Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs

Guidance Development Methodology

March 2022

Scottish Dental Clinical Effectiveness Programme
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NICE has accredited the process used by the **Scottish Dental Clinical Effectiveness Programme** to produce the second edition of its *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs* guidance. Accreditation is valid for 5 years from 15 March 2021. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

For further information about SDCEP's accreditation, visit www.sdcep.org.uk/how-we-work/nice-accreditation.

Contents

1 Overview of the SDCEP Guidance Development Process

SDCEP first published *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs* in 2015. The first edition of the guidance was developed following SDCEP's standard guidance development process (www.sdcep.org.uk/how-we-work/guidance-development-process/), which is accredited by the National Institute for Health and Care Excellence (NICE; www.nice.org.uk/about/what-we-do/accreditation). Details of the methodology used, including the literature searches, evidence appraisal and synthesis, considered judgements and development of the recommendations, and external consultation are documented in the *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs Guidance Development Methodology (2015)* which is available on request.

A scheduled full review of the topic was initiated in 2020 in accordance with SDCEP's five-year guidance review policy and the updated second edition of the guidance was published in 2022. The updating followed the relevant steps of the process described in the SDCEP *Guidance Development Process Manual* (Version 2.0, February 2019), with modifications appropriate for an update, as outlined below:

- Reconvening of Guidance Development Group (GDG);
- Scoping including horizon scanning literature review and research on stakeholder attitudes to the topic and existing guidance;
- Agreement on scope and key clinical questions;
- Preparation of draft updated guidance including:
  - Systematic literature review,
  - Evidence appraisal, synthesis and summary,
  - Considered judgements,
  - Review and revision of existing recommendations, formulation of new recommendations and grading;
- External peer review;
- Review of peer review feedback and revision of the guidance and other related products;
- Final draft sign off;
- Design for publication and print;
- Dissemination and implementation.

Specific details of the methodology used for the development of the second edition 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/) 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 Guidance Development Group (GDG) for this guidance update comprised individuals from a range of branches of the dental and medical professions and two patient representatives.

Name	Role
Steven Johnston (Chair)	Senior Dental Officer, Public Dental Service, NHS Orkney
Carol Armstrong	Dental Therapist (Special Care), NHS Dumfries & Galloway
Dean Barker	Consultant in Restorative Dentistry, University of Aberdeen Dental Hospital & Institute of Dentistry
Nicholas Beacher	Clinical Lecturer, University of Glasgow; Honorary Specialty Dentist/ Specialist in Special Care Dentistry, NHS Greater Glasgow & Clyde
Mark Bradley	General Dental Practitioner, Kilmarnock
Adrian Brady	Consultant Cardiologist, NHS Greater Glasgow & Clyde; Honorary Professor, University of Glasgow
Diane Eaton	Independent Anticoagulation Patient Expert, formerly of Anticoagulation UK
Patricia Green	Patient Representative, Aviemore
Steve McGlynn	Specialist Principal Pharmacist (Cardiology), NHS Greater Glasgow & Clyde; Honorary Senior Teaching Fellow, University of Strathclyde
Namita Nayyer	Consultant in Oral Surgery, NHS Borders
Gillian Nevin	General Dental Practitioner, Coupar Angus; Assistant Postgraduate Dental Dean (CPD), NHS Education for Scotland
Christine Randall	Lead Pharmacist for Dental Medicines Information and Pharmacovigilance and Assistant Director, North West Medicines Information Centre, Liverpool
Simon Randfield	General Practitioner, NHS Forth Valley
Ryan Rodgers	Consultant Haematologist, NHS Greater Glasgow & Clyde
Elizabeth Theaker	Consultant in Oral Medicine/Honorary Senior Lecturer, Dundee Dental Hospital and School
John Wall	General Dental Practitioner, Peebles

Scheduled meetings of the GDG took place as part of the guidance development process.

3 Scoping Research

SDCEP's research collaborators TRiaDS (Translation Research in a Dental Setting; www.triads.org.uk) carried out research during the development of the first edition of the *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs* guidance and after its publication. Following the TRiaDS framework for translating guidance recommendations into practice,[1] this focused on evaluating whether users of the guidance had changed their practice since its publication and investigated factors that influence practitioner behaviour with respect to aspects of the recommended management of dental treatment for patients taking anticoagulant or antiplatelet medication. This work was presented to the guidance development group (GDG) convened to update the guidance.

TRiaDS carried out additional research to inform the scope and content of the guidance update. Dental practitioner and patient scoping interviews were conducted in June 2021, to gain feedback on the first edition of the guidance. Invitations to participate were sent to the Scottish Dental Practice Based Network (SDPBRN) Rapid Evaluation Practitioners, NHS Tayside's Public Involvement Team and the Patient and Public Involvement and Engagement Co-ordinator for the Health Service Research Unit in the University of Aberdeen, for distribution to their network members. Practitioners were asked about their use of the guidance, challenges to implementing the recommendations and suggestions for additional content or improvements. Patient experiences and views on the resources provided with the guidance were also sought via a survey posted online by relevant patient support organisations. Feedback and suggestions for improvements were considered by the GDG during the development of the updated guidance and resources.

The scope for the guidance update agreed by the GDG is included in Appendix 1. The aims and target patient groups are essentially the same as for the first edition of the guidance, with the addition of patients taking edoxaban. The scope for the update also recognises that use of the guidance could impact on medical professionals including general medical practitioners, pharmacists, haematologists and cardiologists involved in the care of patients taking anticoagulants or antiplatelet drugs.

4 Key Clinical Questions

The second edition of the guidance considered the same five clinical questions addressed in the first edition of the guidance (with the inclusion of edoxaban in Question 3), as listed below.

Key recommendations were not made in the first edition of the guidance for Questions 4 (injectable anticoagulants) and 5 (additional haemostatic measures) because of insufficient evidence and other considerations. For the second edition, the GDG considered whether the existing recommendations for Questions 1-3 should remain extant and whether key recommendations could be made for Questions 4 and 5.

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 DOACs be continued or interrupted for dental treatment? (To include apixaban, dabigatran, rivaroxaban and edoxaban)
4. Should the injectable anticoagulants be continued or interrupted for dental treatment? (To include dalteparin, enoxaparin and tinzaparin)
5. Should other measures to minimise bleeding be used for dental treatment on patients taking anticoagulants or antiplatelet drugs?

As for the first edition of the guidance, these clinical questions informed the evidence search strategy and formed the basis for the evidence summaries and considered judgements made by the GDG.

5 Literature Search

Since the clinical questions for the guidance update were essentially as for the first edition of the guidance, the evidence search approach was based on that used previously (detailed in *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs Guidance Development Methodology* (2015); available on request). Preliminary scoping searches suggested that a number of systematic reviews directly relevant to the clinical questions had been published since the first edition of the guidance. Consequently, the search combined anticoagulant/antiplatelet terms with dental terms, but not with terms for other types of surgical procedure or for general bleeding risk as used in the wider searches carried out for the first edition of the guidance.

In accordance with SDCEP's standard process, the evidence search and screening focussed on systematic reviews and guidelines, before considering primary studies.

For this guidance update, a comprehensive literature search of online databases MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, CINAHL, Epistemonikos and Database of Abstracts of Reviews of Effects was conducted by the Cochrane Oral Health Information Specialist on 14 April 2021 and updated on 19 July 2021. The searches of MEDLINE, EMBASE and CINAHL were from the date of the search for the first edition of guidance (October 2014). Filters for systematic reviews and guidelines were applied. The searches retrieved 560 articles. Details of the searches can be found in Appendix 2.

Potentially eligible articles were identified independently by two reviewers from the list of titles and abstracts retrieved. An article was considered potentially eligible if it met both 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 one or more electronic databases and details of included studies. An article was included as a guideline if it made recommendations for clinical practice.

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

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

6 Evidence Appraisal and Synthesis

Eligible articles that were potentially relevant for each of the key clinical questions were identified and appraised for their quality of development, evidence base and applicability to the clinical questions.

Of the 26 eligible systematic reviews identified, the 20 most recent were fully appraised. The remaining six older reviews described the same studies or reported the same conclusions as more recent reviews. A reviewer assessed the full text of each article and extracted the information applicable to the clinical question(s).

For the updating of this guidance, systematic reviews were assessed for methodological quality using AMSTAR criteria.[2,3] The rating for overall confidence in each systematic review was assigned as a level from low to high, rather than using a numerical score. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach was used to assess and rate the certainty of the reported evidence (www.gradeworkinggroup.org). The evidence certainty was rated as high, moderate, low or very low. The GRADE framework is a widely accepted system for grading both the evidence and the recommendations and is used internationally by other guideline producers.

The individual data extraction and evidence appraisal forms for each of the relevant articles are available on request. A summary of the 20 systematic reviews appraised to inform this guidance, including the AMSTAR and GRADE ratings, can be found in Appendix 3. Details of the evidence reported in the reviews are included in the Considered Judgement Forms in Appendix 4.

Although three guidelines with relevance to the clinical questions were identified for this update, they either did not describe the methodology used or were mainly non-dental and so were not formally appraised.

7 Considered Judgements, Review and Development of Recommendations

The synthesised evidence for each clinical question, published since the first edition of the guidance, was summarised (see Appendix 4) and distributed to the GDG to inform and facilitate the review and updating of the recommendations in the guidance. Significant changes to the evidence base since the development of the recommendations in the first edition of the guidance were noted.

The process for the review of the recommendations followed the GRADE approach, with considered judgements based on the certainty of evidence, balance of benefits and harms, patient values and preferences, and the acceptability and feasibility of the treatment options. The impact of potential barriers to implementation of the recommendations, which were identified during development of the first edition and after publication, through stakeholder involvement and external consultation, was also considered. The relative importance of each of the criteria for a given recommendation was decided by the GDG. Decisions on the recommendations were reached by group consensus.

According to GRADE the strength of a recommendation may be defined as:

Strength	**Details**
Strong recommendation	The guideline panel is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). A strong recommendation implies that most or all individuals will be best served by the recommended course of action.
Weak (or **conditional**) recommendation	A weak recommendation is one for which the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists. A weak recommendation implies that not all individuals will be best served by the recommended course of action.

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. The recommendation strength (strong or conditional) and the certainty of evidence rating (high, moderate, low or very low) are stated in the guidance

along with each recommendation, for clarity. Brief explanations of the basis for each recommendation are also included in the guidance text.

The considered judgement process described above was followed both for reviewing the key recommendations developed for the first edition of the guidance, and for developing new recommendations. The recommendations are marked in the guidance as follows to indicate whether there has been any change, with the date signifying when the underpinning evidence was reviewed through the considered judgement process:

- [unchanged 2022] indicates that the recommendation from the previous edition of the guidance has been reviewed and is unchanged.
- [amended 2022] indicates that the recommendation from the previous edition of the guidance has been reviewed and amended during the guidance updating. An explanation of the amendment is provided in the guidance text.
- [new 2022] indicates a new recommendation developed for this edition of the guidance.

8 External Peer Review

Topic experts were invited to contribute to targeted external peer review in November 2021, by providing feedback on the updated guidance, the recommendations and, in particular, the guidance updating process used. The 14 peer reviewers who provided feedback represented a range of dental and medical expertise and experience. Some of the peer reviewers also had knowledge of guidance methodology.

The peer reviewers were asked to declare any interests.

Name	Role
Susan Baines	Consultant in Special Care Dentistry, NHS Lothian
Malcolm Balfour	General Dental Practitioner, Kilmarnock
Mark Burrell	Specialty Dentist OMFS/Clinical Lead OMFS, Aberdeen Royal Infirmary
Moira Duncan	General Dental Practitioner, Kircaldy
Trudy Foster	General Medical Practitioner, Falkirk
Kirsteen Griffiths	Senior Pharmacist, Anticoagulant Services, NHS Ayrshire and Arran
Mohammed Kahn	Consultant Haematologist, Aberdeen Royal Infirmary
Andrew Kinnear	Dental Officer, NHS Shetland; Oral and Maxillofacial Surgery Coordinator for Shetland
Thomas Lamont	Senior Lecturer and Honorary Consultant in Restorative Dentistry, Dundee Dental School and Hospital

Laura MacDonald	Managing Editor, Cochrane Oral Health
Michaelina Maclusky	Honorary Consultant Oral Surgeon, NHS Tayside; Senior Clinical Lecturer University of Dundee
Chris McDonald	Consultant Oral and Maxillofacial Surgeon, NHS Grampian
Chloe Wishart	Clinical Haematology Pharmacist, Liverpool University Hospitals NHS Foundation Trust
Abhi Pal	President, College of General Dentistry

All comments received through the external peer review process were reviewed, the feedback was considered by the GDG, and the guidance was amended accordingly prior to publication.

9 Updating the Guidance

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

10 Conflicts of Interest

All contributors to SDCEP, including members of the GDG and external expert peer reviewers, 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 details of interests 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.

Declared interests which could have potentially constituted a conflict of interest were considered by the SDCEP Programme Development Team (PDT) and the GDG chair 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).

