromboembolic events was uncertain.
- Data from the 4 dental trials was not analysed separately, but 3 of the trials were assessed in Patatanian and Fugate (2006) and Randall (2007); no more recent trials considering tranexamic acid for dental procedures were identified in this review.

2. Quality and quantity of evidence

Comment here on the quality and quantity of the evidence available for this question. The quality of evidence reflects the extent to which confidence in the estimate of the effect is adequate to support a particular recommendation. Note where evidence is lacking.

- The evidence for the effect of tranexamic acid on bleeding after dental treatment comes from a series of small studies with various interventions and comparisons, making it difficult to perform any kind of formal meta-analysis or statistical pooling. Simple pooling of data from some of the studies (Randall, 2007) suggests that tranexamic acid might be less beneficial when used in addition to other haemostatic measures. The quality of evidence contained in Patatanian and Fugate (2006) and Randall (2007) regarding this lack of significant effect of tranexamic acid or fibrin glue when carried out in addition to haemostatic dressing and sutures was rated as low according to GRADE. This is because the evidence comes from fairly small controlled trials which lack blinding and/or randomisation.
- The Cochrane review (Ker et al., 2013) found that topical tranexamic acid significantly reduces surgical bleeding. The evidence for this outcome was rated in the review as low quality, according to GRADE criteria. This was a consequence of serious risk of bias (included trials at unclear or high risk of bias for allocation concealment) and serious inconsistency (substantial statistical heterogeneity detected). In terms of the recommendations for this guidance, this evidence would be further downgraded to rate as very low because of the indirectness resulting from the majority of the trials being non-dental.
- No recent studies were identified.

In summary, while topical tranexamic acid appears to have a significantly beneficial effect in reducing bleeding in dental and other types of surgery (compared to placebo or no treatment), it is less clear whether it offers significant benefit when used in combination with other haemostatic measures.

Recommendations from other guidelines for information:

British Committee for Standards in Haematology Guidelines for the Management of Patients on Oral Anticoagulants requiring Dental Surgery. (Perry et al., 2007)
- Recommends that the risk of bleeding in patients on oral anticoagulants undergoing dental surgery may be minimised by the use of oxidised cellulose (Surgicel) or collagen sponges and
Management of dental patients taking common hemostasis-altering medications. (Aframian et al., 2007)
- Recommends that a 2-day regimen of postoperative 4.8% tranexamic acid mouthwash is beneficial after oral surgical procedures in patients on warfarin.
- Again, this recommendation is based on some of the studies considered in the summary of evidence above.

- In patients who require a minor dental procedure, we suggest continuing VKAs with coadministration of an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure instead of alternative strategies.
- This recommendation is based in part on low quality evidence from studies which compared continued anticoagulation and use of tranexamic mouthwash with interrupting anticoagulant (see Warfarin Considered Judgement form for more detail).

- For dental procedures on patients taking dabigatran, rivaroxaban or apixaban consider prescribing tranexamic acid 5% mouth wash; instruct the person to use 10 ml as a mouth wash 4 times a day for 5 days.

3. Consistency
Comment here on the degree of consistency demonstrated by the available evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence.

Some articles suggest that the use of tranexamic may be beneficial; others consider that the balance of evidence and other factors favour a recommendation not to use tranexamic acid routinely.

4. Subgroup considerations
Comment here on any subgroup considerations e.g. should recommendations for patients at high or low risk be considered separately?

5. Balance of effects
Comment here on the desirable and undesirable effects of the intervention and how substantial the effects are. Indicate whether the overall balance of effects favours the intervention or comparison.

While topical tranexamic acid may reduce surgical blood loss, the effect on the risk of thromboembolic events is uncertain.

6. Generalisability and applicability
Comment here on how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline.
There were no reasons identified to suggest that the results from the evidence above would not be generalisable.

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<th>7. Values and preferences</th>
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<td>How much do people value the main outcomes? Uncertainty and variability in how much those affected value the outcomes of interest can be a reason not to make a strong recommendation and might affect the direction of a recommendation.</td>
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<tr>
<td>May be expensive and inconvenient for reasons below.</td>
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<td>Comment on cost effectiveness, resource implications and implementation considerations here, if applicable.</td>
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<tr>
<td>Tranexamic acid is not in the dental formulary and therefore can only be prescribed privately making it expensive. It is also not available as a mouthwash so has to be made up and used off-licence.</td>
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<td>The group agreed that the guidance should not make a recommendation on the use of tranexamic acid for these patients. This is based on the fact that there is no evidence to suggest that it offers benefit when used in conjunction with other haemostatic measures, that it is expensive, and is not in the NHS dental practice formulary so is not easily available to primary care dentists. In addition tranexamic acid is not available as a mouthwash so would have to be prescribed off licence. It was suggested that these points are noted in the guidance to clarify the issues around tranexamic acid.</td>
</tr>
</tbody>
</table>
References


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Brewer, A. Management of patients requiring dental treatment who are taking the newly introduced oral anticoagulants. Oral & Maxillofacial Surgery Department, The Royal Infirmary, Glasgow. April 2012


Common questions and answers on the practical use of oral anticoagulants in non-valvular atrial fibrillation. UK Medicines Information, South West Medicines Information and Training and Regional Drug and Therapeutics Centre (Newcastle). (www.swmit.nhs.uk/FAQs.htm)


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