Further information on SDCEP's approach to conflicts of interest is available in the SDCEP *Guidance Development Process Manual* (Version 2.0, February 2019).

Details of the Declarations of Interest for all individuals involved in the *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs* guidance update project are available on request. A summary of the disclosures, the consideration of potential conflicts of interest, and management decisions are provided in the following table.

Summary of Disclosures
All of the GDG members, peer reviewers and members of the SDCEP PDT completed and returned the Declaration of Interests form. Paid and unpaid professional roles involving the provision of dental or medical care or education were not considered to be a conflict of interests. Several group members declared membership of committees or societies related to their healthcare roles, but this was also considered unlikely to lead to a conflict of interest. The Clinical Chair of the group had no conflicts of interests. Four of the sixteen external GDG members declared direct financial interests relevant to the guidance topic which could potentially cause, or be perceived to cause, conflicts of interest. One peer reviewer's employment could, as an indirect financial interest, potentially cause, or be perceived to cause, a conflict of interest. None of the SDCEP PDT members had any interests relevant to the guidance.
Details of Interest(s)
1. One GDG member declared receiving occasional teaching, training, lecture and speaker remuneration.
2. One GDG member declared that they had shares in GSK related to the manufacture of dental materials.
3. One GDG member declared receiving sponsorship for lectures at international meetings, consultancy fees and previous research funding from pharmaceutical companies that develop and manufacture anticoagulant drugs.
4. One GDG member declared receiving consultancy and lecture fees from pharmaceutical companies producing haemophilia treatments.
5. One of the peer reviewers is employed by a not-for-profit publisher of healthcare systematic reviews, funded by NIHR.
Consideration of potential to cause conflict(s) of interest *Are these interests likely in any way to affect the impartiality of the group member in his/her role in the guidance development e.g. in making recommendations?*
1. These activities were considered to be part of the individual's professional role in dental education and unlikely to cause any bias. It was agreed that no specific action was required.
2. It was considered unlikely that the guidance would specifically recommend any particular dental materials and, in that case, unlikely that the declared interest would cause a conflict of interests.
3. The guidance only relates to dental treatment and not to prescribing of anticoagulant or antiplatelet drugs. Furthermore, the inclusion of the various anticoagulant and antiplatelet drugs in the guidance is dependent on community prescribing the UK and so is not subject

	to influence by any group member. Therefore, the declared interests were judged unlikely to cause any bias.
4.	The declared interests relate to haemophilia and are not specific to the guidance topic. Consequently, they were not considered to cause a conflict of interests.
5.	Relevant systematic reviews contribute to the evidence base for the recommendations in the guidance and it could be perceived that the peer reviewer could influence the inclusion of specific systematic reviews, for the benefit of the publisher. However, the reviews included in the guidance are identified through systematic searches and independent screening against pre-defined criteria, therefore their inclusion is not subject to potential bias by the peer reviewer.
Decision on the management of the conflict(s) of interest *Should the group member be excluded from any stages of guidance development or decisions, or be asked to withdraw from the process?*	
As the declared interests 1, 3, 4 &5 were not considered to cause conflicts of interests, it was agreed that no specific action was required. Declared interest 2 was also judged unlikely to cause a conflict of interest but was kept under review during the guidance updating. In the event that recommendation of any relevant dental materials was under consideration by the group, the participation of the individual in those decisions would have been reconsidered. All GDG members were notified that if at any point in the guidance development they felt that their impartiality could be affected, then they should raise this within a meeting and/or contact SDCEP or the group chair to advise of this.	

11 Equality Impact Assessment for this Guidance

The possibility of inequalities associated with the guidance was considered at various stages during the development of the first edition of the guidance and during the updating for the second edition. Potential issues were identified through discussions with guidance development group members, from interviews with practitioners, the responses to the patient questionnaire and feedback from external consultation and peer review. Issues identified and actions taken were recorded in an Equality Impact Assessment (EQIA) checklist which is available on request.

12 Environmental Considerations for this Guidance

The potential environmental impact of the recommendations and clinical advice was considered during the development of the updated guidance. For this guidance, the impacts were aligned with the five key areas identified by the Centre for Sustainable Healthcare: travel; equipment and supplies (procurement); energy; waste; biodiversity and green space.[4] This identified actions that might reduce the potential environmental impact, and informed the development of advice points to support sustainable oral health.

Details of the specific environmental sustainability considerations for this guidance, actions identified, and existing good practice can be found in Appendix 5.

For this topic, most of the sustainability advice points included in the guidance relate to actions to reduce unnecessary patient travel. Patient travel has been identified as a major contributor to the carbon footprint of providing dental care.[5]

Appendix 1 Scope

SDCEP Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs - Scope of Guidance Update – July 2021

Background

The Scottish Dental Clinical Effectiveness Programme (SDCEP) *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs* guidance provides recommendations and practical advice to inform bleeding risk assessment and decision making for the treatment of this patient group. Information about the newer generation anticoagulants and antiplatelet drugs as well as the more established medications is included. The guidance was developed by a multidisciplinary group, including medical and dental practitioners and specialists, and a patient representative, using SDCEP's NICE Accredited standard guidance development process.

The first edition of the guidance was published in 2015 and a scheduled review of the guidance topic has commenced in line with SDCEP's five-year guidance review period.

Guidance aim

The *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs* guidance aims to encourage a consistent approach to the management of dental treatment for patients who are taking anticoagulants or antiplatelet drugs by providing evidence, where available, and expert opinion-based recommendations and information relevant to dental treatment, for the existing, new and emerging anticoagulants and antiplatelet drugs. Through the clinical practice advice provided, the guidance also aims to empower dental staff to treat this patient group within primary care thereby minimising the need for consultation and referral to secondary care.

These aims will also be applicable for the second edition of the guidance.

Target patient groups

The guidance is applicable to patients of any age who are taking anticoagulant or antiplatelet drugs and present for outpatient dental treatment. This includes patients taking vitamin K antagonists (warfarin, phenindione, acenocoumarol), oral antiplatelet drugs (aspirin, clopidogrel, dipyridamole, prasugrel, ticagrelor), injectable anticoagulants (dalteparin, enoxaparin, tinzaparin) and DOACs[1] (apixaban, dabigatran, rivaroxaban). The second edition of the guidance will also include edoxaban.

[1] The term DOAC (Direct Oral Anticoagulant) will be adopted throughout the guidance in place of NOAC (Novel Oral Anticoagulant) to reflect the more widely accepted usage of DOAC across healthcare professions.

The clinical management of dental patients who are taking anticoagulants or antiplatelet drugs and being treated as inpatients within a medical hospital setting is beyond the scope of the guidance.

Target end-users

The guidance is primarily directed at dentists, hygienists and therapists in primary care dental practice, including the general dental service and public dental service, and will also be of relevance to the secondary care dental service, those involved in dental education and undergraduate trainees. Patients and carers may also refer to the guidance and use the accompanying patient information. Use of the guidance could impact on medical professionals including general medical practitioners, pharmacists, haematologists and cardiologists involved in the care of patients taking anticoagulants or antiplatelet drugs. The second edition of the guidance may include specific information for dissemination to these professions.

Clinical questions

The five clinical questions addressed in the first edition of the guidance are listed in the *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs Guidance Development Methodology (2015)* which is available on request.

Key recommendations were not made for Questions 4 (injectable anticoagulants) and 5 (additional haemostatic measures) because of insufficient evidence and other considerations. The second edition of the guidance will address the same five clinical questions (with the inclusion of edoxaban in Question 3). The GDG will consider whether the recommendations for Questions 1-3 should remain extant and whether key recommendations can be made for Questions 4 and 5.

Process for guidance review and update

The scheduled review will involve searching, appraising and considering relevant new evidence and other information that might impact on the guidance, and consideration of feedback received about the first edition of the guidance.

All of the key recommendations, clinical advice and other guidance content will be reviewed, with specific consideration of:

- new drugs and drug indications;
- changes in the prevalence of patients taking the different anticoagulant and antiplatelet drugs;
- categorisation of bleeding risk for dental procedures, including for different aspects of implant procedures and for local anaesthesia;
- any new information on anticoagulant/antiplatelet drugs or other medications relating to bleeding risk;
- any new information on bleeding risk associated with other medical conditions;

- any new evidence relating to haemostatic measures (e.g. tranexamic acid), taking practicalities into consideration;
- timing of INR testing, INR levels and criteria for INR stability;
- any new evidence on pre-procedural management of drug regimes and bleeding outcomes;
- timing of drug interruption/restarting;
- advice on injectable anticoagulants;
- advice for managing medically complex patients on antithrombotic drug combinations (e.g. DOACs with clopidogrel and aspirin).

An updated systematic search for evidence relating to the clinical questions will be carried out by the Cochrane Oral Health Information Specialist. The search will be based on that used for the first edition of the guidance (described in the *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs Guidance Development Methodology (2015)*, available on request) and will include articles published since the original search in October 2014. Preliminary scoping searches suggest that a number of systematic reviews directly relevant to the clinical questions have been published in the last six years. Consequently, the search will combine anticoagulant/antiplatelet terms with dental terms, but not with terms for other types of surgical procedure or for general bleeding risk as used in the wider searches carried out for the first edition of the guidance.

In accordance with SDCEP's standard process, the evidence search and screening will focus on systematic reviews and guidelines, before considering primary studies, and the articles will be appraised using GRADE or AGREE II.

Information will also be sought on the views of practitioners and patients, relating to the guidance and dental treatment for patients taking these drugs. Other information in the guidance, such as indications for anticoagulant and antiplatelet drug use and drug interactions, will be updated according to national drug information sources and expert group member input.

The Guidance Development Group (GDG) will review summarised evidence and information to inform the updating of the guidance content. If significant new evidence that could affect the key recommendations is identified, the GDG will follow a considered judgement process to review and change the recommendations accordingly.

The GDG will also review the supporting tools accompanying the guidance, including the Quick Reference Guide, Patient Information Leaflets, Post-treatment Advice Sheets, and Local Contacts for Advice and Referral sheets. Additional patient feedback on the patient information will be sought.

If significantly changed from the first edition, a draft of the updated guidance will be subject to external peer review. A short open consultation may also be carried out if required.

The updated guidance will be published online via the SDCEP website and SDCEP Dental Companion app.

Notification of online publication will be widely disseminated to the dental profession in Scotland and to UK dental organisations and bodies. Patient information will also be shared with relevant patient support charities. Specific information may be targeted to the medical profession including general medical practice, pharmacy, haematology, cardiology and those providing anaesthesia for dental procedures.

Appendix 2 Evidence Searches

Summary of search from October 2014 to April 2021

Database	Date of search	Records retrieved
Cochrane Database of Systematic Reviews	14 April 2021	Reviews: 102 Guidelines: N/A
DARE	14 April 2021	Reviews: 16 Guidelines: N/A
MEDLINE via OVID	14 April 2021	Reviews: 106 Guidelines: 109
EMBASE via OVID	14 April 2021	Reviews: 69 Guidelines: 161
CINAHL via EBSCO	14 April 2021	Reviews: 34 Guidelines: 21
Epistemonikos search strategy	14 April 2021	Reviews: 97 Guidelines: n/a
	Totals	Reviews: 424 Guidelines: 291
	After de-duplication	**534**

Summary of update search from April 2021 to July 2021

Database	Date of search	Records retrieved
Cochrane Database of Systematic Reviews	19 July 2021	Reviews: 11 Guidelines: N/A
DARE	N/A	DARE not updated since 2016
MEDLINE via OVID	19 July 2021	Reviews: 28 Guidelines: 17
EMBASE via OVID	19 July 2021	Reviews: 5 Guidelines: 16
CINAHL via EBSCO	19 July 2021	Reviews: 0 Guidelines: 0
Epistemonikos search strategy	19 July 2021	Reviews: 5 Guidelines: n/a
	Totals	Reviews: 49 Guidelines: 33
	After de-duplication	**26**

COCHRANE DATABASE OF SYSTEMATIC REVIEWS (CDSR) 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 gingivectom* 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 [mh Anticoagulants]
#15 [mh ^"Fibrinolytic agents"]
#16 [mh "Heparin, low-molecular weight"]
#17 [mh "Platelet Aggregation Inhibitors"]
#18 [mh ^warfarin]
#19 [mh ^dicumarol]
#20 [mh ^acenocoumarol]
#21 [mh ^phenindione]
#22 [mh ^aspirin]
#23 [mh ^dipyridamole]
#24 (anticoagula* or anti-coagula*)
#25 "indirect thrombin inhibitor*"
#26 (fibrinolytic next (agent* or drug*))
#27 (antithrombic next (agent* or drug*))
#28 (thrombolytic next (agent* or drug*))
#29 (antiplatelet* or anti-platelet*)
#30 (platelet* near/2 inhibitor*)
#31 (platelet* next (antagonist* or aggregant*))
#32 ("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*)
#33 (NOAC or "thrombin inhibitor*" or "Factor Xa inhibitor*" or "vitamin K inhibitor*")
#34 (warfarin or aldocumar or coumadin* or marevan or tedicumar or warfant or jantoven or uniwarfarin)
#35 (dicumarol or dicoumarin or dicoumarol or bishydroxycoumain or coumarin)
#36 (acenocoumarol or acenocoumarin or nicoumalone or sinkumar or sinthrome or sintrom or syncumar or synthrom)
#37 (phenindione or dindevan or fenilin or phenylindanedione or phenyline or pindione)
#38 (dabigatran or pradax* or prazaxa)
#39 (rivaroxaban or xarelto)
#40 (apixaban or eliquis or edoxaban or lixiana)
#41 (aspirin* or "acetylsalicylic acid" or acetysal or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopir* or solprin or solupsan or zorprin)
#42 (clopidogrel or iscover or plavix)

#43 (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")
#44 (prasugrel or efient or effient or prasita)
#45 (ticagrelor or brilinta or brilique or possia)
#46 (tinzaparin or innohep)
#47 (fondaparinux or arixtra or quixidar)
#48 (vorapaxar or zontivity)
#49 (idarucizumab or Praxbind or "andexanet alfa" or Ondexxya)
#50 {or #14-#49}
#51 #13 and #50

DARE via OVID Search Strategy

1 (dental$ or dentist$).mp. [mp=title, full text, keywords]
2 ((oral or periodont$) adj5 surg$).mp. [mp=title, full text, keywords]
3 (pulpotom$ or pulpect$ or endodont$ or "pulp cap$" or apicoectom$ or apicectom$ or gingivectom$ or gingivoplast$).mp. [mp=title, full text, keywords]
4 ((dental or tooth or teeth or molar$) adj5 (fill$ or restor$ or extract$ or remov$ or "cavity prep$" or caries or carious or decay$ or scal$ or polish$ or "root plan$")).mp. [mp=title, full text, keywords]
5 (root canal and (therap$ or treat$)).mp. [mp=title, full text, keywords]
6 (tooth adj3 replant$).mp. [mp=title, full text, keywords]
7 ((dental or oral) adj2 implant$).mp. [mp=title, full text, keywords]
8 ((dental or teeth or tooth) adj2 (anesthes$ or anaesthes$ or "nerve block$")).mp. [mp=title, full text, keywords]
9 "root surface instrumentation".mp. [mp=title, full text, keywords]
10 (crown$ or bridge$ or prosthodontic$).mp. [mp=title, full text, keywords]
11 ((oral or mouth or dental) adj5 biops$).mp. [mp=title, full text, keywords]
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13 (anticoagula$ or anti-coagula$).mp. [mp=title, full text, keywords]
14 "indirect thrombin inhibitor$".mp. [mp=title, full text, keywords]
15 (fibrinolytic adj (agent$ or drug$)).mp. [mp=title, full text, keywords]
16 (antithrombic adj (agent$ or drug$)).mp. [mp=title, full text, keywords]
17 (thrombolytic adj (agent$ or drug$)).mp. [mp=title, full text, keywords]
18 (antiplatelet$ or anti-platelet$).mp. [mp=title, full text, keywords]
19 (platelet$ adj2 inhibitor$).mp. [mp=title, full text, keywords]
20 (platelet$ adj (antagonist$ or aggregant$)).mp. [mp=title, full text, keywords]
21 ("low molecular weight heparin" or dalteparin or enoxaparin$ 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$).mp. [mp=title, full text, keywords]
22 (NOAC or "thrombin inhibitor$" or "Factor Xa inhibitor$" or "vitamin K inhibitor$").mp. [mp=title, full text, keywords]
23 (warfarin or aldocumar or coumadin$ or marevan or tedicumar or warfant or jantoven or uniwarfarin).mp. [mp=title, full text, keywords]

24 (dicumarol or dicoumarin or dicoumarol or bishydroxycoumain or coumarin).mp. [mp=title, full text, keywords]
25 (acenocoumarol or acenocoumarin or nicoumalone or sinkumar or sinthrome or sintrom or syncumar or synthrom).mp. [mp=title, full text, keywords]
26 (phenindione or dindevan or fenilin or phenylindanedione or phenyline or pindione).mp. [mp=title, full text, keywords]
27 (dabigatran or pradax$ or prazaxa).mp. [mp=title, full text, keywords]
28 (rivaroxaban or xarelto).mp. [mp=title, full text, keywords]
29 (apixaban or eliquis or edoxaban or lixiana).mp. [mp=title, full text, keywords]
30 (aspirin$ or "acetylsalicylic acid" or acetysal or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopir$ or solprin or solupsan or zorprin).mp. [mp=title, full text, keywords]
31 (clopidogrel or iscover or plavix).mp. [mp=title, full text, keywords]
32 (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").mp. [mp=title, full text, keywords]
33 (prasugrel or efient or effient or prasita).mp. [mp=title, full text, keywords]
34 (ticagrelor or brilinta or brilique or possia).mp. [mp=title, full text, keywords]
35 (tinzaparin or innohep).mp. [mp=title, full text, keywords]
36 (fondaparinux or arixtra or quixidar).mp. [mp=title, full text, keywords]
37 (vorapaxar or zontivity).mp. [mp=title, full text, keywords]
38 (idarucizumab or Praxbind or "andexanet alfa" or Ondexxya).mp. [mp=title, full text, keywords]
39 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40 12 and 39

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 Anticoagulants/

15 Fibrinolytic agents/
16 Platelet aggregation inhibitor/
17 exp Heparin, Low-Molecular-Weight/
18 Warfarin/
19 Dicumarol/
20 Acenocoumarol/
21 Phenindione/
22 Aspirin/
23 Dipyridamole/
24 (anticoagula$ or anti-coagula$).ti,ab.
25 "indirect thrombin inhibitor$".mp.
26 (fibrinolytic adj (agent$ or drug$)).ti,ab.
27 (antithrombic adj (agent$ or drug$)).ti,ab.
28 (thrombolytic adj (agent$ or drug$)).ti,ab.
29 (antiplatelet$ or anti-platelet$).ti,ab.
30 (platelet$ adj2 inhibitor$).ti,ab.
31 (platelet$ adj (antagonist$ or aggregant$)).ti,ab.
32 ("low molecular weight heparin" or dalteparin or enoxaparin$ 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$).ti,ab.
33 (NOAC or "thrombin inhibitor$" or "Factor Xa inhibitor$" or "vitamin K inhibitor$").ti,ab.
34 (warfarin or aldocumar or coumadin$ or marevan or tedicumar or warfant or jantoven or uniwarfarin).ti,ab.
35 (dicumarol or dicoumarin or dicoumarol or bishydroxycoumain or coumarin).ti,ab.
36 (acenocoumarol or acenocoumarin or nicoumalone or sinkumar or sinthrome or sintrom or syncumar or synthrom).ti,ab.
37 (phenindione or dindevan or fenilin or phenylindanedione or phenyline or pindione).ti,ab.
38 (dabigatran or pradax$ or prazaxa).ti,ab.
39 (rivaroxaban or xarelto).ti,ab.
40 (apixaban or eliquis or edoxaban or lixiana).ti,ab.
41 (aspirin$ or "acetylsalicylic acid" or acetysal or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopir$ or solprin or solupsan or zorprin).ti,ab.
42 (clopidogrel or iscover or plavix).ti,ab.
43 (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.
44 (prasugrel or efient or effient or prasita).ti,ab.
45 (ticagrelor or brilinta or brilique or possia).ti,ab.
46 (tinzaparin or innohep).ti,ab.
47 (fondaparinux or arixtra or quixidar).ti,ab.
48 (vorapaxar or zontivity).ti,ab.
49 (idarucizumab or Praxbind or "andexanet alfa" or Ondexxya).ti,ab. 553

50 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51 13 and 50

The above subject search was linked to the Scottish Intercollegiate Guidelines Network filter for identifying systematic reviews in MEDLINE via Ovid (see https://www.sign.ac.uk/what-we-do/methodology/search-filters/)

1. Meta-Analysis as Topic/
2. meta analy$.tw.
3. metaanaly$.tw.
4. Meta-Analysis/
5. (systematic adj (review$1 or overview$1)).tw.
6. exp Review Literature as Topic/
7. systematic review.pt.
8. or/1-7
9. cochrane.ab.
10. embase.ab.
11. (psychlit or psyclit).ab.
12. (psychinfo or psycinfo).ab.
13. (cinahl or cinhal).ab.
14. science citation index.ab.
15. bids.ab.
16. cancerlit.ab.
17. or/9-16
18. reference list$.ab.
19. bibliograph$.ab.
20. hand-search$.ab.
21. relevant journals.ab.
22. manual search$.ab.
23. or/18-22
24. selection criteria.ab.
25. data extraction.ab.
26. 24 or 25
27. Review/
28. 26 and 27
29. Comment/
30. Letter/
31. Editorial/
32. animal/
33. human/
34. 32 not (32 and 33)
35. or/29-31,34
36. 8 or 17 or 23 or 28
37. 36 not 35

38. systematic review.pt.
39. 37 or 38

The subject search was also linked to the Canadian Agency for Drugs and Technologies in Health search filter for identifying guidelines in MEDLINE Ovid (see https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters).

1. exp Clinical pathway/
2. exp Clinical protocol/
3. exp consensus/
4. exp consensus development conference/
5. exp consensus development conferences as topic/
6. critical pathways/
7. exp guideline/
8. guidelines as topic/
9. exp practice guideline/
10. practice guidelines as topic/
11. health planning guidelines/
12. exp treatment guidelines/
13. (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
14. (position statement$ or policy statement$ or practice parameter$ or best practice$).ti,ab,kf,kw.
15. (standards or guideline or guidelines or guidance$).ti,kf,kw.
16. ((practice or treatment$ or clinical) adj guideline$).ab.
17. (CPG or CPGs).ti.
18. consensus$.ti,kf,kw.
19. consensus$.ab. /freq=2
20. ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol$)).ti,ab,kf,kw.
21. recommendat$.ti,kf,kw.
22. (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.
23. (algorithm$ adj2 (screening or examination or test or tested or testing or assessment$ or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.
24. (algorithm$ adj2 (pharmacotherap$ or chemotherap$ or chemotreatment$ or therap$ or treatment$ or intervention$)).ti,ab,kf,kw.
25. or/1-24

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$).ti,ab.
5 ((dental or tooth or teeth or molar$) 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 Anticoagulant agent/
15 Fibrinolytic agent/
16 exp Antithrombocytic agent/
17 Low molecular weight hepain/
18 Warfarin/
19 Dicumarol/
20 Acenocoumarol/
21 or/14-20
22 (anticoagula$ or anti-coagula$).ti,ab.
23 "indirect thrombin inhibitor$".mp.
24 (fibrinolytic adj (agent$ or drug$)).ti,ab.
25 (antithrombic adj (agent$ or drug$)).ti,ab.
26 (thrombolytic adj (agent$ or drug$)).ti,ab.
27 (antiplatelet$ or anti-platelet$).ti,ab.
28 (platelet$ adj2 inhibitor$).ti,ab.
29 (platelet$ adj (antagonist$ or aggregant$)).ti,ab.
30 ("low molecular weight heparin" or dalteparin or enoxaparin$ 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$).ti,ab.
31 (NOAC or "thrombin inhibitor$" or "Factor Xa inhibitor$" or "vitamin K inhibitor$").ti,ab.
32 (warfarin or aldocumar or coumadin$ or marevan or tedicumar or warfant or jantoven or uniwarfarin).ti,ab.
33 (dicumarol or dicoumarin or dicoumarol or bishydroxycoumain or coumarin).ti,ab.
34 (acenocoumarol or acenocoumarin or nicoumalone or sinkumar or sinthrome or sintrom or syncumar or synthrom).ti,ab.
35 (phenindione or dindevan or fenilin or phenylindanedione or phenyline or pindione).ti,ab.
36 (dabigatran or pradax$ or prazaxa).ti,ab.
37 (rivaroxaban or xarelto).ti,ab.
38 (apixaban or eliquis or edoxaban or lixiana).ti,ab.
39 (aspirin$ or "acetylsalicylic acid" or acetysal or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopir$ or solprin or solupsan or zorprin).ti,ab.
40 (clopidogrel or iscover or plavix).ti,ab.

41 (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.
42 (prasugrel or efient or effient or prasita).ti,ab.
43 (ticagrelor or brilinta or brilique or possia).ti,ab.
44 (tinzaparin or innohep).ti,ab.
45 (fondaparinux or arixtra or quixidar).ti,ab.
46 (vorapaxar or zontivity).ti,ab.
47 (idarucizumab or Praxbind or "andexanet alfa" or Ondexxya).ti,ab.
48 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49 13 and 48

The above subject search was linked to the Scottish Intercollegiate Guidelines Network filter for identifying systematic reviews in Embase via Ovid (see https://www.sign.ac.uk/what-we-do/methodology/search-filters/)

1. exp Meta Analysis/
2. ((meta adj analy$) or metaanalys$).tw.
3. (systematic adj (review$1 or overview$1)).tw.
4. or/1-3
5. cancerlit.ab.
6. cochrane.ab.
7. embase.ab.
8. (psychlit or psyclit).ab.
9. (psychinfo or psycinfo).ab.
10. (cinahl or cinhal).ab.
11. science citation index.ab.
12. bids.ab.
13. or/5-12
14. reference lists.ab.
15. bibliograph$.ab.
16. hand-search$.ab.
17. manual search$.ab.
18. relevant journals.ab.
19. or/14-18
20. data extraction.ab.
21. selection criteria.ab.
22. 20 or 21
23. review.pt.
24. 22 and 23
25. letter.pt.
26. editorial.pt.
27. animal/

28. human/
29. 27 not (27 and 28)
30. or/25-26,29
31. 4 or 13 or 19 or 24
32. 31 not 30

The subject search was also linked to the Canadian Agency for Drugs and Technologies in Health search filter for identifying guidelines in Embase Ovid (see https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters).

1. exp practice guideline/
2. consensus/
3. (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
4. (position statement$ or policy statement$ or practice parameter$ or best practice$).ti,ab,kf,kw.
5. (standards or guideline or guidelines or guidance$).ti,kf,kw.
6. ((practice or treatment$ or clinical) adj guideline$).ab.
7. (CPG or CPGs).ti.
8. consensus$.ti,kf,kw.
9. consensus$.ab. /freq=2
10. ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol$)).ti,ab,kf,kw.
11. recommendat$.ti,kf,kw.
12. (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.
13. (algorithm$ adj2 (screening or examination or test or tested or testing or assessment$ or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.
14. (algorithm$ adj2 (pharmacotherap$ or chemotherap$ or chemotreatment$ or therap$ or treatment$ or intervention$)).ti,ab,kf,kw.
15. or/1-14

CINAHL via EBSCO Search Strategy

S1 (MH "Dentistry+")
S2 (dental* or dentist*)
S3 ((oral or periodont*) N5 surg*)
S4 (pulpotom* or pulpect* or endodont* or "pulp cap*" or apicoectom* or apicectom* or gingivectom* or gingivoplast*)
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*"))
S6 ("root canal" and (therap* or treat*))
S7 (tooth N3 replant*)
S8 ((dental or oral) N2 implant*)

S9 ((dental or teeth or tooth) N2 (anesthes* or anaesthes* or "nerve block"))
S10 "root surface instrumentation"
S11 (crown* or bridge* or prosthodontic*)
S12 ((oral or mouth or dental) N5 biops*)
S13 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
S14 (MH "Anticoagulants+")
S15 (MH "Fibrinolytic Agents")
S16 (MH "Heparin, Low-Molecular-Weight")
S17 (MH "Platelet Aggregation Inhibitors+")
S18 (MH "Warfarin")
S19 (MH "Aspirin")
S20 (MH "Dipyridamole")
S21 (anticoagula* or anti-coagula*)
S22 "indirect thrombin inhibitor*"
S23 (fibrinolytic n1 (agent* or drug*))
S24 (antithrombic n1 (agent* or drug*))
S25 (thrombolytic n1 (agent* or drug*))
S26 (antiplatelet* or anti-platelet*)
S27 (platelet* n2 inhibitor*)
S28 (platelet* n1 (antagonist* or aggregant*))
S29 ("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*)
S30 (NOAC or "thrombin inhibitor*" or "Factor Xa inhibitor*" or "vitamin K inhibitor*")
S31 (warfarin or aldocumar or coumadin* or marevan or tedicumar or warfant or jantoven or uniwarfarin)
S32 (dicumarol or dicoumarin or dicoumarol or bishydroxycoumain or coumarin)
S33 (acenocoumarol or acenocoumarin or nicoumalone or sinkumar or sinthrome or sintrom or syncumar or synthrom)
S34 (phenindione or dindevan or fenilin or phenylindanedione or phenyline or pindione)
S35 (dabigatran or pradax* or prazaxa)
S36 (rivaroxaban or xarelto)
S37 (apixaban or eliquis or edoxaban or lixiana)
S38 (aspirin* or "acetylsalicylic acid" or acetysal or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopir* or solprin or solupsan or zorprin)
S39 (clopidogrel or iscover or plavix)
S40 (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") S41 (prasugrel or efient or effient orprasita)
S42 (ticagrelor or brilinta or brilique or possia)
S43 (tinzaparin or innohep)
S44 (fondaparinux or arixtra or quixidar)
S45 (vorapaxar or zontivity)
S46 (idarucizumab or Praxbind or "andexanet alfaor" or Ondexxya)

S47 S14 OR S15 OR S16 OR S17 OR 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
S48 S13 AND S47
S49 (MH "Meta Analysis") OR "meta analys*" OR metaanalys*
S50 (MH "Literature Review+") OR ((systematic N1 (review or overview)))
S51 S49 OR S50
S52 PT commentary OR PT letter OR PT commentary OR (MH "Animals")
S53 S51 NOT S52
S54 (MH "Practice Guidelines") OR TI guideline*
S55 S48 AND S53
S56 S48 AND S54
S57 S55 OR S56

Epistemonikos Search Strategy

(title:((dental* OR dentist* OR tooth OR teeth OR molar* OR "root canal" OR "oral surg*" OR periodont* OR pulpotom* OR pulpect* OR endodont* OR "pulp cap*" OR apicoectom* OR apicectom* OR gingivectom* OR gingivoplast* OR "oral implant*" OR "root surface instrumentation" OR crown* OR bridge* OR prosthodontic* OR (oral AND biops*) OR (mouth AND biops*))) OR abstract:((dental* OR dentist* OR tooth OR teeth OR molar* OR "root canal" OR "oral surg*" OR periodont* OR pulpotom* OR pulpect* OR endodont* OR "pulp cap*" OR apicoectom* OR apicectom* OR gingivectom* OR gingivoplast* OR "oral implant*" OR "root surface instrumentation" OR crown* OR bridge* OR prosthodontic* OR (oral AND biops*) OR (mouth AND biops*)))) AND (title:((anticoagula* OR anti-coagula* OR "indirect thrombin inhibitor*" OR "fibrinolytic agent*" OR "fibrinolytic drug*" OR "antithrombic agent*" OR "antithrombic drug*" OR "thrombolytic agent*" OR "thrombolytic drug*" OR antiplatelet* OR anti-platelet* OR "platelet* inhibitor*" OR "platelet* antagonist*" OR "platelet aggregant*"OR "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* OR NOAC OR "thrombin inhibitor*" OR "Factor Xa inhibitor*" OR "vitamin K inhibitor*" OR warfarin OR aldocumar OR coumadin* OR marevan OR tedicumar OR warfant OR jantoven OR uniwarfarin OR dicumarol OR dicoumarin OR dicoumarol OR bishydroxycoumain OR coumarin OR acenocoumarol OR acenocoumarin OR nicoumalone OR sinkumar OR sinthrome OR sintrom OR syncumar OR synthrom OR phenindione OR dindevan OR fenilin OR phenylindanedione OR phenyline OR pindione OR dabigatran OR pradax* OR prazaxa OR rivaroxaban OR xarelto OR apixaban OR eliquis OR edoxaban OR lixiana OR aspirin* OR "acetylsalicylic acid" OR acetysal OR acylpyrin OR aloxiprimum OR colfarit OR dispril OR easprin OR ecotrin OR endosprin OR magnecyl OR micristin OR polopir* OR solprin OR solupsan OR zorprin OR clopidogrel OR iscover OR plavix OR 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" OR prasugrel OR efient OR effient OR prasita OR ticagrelor OR brilinta OR brilique OR possia OR tinzaparin OR innohep OR fondaparinux OR arixtra OR quixidar OR vorapaxar OR zontivity OR idarucizumab OR Praxbind OR "andexanet alfa" OR Ondexxya)) OR abstract:((anticoagula* OR anti-coagula* OR "indirect thrombin inhibitor*" OR "fibrinolytic

agent*" OR "fibrinolytic drug*" OR "antithrombic agent*" OR "antithrombic drug*" OR "thrombolytic agent*" OR "thrombolytic drug*" OR antiplatelet* OR anti-platelet* OR "platelet* inhibitor*" OR "platelet* antagonist*" OR "platelet aggregant*"OR "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* OR NOAC OR "thrombin inhibitor*" OR "Factor Xa inhibitor*" OR "vitamin K inhibitor*" OR warfarin OR aldocumar OR coumadin* OR marevan OR tedicumar OR warfant OR jantoven OR uniwarfarin OR dicumarol OR dicoumarin OR dicoumarol OR bishydroxycoumain OR coumarin OR acenocoumarol OR acenocoumarin OR nicoumalone OR sinkumar OR sinthrome OR sintrom OR syncumar OR synthrom OR phenindione OR dindevan OR fenilin OR phenylindanedione OR phenyline OR pindione OR dabigatran OR pradax* OR prazaxa OR rivaroxaban OR xarelto OR apixaban OR eliquis OR edoxaban OR lixiana OR aspirin* OR "acetylsalicylic acid" OR acetysal OR acylpyrin OR aloxiprimum OR colfarit OR dispril OR easprin OR ecotrin OR endosprin OR magnecyl OR micristin OR polopir* OR solprin OR solupsan OR zorprin OR clopidogrel OR iscover OR plavix OR 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" OR prasugrel OR efient OR effient OR prasita OR ticagrelor OR brilinta OR brilique OR possia OR tinzaparin OR innohep OR fondaparinux OR arixtra OR quixidar OR vorapaxar OR zontivity OR idarucizumab OR Praxbind OR "andexanet alfa" OR Ondexxya)))

Appendix 3 Summary of Systematic Reviews

The following systematic reviews were identified and appraised as described in Sections 5 & 6. The clinical questions (see Section 4) that the systematic reviews relate to are indicated. The table includes ratings for the methodological quality of each systematic review, based on AMSTAR criteria, and for the GRADE certainty of the evidence included in the reviews.

Systematic Review	Title	Clinical Question(s)	AMSTAR rating	GRADE evidence certainty
Calcia et al., 2021[6]	Is alteration in single drug anticoagulant/antiplatelet regimen necessary in patients who need minor oral surgery? A systematic review with meta-analysis.	1, 2, 3*	moderate/ high	low
Miziara et al., 2021[7]	Risk of bleeding during implant surgery in patients taking antithrombotics: a systematic review.	1, 2, 3, 4	moderate/ high	very low
Moreno-Drada et al., 2021[8]	Effectiveness of local hemostatic to prevent bleeding in dental patients on anticoagulation: a systematic review and network meta-analysis.	5	high	moderate
Bajkin et al., 2020[9]	Dental implant surgery and risk of bleeding in patients on antithrombotic medications: A review of the literature.	1, 2, 3	low	very low
Ockerman et al., 2020[10]	Incidence of bleeding after minor oral surgery in patients on dual antiplatelet therapy: a systematic review and meta-analysis.	2	high	low
Chahine et al., 2019[11]	Anticoagulation Use prior to Common Dental Procedures: A Systematic Review.	1, 3	low	low
de Andrade et al., 2019[12]	Bleeding Risk in Patients Using Oral Anticoagulants Undergoing Surgical Procedures in Dentistry: A Systematic Review and Meta-Analysis.	1, 3*	high	very low
Li et al., 2019[13]	Dental management of patient with dual antiplatelet therapy: a meta-analysis.	2	moderate/ high	low
Manfredi et al., 2019[14]	World workshop on oral medicine VII: Direct anticoagulant agents management for invasive oral procedures: A systematic review and meta-analysis.	3	moderate/ high	very low

Systematic Review	Title	Clinical Question(s)	AMSTAR rating	GRADE evidence certainty
Ockerman et al., 2019[15]	Local haemostatic measures after tooth removal in patients on antithrombotic therapy: a systematic review.	5	moderate	low
Owattanapanich et al., 2019[16]	Efficacy of local tranexamic acid treatment for prevention of bleeding after dental procedures: A systematic review and meta-analysis.	5	moderate	very low
Villanueva et al., 2019[17]	Antiplatelet therapy in patients undergoing oral surgery: A systematic review and meta-analysis.	2	moderate/ high	low
Zabojszcz et al., 2019[18]	Safety of dental extractions in patients on dual antiplatelet therapy - a meta-analysis.	2	moderate	very low
Bensi et al., 2018[19]	Postoperative bleeding risk of direct oral anticoagulants after oral surgery procedures: a systematic review and meta-analysis.	3	moderate/ high	very low
Engelen et al., 2018[20]	Antifibrinolytic therapy for preventing oral bleeding in people on anticoagulants undergoing minor oral surgery or dental extractions.	5	high	moderate
Lusk et al., 2018[21]	Management of Direct-Acting Oral Anticoagulants Surrounding Dental Procedures With Low-to-Moderate Risk of Bleeding.	3	low	very low
Villanueva et al., 2018[22]	Risk of postsurgical hemorrhage in patients with antitrombotic treatment undergoing oral surgery: A systematic review and Metanalysis.	1, 3*	moderate/ high	low
de Vasconcellos et al., 2017[23]	Topical application of tranexamic acid in anticoagulated patients undergoing minor oral surgery: A systematic review and meta-analysis of randomized clinical trials.	5	moderate/ high	moderate
Lanau et al., 2017[24]	Direct oral anticoagulants and its implications in dentistry. A review of literature.	3	low	very low
Shi et al., 2017[25]	Post-operative Bleeding Risk in Dental Surgery for Patients on Oral Anticoagulant Therapy: A Meta-analysis of Observational Studies.	1, 3	moderate	low

*These systematic reviews searched for but did not identify any relevant RCTs that included patients taking DOACs and so did not report any evidence for the DOACs.

Appendix 4 Considered Judgement Forms

Clinical Question 1

Q1: Should warfarin or other vitamin K antagonists be continued or interrupted for dental treatment?

(To include warfarin, acenocoumarol and phenindione)

Recommendation in 2015 edition of guidance

- For a patient who is taking warfarin or another vitamin K antagonist, with an INR below 4, treat without interrupting their anticoagulant medication.
  (Strong recommendation; low quality evidence)

Basis for recommendation:
The recommendation was based on the available evidence from systematic reviews and evidence-based guidelines on the risk of bleeding and thromboembolic events for dental patients continuing or interrupting VKAs, and on extensive clinical experience. The recommendation was rated as strong because of emphasis placed on the potential risk of a thromboembolic event if VKA treatment is interrupted.

The evidence considered previously is documented in the *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs Guidance Development Methodology (2015)* (available on request).

1. Summary of evidence since 2015 edition of guidance

*Summarise the evidence for the effects of the intervention on the important outcomes including the ratings for the **certainty** of the evidence. Comment on the degree of **consistency** demonstrated by the available evidence. Note where evidence is lacking.*

Several relevant systematic reviews (SRs) published since the first edition of the guidance were identified. Some of these include new studies in addition to studies considered previously and several report meta-analysis of the data.

Four SRs[6,11,12,22] found no significant difference in the risk of post-operative bleeding events in patients who continued versus patients who discontinued vitamin K antagonist (VKA) therapy for a variety of invasive oral procedures. Most of the patients were on warfarin, with patients taking acenocoumarol in a limited number of studies. Where reported, patients on continued VKA generally had INR levels between 2 and 3, and VKA therapy was discontinued for 2-4 days. Most of the dental procedures carried out were extractions but also included other types of oral surgery such as implants or biopsies.

Consistent with this, two older systematic reviews,[26,27] identified by the searches but not fully appraised, also reported that continuing an oral anticoagulant did not increase post-operative bleeding compared with interrupting.

Three SRs[7,9,25] compared the post-operative bleeding risk for patients on oral anticoagulants with control groups of patients not taking any anti-thrombotic medication. One SR[25] with meta-analysis of

data from a relatively large number of studies, including different types of dental surgery, found statistically significantly higher rates of bleeding complications (3 fold higher) in patients on VKAs, when compared to no anticoagulant. However, sub-group analysis found no significant difference in bleeding risk for dental extractions or implant surgery alone, suggesting that for patients on oral anticoagulant therapy the risk of bleeding complications for these dental procedures is no higher than for patients not taking anticoagulants. Consistent with this, two other SRs[7,9], that only considered dental implant surgery, reported no significant difference in bleeding risk for patients taking anti-thrombotic drugs (including VKAs) versus none.

Overall, the meta-analysis reported in these SRs suggest that the risk of post-operative bleeding for dental procedures is higher in patients who continue VKAs compared with those not on anticoagulants but might not be higher when only considering extractions or implants. Importantly, there was no significant difference in bleeding risk found comparing patients continuing or interrupting VKAs for dental procedures including extractions and other types of oral surgery. Furthermore, the incidence of post-operative bleeding was low, and most events could be controlled using local haemostatic measures. No thromboembolic events were reported. The key evidence in the various SRs came from RCTs and observational studies and is judged to be **low certainty** overall. The evidence relating to specific procedures, including implants is judged to be of **very low certainty** due to downgrading for small sample sizes.

Does the evidence differ from previously?

The data from these SRs are consistent with the main conclusions of the evidence review carried out for the first edition of the guidance. More recent evidence on dental implants might indirectly support recategorising some implant procedures as low risk of post-operative bleeding complications although there is insufficient data to inform the risk of bleeding for more extensive dental implant procedures.

Additional sources of information

The National Institute of Health and Care Excellence (NICE) Clinical Knowledge Summary[28], American Dental Association (ADA) Oral Health Topic on anticoagulants and antiplatelets[29], other guidelines (including those considered for the first edition of the guidance) and the manufacturers' SPC sheets for the drugs all advise that warfarin need not be interrupted for dental procedures such as extractions. NICE also recommend checking the INR 72 hours before dental surgery and advise that the risk of significant bleeding with a stable INR between 2 and 4 is very small.

See Section 10 of this form for further details of the evidence and additional sources of information.

2. Balance of effects

Comment 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.

The risk of post-operative bleeding events for dental procedures in patients taking VKAs is likely to be low and may not be significantly different compared to interruption of VKAs.

There is insufficient data in the evidence considered to estimate the risk of thromboembolic events for patients interrupting VKA therapy for dental procedures. However, due to the long half-lives of VKAs a

prolonged period of interruption is usually required (~5 days) leaving the patient at sub-therapeutic anticoagulation levels for several days, with the potential risk of a serious thromboembolic event.
3. Subgroup considerations *Comment here on any subgroup considerations e.g. should recommendations for patients at high or low risk be considered separately?*
Patients with an INR>4 are likely to have a higher risk of bleeding and the existing recommendation to treat without interrupting medication does not apply to this subgroup.
4. Values and preferences *Summarise any evidence or information on values and preferences.*
Previously, indirect evidence was identified suggesting that patients would place a higher value on avoiding a thromboembolism than avoiding a bleeding complication, considering the potential outcomes of each. No new information on patient values and preferences specifically regarding continuing versus interrupting VKAs was identified. Patient representatives involved in the guidance update indicated a preference to have INR levels checked as close to the dental procedure as possible; ideally within 24 hours or within 72 hours at most.
6. Acceptability *Is the intervention acceptable to patients, dental team and other stakeholders?*
Either continuing or interrupting a patient's VKA treatment may not be acceptable to all patients, caregivers or providers. Practitioners and patients who are already familiar with the guidance might find it more acceptable to continue to follow the established key recommendation.
7. Feasibility *Comment on cost, resource implications and implementation considerations, if applicable.*
The existing recommendation to not interrupt VKAs for most dental treatment is standard practice nationally and internationally. Increased accessibility of point of care INR testing may enhance the feasibility of treating patients on continued warfarin therapy. The alternative treatment option of interrupting VKAs could require consultation with the prescribing clinician which may delay dental treatment and impose a burden on patient, dentist and clinician.
8. Other factors *Indicate any other factors taken into account.*

Vitamin K1 (phytomenadione) is available as a specific VKA reversal agent for major or life-threatening bleeding.

9. Considered judgment and key recommendation

Summarise the group's judgements for the recommendation including 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.

The conclusions from the evidence on bleeding risk and risk of a thromboembolic event have not changed significantly. The group judged that the balance of risks was still in favour of continuing rather interrupting warfarin therapy for dental treatment and agreed unanimously to the key recommendation as previously:

- For a patient who is taking warfarin or another vitamin K antagonist, with an INR below 4, treat without interrupting their anticoagulant medication.

It was agreed that although based on low certainty evidence, as before this should be a **strong** recommendation because of the potential risk of a serious thromboembolic event if warfarin treatment is interrupted.

10. Additional information

Include any further information that is relevant to the considered judgement.

Details of Systematic Reviews

Seven systematic reviews (SRs) were identified that assessed bleeding risk associated with dental procedures and included patients taking Vitamin K Antagonists (VKAs).[6,7,9,11,12,22,25] These SRs analysed data from overlapping groups of studies, including some published since 2015, and carried out different comparisons. Four of the SRs compared bleeding outcomes for patients who continued VKA therapy with those whose VKA was interrupted for the dental treatment.[6,11,12,22] The others compared the risk for patients on VKA therapy with control groups of patients not taking any anti-thrombotic medication or assessed the bleeding risk without comparing groups. Some of the reviews specifically considered patients taking VKAs, while some included different types of antithrombotic drugs within their analyses.

VKA continuation versus interruption

Calcia et al. (2021)[6] compared the risk of bleeding events for interruption of single oral anticoagulant drugs with continuation for minor oral surgery. This SR found no statistically significant difference in the risk of intraoperative bleeding events (up to 15 mins after procedure) for patients who continued VKA therapy compared with those whose therapy was interrupted (RR = 1.79, 95%CI: 1.00–3.21, p =0.05; 2 studies, 169 participants). There was also no significant difference in the risk of post-operative

bleeding events (at least 1hr after procedure) for patients who continued VKA therapy compared with interruption (RR = 0.77, 95%CI: 0.50–1.19, *p* =0.42; 6 studies, 533 participants).

Warfarin was the most common VKA reported in the studies (one, 2020 study included patients taking acenocoumarol) and drug interruption varied from 2-4 days. Most of the oral surgery procedures were extractions, although soft tissue procedures such as biopsies were reported in one study. All bleeding events were controlled with local hemostatic measures. Although the included studies were all RCTs, the evidence was judged to be of low certainty because of downgrading due to the high risk of bias in all of the studies and the low numbers of participants included in the analyses.

De Andrade et al. (2019)[12] searched for RCTs on bleeding risk for dental patients on any oral anticoagulant and due to stringent exclusion criteria only found 3 older studies on warfarin. In agreement with Calcia et al., meta-analysis revealed no statistically significant difference in bleeding risk between the groups that continued or interrupted the use of warfarin for either trans-operative (RR = 1.67, 95% CI = 0.97 to 2.89) or post-operative bleeding (RR = 1.44, 95% CI = 0.71 to 2.92; 2 studies, 323 participants).

The 2 studies used for meta-analysis only included patients taking warfarin, either continuously or interrupted for 2 days prior to the oral surgery and patients with INR values between 2 and 3. The evidence was rated by the authors as very low certainty due to downgrading for risk of bias and imprecision.

Chahine et al. (2019)[11] also compared post-operative bleeding for dental procedures in patients continuing their anticoagulant with control groups including patients whose anticoagulants had been interrupted. This SR considered RCTs or controlled clinical trials and provided a qualitative synthesis without any meta-analysis. While one study found a statistically significant increase in mild bleeding in the VKA group when compared with no anticoagulation, the rest of the studies found no significant differences in bleeding outcomes between continuing or interrupting anticoagulation. No TE events were reported by any of the studies.

Most studies were on patients taking warfarin or another VKA and most assessed dental extractions, with some including implant surgery, excision of cystic formations, biopsies, alveoloplasty, frenectomy, periodontal surgeries, and microsurgical endodontics (apicectomy).

Villanueva et al. (2018)[22] concluded that although more oral postoperative bleeding episodes were found in patients continuing oral anticoagulant therapy compared with patients discontinuing or modifying their therapy, this difference was neither statistically nor clinically significant (RR = 1.41, 95% CI 0.93 - 2.16, *p*= 0.11; 5 studies, 549 patients).

None of the studies reported the occurrence of thromboembolic events or mortality after the intervention. All patients were taking VKAs and were in the therapeutic range (INR 2-3). The bleeding episodes that occurred were controlled with local haemostatic measures. The evidence was rated as low certainty due to downgrading for risk of bias and imprecision.

<u>VKA therapy versus no VKA</u>

Shi et al. (2017)[25] compared the risk of post-operative bleeding events after minor dental surgery in patients on continuous oral anticoagulant therapy (OAT; VKAs or DOACs) versus patients not taking any anticoagulant drug.

The total post-operative bleeding rate for OAT patients was 4.33% (91/2102) compared to 1.10% (25/2271) of the non-OAT patients. Only two patients developed severe bleeding. Meta-analysis for post-operative bleeding risk for all dental procedures found an overall risk ratio (RR) of 2.794 (95% CI = 1.722–4.532, *p*=0.000; 12 studies, 4373 participants) indicating a higher post-operative bleeding risk for patients taking a VKA or a DOAC compared with non-OAT patients. Sub-group analysis of data for the individual drug types confirmed a significant difference in risk of post-operative bleeding for VKAs versus no OAT (RR=3.067, 95% CI: 1.838–5.118, *p* =0.000; 10 studies).

Further sub-group analysis gave a pooled RR of 2.136 (95% CI: 0.825–5.531, *p* =0.118, 4 studies) for dental implant surgery and 2.003 (95% CI: 0.987–4.063, *p* =0.054, 4 studies) for dental extractions, neither of which were statistically significant, suggesting that these procedures do not have a higher bleeding risk for OAT patients compared with non-OAT patients.

The evidence is derived from observational studies and is judged to be of low certainty.

Miziara et al. (2021)[7] assessed post-operative bleeding focusing on implant procedures including implant reopening, bone grafting, maxillary sinus lifting with lateral window and implant placement. The review found no statistically significant difference in the pooled bleeding risk comparing patients on various anti-thrombotics (warfarin, antiplatelet drugs, DOACs or LMWHs) with patients not taking antithrombotic drugs (OR=2.19; 95% CI: 0.88–5.44, *p* =0.09; 5 studies, 317 procedures). The individual bleeding risk for VKAs was not estimated.

None of the studies included reported major postoperative bleeding and the bleeding was managed with local haemostatic measures. The authors concluded that the absolute risk is low and there is no need to discontinue or alter the dose of the antithrombotic drug for implant placement surgery. The evidence is rated as very low certainty due to the study type (all prospective cohort studies) and the low numbers of participants.

Bajkin et al. (2020)[9] aimed to address a similar question to Miziara et al. but did not carry out meta-analysis or make a direct comparison of bleeding risk for dental implants for patients on antithrombotics versus control groups. This SR included additional studies (9 studies in total) and provides estimates of bleeding risk for individual drug type. The review found a post-operative bleeding rate of 5.7% (6 events in 105 procedures) for patients taking VKAs, from 4 studies including some patients taking both oral anticoagulant and antiplatelet drugs. INR levels were less than 3.5 in all cases. The overall bleeding incidence for any antithrombotic was 2.2% (10/456) and all bleeding events were controlled using local measures. No data on thromboembolic events was reported in the included studies. The evidence is likely to be of very low certainty due to limitations because of the study types and the low numbers of participants.

Additional systematic reviews (not fully appraised)

Two further SRs, including some of the same studies as the other SRs, also concluded that the bleeding risk for patients continuing was no higher than for patients interrupting their oral anticoagulant

therapy. **Yang et al. (2016)**[26] reported no significant difference in the post-operative bleeding risk between patients continuing or discontinuing oral anticoagulant therapy while undergoing dental extractions (RR= 1.31, 95 % CI: 0.79-2.14, *p* > 0.29; 6 studies, 591 patients). **Ruiz-Gutierrez (2016)**[27] carried out a meta-analysis of 5 clinical trials and reported an OR of 1.83 (CI 1.09-3.07, *p* =0.02; 5 studies, 588 patients) comparing post-operative bleeding for patients who interrupted or modified their OAC with those who continued treatment, suggesting that continuing an OAC did not increase post-operative bleeding.

Additional sources of information:

(i) **NICE Clinical Knowledge Summary – Anticoagulation oral. Scenario: Warfarin** (April 2021)[28]

- *In most cases, warfarin need not be stopped before routine dental surgery, for example tooth extraction.*
- *It is recommended that the INR is checked 72 hours before dental surgery. The risk of significant bleeding in people with a stable INR within the range of 2–4 is very small, but the risk of thrombosis may be increased if oral anticoagulants are temporarily discontinued.*

These recommendations are based on the British Society for Haematology (BSH) 2016 guideline *Peri-operative management of anticoagulation and antiplatelet therapy* and the Summary of Product Characteristics (SPC) for warfarin.

(ii) **American Dental Association – Oral Health Topics - Oral Anticoagulant and Antiplatelet Medications and Dental Procedures** (updated September 2020)[29]

There is general agreement based on strong evidence that treatment regimens with these older anticoagulants/antiplatelet agents (including warfarin) *should not be altered before dental procedures.*

This is based on a review of articles, including SRs discussed above or for the first edition of the guidance, and the 2016 Clinical Practice Statement from the American Academy of Oral Medicine.

(iii) **American Academy of Oral Medicine (AAOM) Clinical Practice Statement: Management of Patients on Warfarin Therapy** (2016)[30]

Policy statement includes:

1. *The AAOM considers major considerations in the dental management of these patients to include:*
   a. *identifying patients taking warfarin and other anticoagulants*
   b. *understanding the levels of INR test results and their impact on the potential for bleeding during and following dental procedures*
   c. *development of an action plan if a bleeding emergency occurs during/immediately after an invasive dental procedure*
   d. *the importance of having an INR lab result within 24 hours of highly invasive procedures*
   e. *having knowledge of comorbid conditions (i.e., liver, kidney, platelet disorders, acute infection) or other medications that can also affect coagulation and clotting*
   f. *understanding of local hemostatic measures that can be implemented for these patients*
   g. *understanding potential drug interactions*

Regarding INR levels:
Current literature, including prospective randomized studies, indicates that moderately invasive surgery (e.g. uncomplicated tooth extractions) is safe with an INR up to 3.5, with some experts stating it is safe up to 4.0.

(iv) **New South Wales Clinical Excellence Commission Guidelines on Perioperative Management of Anticoagulant and Antiplatelet Agents** (Dec 2018)[31]

In this guideline, minimal bleeding risk procedures include minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings.
The guideline advises:
Patients who are having selected minimal or low bleeding risk procedures for example endoscopy in high thrombotic risk patients may not require warfarin therapy to be withheld. For patients undergoing a procedure who are taking warfarin, it is important to confirm that the International Normalised Ratio (INR) is not supratherapeutic at the time of the procedure.
No methodology is reported for this guideline.

(v) **American College of Surgeons' Guidelines for the Perioperative Management of Antithrombotic Medication** (2018)[32]

Certain minimally invasive procedures like dental extraction, cataract removal, joint injections, and diagnostic endoscopic procedures have minimal bleeding risk and do not require discontinuation of antithrombotic agents.
No specific advice for VKAs provided.

(vi) **British National Formulary (BNF) Prescribing in Dental Practice**[33]

From Thromboembolic disease section:

For a patient requiring long-term therapy with warfarin sodium, the patient's medical practitioner should be consulted and the International Normalised Ratio (INR) should be assessed 72 hours before the dental procedure. This allows sufficient time for dose modification if necessary. In those with an unstable INR (including those who require weekly monitoring of their INR, or those who have had some INR measurements greater than 4.0 in the last 2 months), the INR should be assessed within 24 hours of the dental procedure. Patients requiring minor dental procedures (including extractions) who have an INR below 4.0 may continue warfarin sodium without dose adjustment. There is no need to check the INR for a patient requiring a non-invasive dental procedure.

If it is necessary to remove several teeth, a single extraction should be done first; if this goes well further teeth may be extracted at subsequent visits (two or three at a time). Measures should be taken to minimise bleeding during and after the procedure. This includes the use of sutures and a haemostatic such as oxidised cellulose, collagen sponge or resorbable gelatin sponge. Scaling and root planing should initially be restricted to a limited area to assess the potential for bleeding.

(vii) **Extracts from Summary of Product Characteristics (SPC) sheets**:

Warfarin (https://www.medicines.org.uk/emc/product/2803/smpc)

- *Warfarin need not be stopped before routine dental surgery, eg, tooth extraction*

Acenocoumarol (https://www.medicines.org.uk/emc/product/2058)

- *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.*

Phenindione (https://www.medicines.org.uk/emc/product/5678/smpc)

- *Dindevan need not be stopped before routine dental surgery e.g. tooth extraction*.

Clinical Question 2

Q2: Should antiplatelet drugs be continued or interrupted for dental treatment?

(To include aspirin, clopidogrel, dipyridamole, prasugrel, ticagrelor and combined therapies)

Recommendation in 2015 edition of guidance:

- For a patient who is taking single or dual antiplatelet drugs, treat without interrupting their antiplatelet medication.
  (Strong recommendation; low quality evidence)

Basis for recommendation:
The recommendation was based on the available evidence from systematic reviews and evidence-based guidelines on bleeding risk for patients on single or dual antiplatelet therapy and on the effect of discontinuing therapy on the risk of thromboembolic events. The recommendation was rated as strong because of emphasis placed on the potential risk of a thromboembolic event if antiplatelet treatment is interrupted.

The evidence considered previously is documented in the *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs Guidance Development Methodology (2015)* (available on request).

1. Summary of evidence since 2015 edition of guidance

*Summarise the evidence for the effects of the intervention on the important outcomes including the ratings for the **certainty** of the evidence. Comment on the degree of **consistency** demonstrated by the available evidence. Note where evidence is lacking.*

Several relevant systematic reviews (SRs) published since the first edition of the guidance were identified. Some of these include new studies in addition to studies considered previously and most report meta-analysis of the data.

Two SRs[6,34] found no significant difference in the risk of post-operative bleeding events in patients who continued versus patients who discontinued antiplatelet therapy for a variety of invasive oral procedures. Most of the patients were on single antiplatelet therapy (SAPT), either aspirin or clopidogrel, with some patients in one study on dual antiplatelet therapy (DAPT) with aspirin and clopidogrel. One of the SRs[6] found a 3-4 fold increased risk of intraoperative bleeding for patients continuing compared to interrupting aspirin, although this was based on a small sample size.

Three SRs[10,13,18] compared the post-operative bleeding risk for patients on DAPT with control groups of patients not taking any anti-thrombotic medication and found significantly higher rates of bleeding complications in patients on DAPT (risk ratios ranged from 2-4 fold higher[10,13]). Most of the studies included patients taking aspirin and clopidogrel, although two studies included patients on aspirin and prasugrel. The dental procedures were mostly extractions but also included other oral surgery procedures. According to one of the SRs[18], there may be higher odds of post-operative bleeding for

DAPT than SAPT (clopidogrel) compared to control groups but no significant difference in the odds for aspirin alone.

Two further SRs[7,9], that only considered dental implant surgery, reported no significant difference in bleeding risk for patients taking anti-thrombotic drugs (including antiplatelets) versus none. One did not provide an individual estimate of risk for antiplatelet drugs[7] and the other estimated a bleeding rate of 0.4% for implants in patients taking antiplatelets (compared to an overall rate of 2.2% for all antithrombotics).[9]

Although the meta-analysis reported in the different SRs indicate that the risk of post-operative bleeding for extractions or other dental procedures is significantly higher in patients who continue DAPT compared with those not on APT, the incidence of post-operative bleeding was low (ranging from 0.4 to 3.8%) and all events could be controlled using local haemostatic measures. No thromboembolic events were reported although the length of follow up in the studies may have been insufficient to measure events. Data on bleeding risks for antiplatelet drugs other than aspirin and clopidogrel is very limited. The evidence in the various SRs came from RCTs and observational studies and is rated as **low certainty** overall.

Does the evidence differ from previously?

The data from these SRs are consistent with the main conclusions of the evidence review carried out for the first edition of the guidance.

Additional sources of information

The National Institute of Health and Care Excellence (NICE) Clinical Knowledge Summary[28] and the American Dental Association (ADA) Oral Health Topic on anticoagulants and antiplatelets[29] acknowledge the increased risk of bleeding complications, particularly with DAPT, but recommend that antiplatelet drugs are not interrupted for dental surgery because of the increased risk of thromboembolic complications for patients with indications for antiplatelet therapy. The 2013 SIGN guideline[35] suggests considering temporary discontinuation of clopidogrel but the recommendations are not specific for dental surgery. An Australian guideline[31] advises interruption of antiplatelet agents, although 'minimal risk' procedures (including dental procedures) appear to be combined with 'low risk' procedures (non-dental) for this recommendation. The drug manufacturers' SPC sheets advise that bleeding time might be prolonged and recommend how long to discontinue drugs but, apart from aspirin, do not specify whether drugs should be continued or interrupted for dental surgery.

See Section 10 of this form for further details of the evidence and additional sources of information.

2. Balance of effects

Comment 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.

The risk of post-operative bleeding complications is likely to be higher for patients on dual antiplatelet therapy than those on single antiplatelet therapy or none. However, the risk is likely to be low with most bleeding events manageable with local haemostatic measures.

Although there is a lack of evidence from the dental studies considered, there may be an increased risk of serious adverse thromboembolic events for some patients with indications for antiplatelet drugs if discontinued or interrupted.
3. Subgroup considerations *Comment here on any subgroup considerations e.g. should recommendations for patients at high or low risk be considered separately?*
Many of the studies assessed in the systematic reviews excluded participants with a higher bleeding risk due to other medical conditions or medications. Therefore, recommendations based on the available evidence may not be applicable for this patient group. The 2015 edition of the guidance advises consulting with a general medical practitioner or specialist for such patients.
4. Values and preferences *Summarise any evidence or information on values and preferences.*
Previously, indirect evidence was identified suggesting that patients would place a higher value on avoiding a thromboembolism than avoiding a bleeding complication, considering the potential outcomes of each. No new information on patient values and preferences regarding continuing versus interrupting antiplatelet therapy was identified.
6. Acceptability *Is the intervention acceptable to patients, dental team and other stakeholders?*
Either continuing or interrupting a patient's antiplatelet treatment may not be acceptable to all patients, caregivers or providers. Practitioners and patients who are already familiar with the guidance might find it more acceptable to continue to follow the established key recommendations.
7. Feasibility *Comment on cost, resource implications and implementation considerations, if applicable.*
The existing recommendation to not interrupt antiplatelet therapy for most dental treatment is likely to be standard practice for many practitioners. Interrupting antiplatelet medication may delay treatment and be less convenient for patient, dentist (and prescribing clinician, if contacted).
8. Other factors *Indicate any other factors taken into account.*
In non-dental studies, discontinuation of single or dual antiplatelet therapy has been associated with an increased risk of adverse thromboembolic events.[36-38]

9. Considered judgment and key recommendation

Summarise the group's judgements for the recommendation including 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.

The conclusions from the evidence on bleeding risk and risk of a thromboembolic event have not changed significantly. The group judged that the balance of risks was still in favour of continuing rather interrupting single or dual antiplatelet therapy for dental treatment and agreed unanimously to the key recommendation as previously:

- For a patient who is taking single or dual antiplatelet drugs, treat without interrupting their antiplatelet medication.

It was agreed that although based on low certainty evidence, as before this should be a **strong** recommendation because of the potential risk of a serious thromboembolic event if antiplatelet therapy is interrupted.

10. Additional information

Include any further information that is relevant to the considered judgement.

Details of Systematic Reviews:

Seven systematic reviews (SRs) were identified that assessed bleeding risk associated with dental procedures and included patients taking antiplatelet drugs. [6,7,9,10,13,18,34] These SRs analysed data from overlapping groups of studies and carried out different comparisons. Two of the SRs compared bleeding outcomes for patients who continued antiplatelet therapy (APT) with those whose APT was interrupted for the dental treatment.[6,34] The others compared the risk for patients on dual (DAPT) or single (SAPT) antiplatelet therapy with control groups of patients not taking any anti-thrombotic medication, or assessed the bleeding risk without comparing groups. Some of the reviews only considered patients taking antiplatelet drugs, while some included different types of antithrombotic drugs within their analyses.

Antiplatelet continuation versus interruption

Calcia et al. (2021)[6] compared the risk of bleeding events for interruption of single antiplatelet drugs with continuation for minor oral surgery. This SR found a statistically significant increase in the risk of intraoperative bleeding events (up to 15 mins after procedure) for patients who continued antiplatelet therapy with aspirin compared with those whose therapy was interrupted (RR = 3.74, 95%CI: 1.84–7.58, *p* =0.0003; 2 studies, 137 participants). There was no significant difference in the risk of post-operative bleeding events (at least 1hr after procedure) for patients who continued antiplatelet therapy with aspirin or clopidogrel compared with interruption (RR = 1.12, 95%CI: 0.38–3.26, *p* =0.59; 6 studies, 437 participants).

All of the studies included patients taking aspirin, two included patients taking clopidogrel. Patients on dual therapy were excluded. Interruption of antiplatelet therapy was for 5-7 days. Most of the oral surgery procedures were extractions, although one study included multiple extractions and procedures with mucoperiosteal flap or bone removal. The haemostatic measures used and post-operative monitoring period varied between studies. All bleeding events were controlled with local hemostatic measures. Although the included studies were all RCTs, the evidence was judged to be of low certainty because of downgrading due to the high risk of bias in all of the studies and the low numbers of participants included in the analyses.

Villanueva et al. (2019)[34] also compared continuing versus interrupting antiplatelet therapy (APT) for oral surgery and found no statistically significant difference in the risk of postoperative bleeding for patients with interrupted APT compared with continued APT (RR=0.97, 95% CI 0.41 to 2.34, *p* =0.95; 5 studies, 542 patients). Most studies included patients taking aspirin, only one of the studies included patients taking clopidogrel with or without aspirin. None specifically mentioned patients taking any other antiplatelet drug.

The type and number of oral surgery procedures included single or multiple dental extractions, single tooth extractions with or without alveoloplasty as well as other minor oral surgery procedures such as apicoectomies and periodontal surgery. None of the studies reported on the occurrence of stroke or ischemic cardiac events. Although the included studies were all RCTs, the overall certainty of evidence was rated as low due to risk of bias and imprecision.

Antiplatelet therapy versus no antiplatelet

Ockerman et al. (2020)[10] compared dual antiplatelet therapy (DAPT) with single (SAPT) or no antiplatelet therapy (no APT) and found that the risk of perioperative bleeding (during or immediately after surgery) for minor oral surgery was higher for patients on DAPT compared to those on SAPT (RR = 10.16, 95% CI 1.74 to 59.28, *p* = 0.010; 2 studies, 657 patients), and for DAPT compared to no APT (RR = 6.50, 95% CI 0.94 to 44.77, *p* = 0.057; 4 studies, 1552 patients) although the latter result was not statistically significant. When the data were analysed as risk differences, these were not statistically significant in either case (RD 35% or 0.35, 95% CI 0.27 to 0.96, *p* = 0.269 for DAPT compared with SAPT; and RD 19% or 0.19, 95% CI 0.01 to 0.39, *P* = 0.060 for DAPT compared with no APT).

The risk of post-operative bleeding was found to be significantly higher for DAPT compared to SAPT (RR 2.61, 95% CI 1.26 to 5.42, *p* = 0.010; 7 studies, 1466 patients) or no APT (RR 3.63, 95% CI 1.09 to 12.03, *p* = 0.035; 6 studies, 2358 patients). However, the risk differences were only 1% for each comparison and not statistically significant and the review authors suggested that the higher post-operative bleeding risk for DAPT may be clinically irrelevant. The incidence of post-operative bleeding for patients on continued DAPT ranged from 1.1-3.8% in the different comparisons.

Most of the studies included patients taking aspirin and clopidogrel as dual or single therapies, 2 studies included patients on aspirin/prasugrel dual therapy. The oral surgery procedures were mostly dental extractions but also included alveoloplasty, apical surgery, cyst removal, and periodontal treatment. Local haemostatic measures were sufficient to stop bleeding in all reported cases. The evidence from the included observational studies is judged to be of low certainty.

Li et al. (2020)[13] assessed post-operative bleeding risk for dental extractions in patients on DAPT (aspirin and clopidogrel). The incidence of post-operative haemorrhage was 2.80% (15/535) in the continuing DAPT group and 1.03% (30/2907) in the no DAPT group. Overall, the risk of post-operative haemorrhage with continuation of DAPT was statistically significantly higher than without DAPT (RR = 1.95, 95% CI:1.07-3.54; *p* = 0.03; 10 studies, 3442 patients in total), which is consistent with the findings of Ockerman et al. The evidence was derived from 3 RCTs and 7 observational studies and was rated as low certainty overall due to risk of bias.

Similarly, **Zabojszcz et al. (2019)**[18] carried out direct comparisons of bleeding events with dental extractions in patients on antiplatelet drugs compared with no antiplatelet drugs and found increased odds of post-operative bleeding for patients on DAPT (clopidogrel and aspirin) or SAPT (clopidogrel or aspirin). DAPT versus no APT, OR=34.77 (CI 1.33-906.16, *p* =0.03; 3 studies, 2205 participants, 96 on DAPT); clopidogrel versus no APT, OR=5.32 (CI 1.47-19.30, *p* =0.01; 3 studies, 2230 participants, 121 on SAPT); aspirin versus no APT, OR=2.16 (CI 0.61-7.65, *p* =0.23; 3 studies, 2420 participants, 311 on SAPT). The results for aspirin monotherapy were not statistically significant. The incidence of bleeding events across all 3 studies was low (1.59%; 42/2673) and all were minor bleeding complications. The evidence is judged to be of very low certainty because of downgrading for risk of bias and imprecision.

Two recent SRs specifically assessed bleeding risk associated with dental implant procedures for patients on antithrombotic therapy.[7,9] Both included studies on VKAs and DOACs as well as antiplatelet drugs.

Miziara et al. (2021)[7] assessed post-operative bleeding focusing on implant procedures including implant reopening, bone grafting, maxillary sinus lifting with lateral window and implant placement. The review found no statistically significant difference in bleeding risk comparing patients on anti-thrombotics (warfarin, antiplatelet drugs or DOACs) with patients not taking antithrombotic drugs (OR=2.19; 95% CI: 0.88–5.44, *p* =0.09; 5 studies, 317 procedures). The antiplatelet drugs included were not specified and there was no individual estimate of bleeding risk for these drugs. The evidence is rated as very low certainty due to the study type (all prospective cohort studies) and the low numbers of participants.

Bajkin et al. (2020)[9] aimed to address a similar question to Miziara et al. but did not carry out meta-analysis or make a direct comparison of bleeding risk for dental implants for patients on antithrombotics versus control groups. This SR included additional studies (9 studies in total) and provides estimates of bleeding risk for each drug type individually. The review found a bleeding rate of 0.4% (1 event in 253 procedures; 4 studies) for patients taking antiplatelet drugs, including some patients on dual clopidogrel/aspirin. The overall bleeding incidence for any antithrombotic was 2.2% (10/456). All bleeding incidences were controlled using local measures. No data on TE events was reported in the included studies. The evidence is likely to be of very low certainty due to limitations because of the study types and the low numbers of participants.

Additional systematic reviews (not fully appraised)

Two other narrative systematic reviews (Saez-Alcaide et al., 2017[39]; Nathwani et al., 2016[40]) discussed various studies, most of which were analysed in the newer SRs, and concluded that while there is some evidence to suggest that DAPT might increase the risk of postoperative bleeding, most events can be

controlled with local haemostatic measures and that antiplatelet drugs should not generally be interrupted for dental procedures.

Additional sources of information:

(i) **NICE Clinical Knowledge Summary – Antiplatelet treatment** (August 2020)[41]

- *Advise people taking antiplatelet medications to inform dentists or medical teams before any surgery is scheduled.*
- *Dual antiplatelet therapy (DAPT) increases the risk of surgical bleeding complications. The bleeding risk is further increased if ticagrelor or prasugrel are used rather than clopidogrel.*
- *For people undergoing dental surgery antiplatelet therapy should continue uninterrupted.*

These recommendations are based on the European Society of Cardiology (ESC) 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS, the Scottish Dental Clinical Effectiveness Programme (SDCEP) Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs [SDCEP, 2015], and the Summary of Product Characteristics for clopidogrel, ticagrelor and prasugrel.

The ESC guideline advises: *In surgical procedures with low bleeding risk, every effort should be taken not to discontinue DAPT perioperatively.*

(ii) **SIGN 129 Antithrombotics: indications and management** (updated 2013, to be withdrawn in 2022)[35]

- *Aspirin discontinuation is not generally required prior to invasive procedures. The risk-benefit ratio of interrupting aspirin prophylaxis should be assessed individually, with consideration given to the type of planned procedure.*
- *Discontinuation of dipyridamole is not generally required prior to invasive procedures, but as is the case for aspirin, the risks of interrupting therapy, and of bleeding if continued, should be individually assessed.*
- *Consideration should be given to temporary discontinuation of clopidogrel seven days prior to invasive procedures if the risk of increased bleeding is deemed to exceed the risk of thrombosis.*
- *If a coronary stent has been placed within the last 12 months, cardiology advice should be sought prior to discontinuation of clopidogrel.*

None of the recommendations refer to dental treatment and the supporting evidence is for non-dental surgery.

(iii) **American Dental Association – Oral Health Topics – Oral Anticoagulant and Antiplatelet Medications and Dental Procedures** (updated September 2020)[29]

There is general agreement based on strong evidence that treatment regimens with these older anticoagulants/antiplatelet agents (including clopidogrel, prasugrel, ticagrelor and/or aspirin) *should not be altered before dental procedures.*

This is based on a review of articles, including SRs discussed above or for the first edition of the guidance, and the following consensus opinion.

The American Heart Association, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American College of Surgeons, and the American Dental Association published a consensus opinion about drug-eluting stents and antiplatelet therapy (e.g., aspirin, clopidogrel, ticlopidine). The consensus opinion states that healthcare providers who perform invasive or surgical procedures (e.g., dentists) and are concerned about periprocedural and postprocedural bleeding should contact the patient's cardiologist regarding the patient's antiplatelet regimen and discuss optimal patient management, before discontinuing the antiplatelet medications. Given the importance of antiplatelet medications post-stent implantation in minimizing the risk of stent thrombosis, the medications should not be discontinued prematurely.[42]

(iv) **New South Wales Clinical Excellence Commission Guidelines on Perioperative Management of Anticoagulant and Antiplatelet Agents** (Dec 2018)[31]

In this guideline, minimal bleeding risk procedures include minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings.
The guideline advises: *Generally, for patients with a low risk of thromboembolism and a minimal/ low risk of procedural bleeding, aspirin can be continued. For patients taking dual antiplatelet therapy, generally aspirin can be continued however other antiplatelet agents should be ceased according to Table 10. The treating surgeon should advise when antiplatelet agents can be recommenced. Generally antiplatelet agents should be recommenced as soon as possible following the surgery or procedure.*
Table 10 recommends discontinuing aspirin, clopidogrel, prasugrel or ticagrelor for at least 5-7 days before the procedure (if required).

No methodology is reported for this guideline.

(v) **American College of Surgeons' Guidelines for the Perioperative Management of Antithrombotic Medication** (2018)[32]

Certain minimally invasive procedures like dental extraction, cataract removal, joint injections, and diagnostic endoscopic procedures have minimal bleeding risk and do not require discontinuation of antithrombotic agents.
No specific advice for antiplatelet drugs provided.

(vi) **Extracts from Summary of Product Characteristics (SPC) sheets**:

Aspirin (https://www.medicines.org.uk/emc/product/10173/smpc)

- *There is an increased risk of haemorrhage and prolongation of bleeding time particularly during or after surgery (even in cases of minor procedures, e.g. tooth extraction). Use with caution before surgery, including tooth extraction. Temporary discontinuation of treatment may be necessary.*

Clopidogrel (https://www.medicines.org.uk/emc/product/5751/smpc)

- *Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken.*

- *Patients should be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician.*

Dipyridamole (https://www.medicines.org.uk/emc/product/3557/smpc)

- *Addition of dipyridamole to acetylsalicylic acid does not increase the incidence of bleeding events. When dipyridamole was administered concomitantly with warfarin, bleeding was no greater in frequency or severity than that observed when warfarin was administered alone.*

Prasugrel (https://www.medicines.org.uk/emc/product/6466/smpc)

- *Patients should be told that it might take longer than usual to stop bleeding when they take prasugrel (in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician.*
- *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.*

Ticagrelor (https://www.medicines.org.uk/emc/product/7606/smpc)

- *Patients should be advised to inform physicians and dentists that they are taking ticagrelor before any surgery is scheduled and before any new medicinal product is taken.*
- *If a patient is to undergo elective surgery and antiplatelet effect is not desired, ticagrelor should be discontinued 5 days prior to surgery.*

Clinical Question 3

Q3: Should the DOACs be continued or interrupted for dental treatment?

(To include apixaban, dabigatran, rivaroxaban and edoxaban)

Recommendations in 2015 edition of guidance:

- For a patient who is taking a NOAC and requires a dental procedure with a low risk of bleeding complications, treat without interrupting their anticoagulant medication.
  (Conditional recommendation; very low quality evidence)
- For a patient who is taking a NOAC and requires a dental procedure with a higher risk of bleeding complications, advise them to miss (apixaban, dabigatran)/delay (rivaroxaban) their morning dose on the day of their dental treatment.
  (Conditional recommendation; very low quality evidence)

Basis for recommendation:
There was a lack of direct clinical evidence to favour either continuing or interrupting NOAC medication for invasive dental treatments. The only available evidence came from clinical trials comparing spontaneous or peri-procedural bleeding for each NOAC with other antithrombotic drugs. No direct evidence was found that specifically assessed bleeding risk for dental procedures.

The recommendations were based on the balance of likely effects of each option for each dental procedure, the known characteristics of the drugs, such as their short half-lives and rapid onset of action and consensus of expert opinion. They were judged to be conditional recommendations because of the lack of evidence and the fine balance between the potential risks and benefits of the treatment options.

The evidence considered previously is documented in the *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs Guidance Development Methodology (2015)* (available on request).

1. Summary of evidence since 2015 edition of guidance

*Summarise the evidence for the effects of the intervention on the important outcomes including the ratings for the **certainty** of the evidence. Comment on the degree of **consistency** demonstrated by the available evidence. Note where evidence is lacking.*

Several systematic reviews (SRs) summarise more recent direct evidence from dental studies that relates to the key question of whether DOACs should be continued or interrupted for dental treatment.

The most relevant evidence is included in a systematic review (SR) and meta-analysis which found no significant difference in post-operative bleeding events in patients who continued versus patients who discontinued DOAC therapy for a variety of invasive oral procedures.[14] The analysis included a small number of patients taking edoxaban.

Four SRs[7,9,19,25] assessed bleeding risk for dental procedures in patients on DOAC therapy compared to non-anticoagulated participants, or with no comparison and suggest that there may be a higher risk of post-operative bleeding complications in patients taking DOACs compared with no anticoagulant. The estimates of risk range from 3-fold higher, from analysis including a variety of dental procedures[19], to no significant difference when only including dental implant procedures.[25] One SR reported no significant difference in bleeding risk for implants in patients taking anti-thrombotic drugs (including DOACs) versus none but did not provide an individual estimate of risk for DOACs[7] and another estimated a bleeding rate of 3.3% for implants in patients taking DOACs (compared to an overall rate of 2.2% for all antithrombotics).[9]

Almost all bleeding events recorded in the included studies across the SRs were managed with local measures. No thromboembolic events were reported, although follow-up periods may not have been sufficiently long to detect these. There was limited data for edoxaban. Most of the studies excluded patients with a higher bleeding risk due to other medical conditions or medications.

No relevant RCTs on DOACs were found so all included studies were observational. Overall the evidence from the systematic reviews is judged to be of **very low certainty** due to downgrading for risk of bias and imprecision resulting from the small sample sizes.

Does the evidence differ from previously?

There is now direct evidence available from systematic reviews of dental studies relevant to the question of whether DOACs should be continued or interrupted for dental treatment. These suggest that while the risk of post-operative bleeding events for dental procedures in patients taking DOACs may be higher than non-anticoagulated patients, the risk is likely to be low, and may not be significantly different compared to interruption of DOACs. The results should be interpreted with caution due to their very low certainty.

Additional sources of information

The National Institute of Health and Care Excellence (NICE) Clinical Knowledge Summary[28], European Heart Rhythm Association (EHRA) guide[43], American Dental Association (ADA) Oral Health Topic on anticoagulants and antiplatelets[29], and Australian Clinical Excellence Commission (CEC) guidelines[31] either advise not to interrupt DOACs or that interruption may not be required for most dental procedures. However, some of these sources advise performing procedures 12-24 hours after the last dose, which may require missing a dose. The drug manufacturers' SPC sheets provide recommendations for interruption schedules but do not specify whether DOACs should be interrupted for dental surgery.

See Section 10 of this form for further details of the evidence and additional sources of information.

2. Balance of effects

Comment 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.

There may be a higher risk of post-operative bleeding complications for patients taking DOACs compared with no anticoagulant, although bleeding events are usually manageable with local

haemostatic measures. Estimates of bleeding rates vary and there is limited evidence for the more complex and invasive dental procedures. Recent meta-analysis suggests that there is no significant difference between continuing and interrupting DOACs.

There is insufficient data in the evidence considered to estimate the risk of thromboembolic events for patients interrupting DOAC therapy for dental procedures. Although it may be that the absolute risk of a thromboembolic event if DOAC therapy is briefly interrupted is less that the risk of bleeding complications if DOAC therapy is continued, the outcome is potentially much more serious. Because of the short half-lives and rapid onset of action of the DOACs, only a relatively brief interruption would be required.

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

Many of the studies assessed in the systematic reviews excluded participants with a higher bleeding risk due to other medical conditions or medications. The 2015 edition of the guidance advises consulting with a general medical practitioner or specialist for such patients.

4. Values and preferences
Summarise any evidence or information on values and preferences.

Although no evidence regarding patient preferences around continuing versus interrupting DOAC therapy for dental procedures was identified, 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. A patient on the group noted their concern about being asked to stop a DOAC 24-48 hours before a dental procedure and preference to restart medication as soon as possible if interrupted.

Recent interviews conducted by TRiaDS researchers (unpublished) suggest that some practitioners might prefer to advise drug interruption even for dental procedures with a low bleeding risk.

6. Acceptability
Is the intervention acceptable to patients, dental team and other stakeholders?

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

Practitioners and patients who are already familiar with the guidance might find it more acceptable to continue to follow the established key recommendations.

7. Feasibility
Comment on cost, resource implications and implementation considerations, if applicable.

Interrupting anticoagulant medication may delay treatment and be less convenient for patient, dentist (and prescribing clinician, if contacted). The existing recommendations do not require the dentist to have information on renal function to determine the timing for interrupting DOACs.

The existing DOAC recommendations are feasible to implement for at least some practitioners, as reported in surveys and interviews (TRiaDS, unpublished).

8. Other factors
Indicate any other factors taken into account.

Reversal agents are now available for dabigatran, apixaban and rivaroxaban for life-threatening or uncontrolled bleeding (specialist supervision in hospital).

9. Considered judgment and key recommendation
Summarise the group's judgements for the recommendation including 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.

Although there is now direct evidence about the risk of bleeding complications for dental patients taking DOACs, this is of very low certainty and there is very limited evidence about the more invasive dental procedures. The group agreed that for low bleeding risk dental procedures, the balance of risks and other factors is in favour of not interrupting DOAC medication, whereas for higher bleeding risk procedures, for which the evidence is very uncertain, the balance supports a brief interruption.

The group also agreed that although there is limited dental evidence about bleeding risk for edoxaban, the available information supports its inclusion in the recommendations.

The key recommendations for low and higher bleeding risk dental procedures as in the 2015 edition of the guidance were judged to be applicable, as follows:

- For a patient who is taking a DOAC and requires a dental procedure with a low risk of bleeding complications, treat without interrupting their anticoagulant medication.
- For a patient who is taking a DOAC and requires a dental procedure with a higher risk of bleeding complications, advise them to miss (apixaban, dabigatran) or delay (rivaroxaban, edoxaban) their morning dose on the day of their dental treatment.

The group judged that, as previously these should be **conditional** recommendations based on the very low certainty of the evidence and fine balance of risks.

The group also recommended that the guidance should note that anticoagulant therapy is prescribed for significant clinical indications and should not be interrupted unnecessarily (e.g. for low bleeding risk procedures).

10. Additional information

Include any further information that is relevant to the considered judgement.

Details of Systematic Reviews

Eight recent systematic reviews (SRs) were identified that assessed bleeding risk associated with dental procedures and included patients taking DOACs.[7,9,11,14,19,21,24,25] These SRs analysed data from overlapping groups of studies and carried out different comparisons. Some of the reviews only considered patients taking DOACs, while some included different types of antithrombotic drugs within their analyses. Two of the SRs compared bleeding outcomes for patients who continued DOACs with those whose DOAC therapy was interrupted for the dental treatment.[11,14] The others compared the risk for patients on various antithrombotic drugs with control groups of patients not taking any anti-thrombotic medication or assessed the bleeding risk without comparing groups.[7,9,19,21,24,25]

DOAC continuation versus interruption

Manfredi et al. (2019)[14] carried out meta-analysis of patients continuing versus discontinuing their DOAC therapy for invasive oral procedures and found no statistically significant difference in the odds of postoperative bleeding for each group (overall odds ratio, OR = 0.92, 95% CI = 0.37–2.27, p = 0.85; 6 studies, 283 participants). An indirect comparison of data from 21 studies estimated a frequency of post-operative bleeding events of 11.8% (59/497) in patients who continued DOAC therapy and 13.5% (27/200) in patients who discontinued their DOAC. All bleeding events recorded in the included studies were managed with local measures and did not require hospitalisation or blood transfusion. No thromboembolic events were reported for either patient group.

The dental procedures carried out included single or multiple dental extractions, single or multiple dental implants or exposures, scaling and root planing, mucosal biopsies, cyst enucleation, abscess incision and drainage, gingivectomy, and ridge augmentation. Rivaroxaban was the most frequently used DOAC (369 out of the 740 total patients), followed by dabigatran (183/740), apixaban (154/740) and edoxaban (22/740). The timing of discontinuation varied between studies but was not reported in the systematic review.

The review authors concluded that they found no important differences in bleeding events in patients who continued versus patients who discontinued DOAC therapy for invasive oral procedures. The evidence is judged to be of very low certainty. All included studies were observational and the evidence rating was downgraded to very low due to a high risk of bias in most of the studies and the small study sizes.

Chahine et al. (2019)[11] also compared post-operative bleeding for dental procedures in patients continuing their anticoagulant with control groups including patients whose anticoagulants had been interrupted. This SR only considered RCTs or controlled clinical trials and provided a qualitative synthesis without any meta-analysis. Only one of the 10 studies included patients on DOACs (rivaroxaban, apixaban or dabigatran). There were no incidences of post-operative bleeding in the group continuing the DOAC for dental implants in this study.

Two other SRs, **Lusk et al. (2018)**[21] and **Lanau et al. 2017**,[24] assessed some of the studies included in Manfredi et al. but both only provide a qualitative analysis and no direct comparison of bleeding risk for continuation versus interruption of DOACs. Both concluded that the risk of post-operative bleeding complications is low for dental procedures in patients continuing their DOAC and that bleeding is manageable with conventional haemostatic measures.

Three other SRs that searched for RCTs assessing bleeding outcomes for patients continuing or interrupting oral anticoagulants or antiplatelets did not find any relevant RCTs for DOACs.[6,12,22]

DOAC (including continuation, modification or interruption) versus no DOAC

Bensi et al. (2018)[19] assessed many of the studies included in the SR of Manfredi et al.[14] but conducted a different analysis, comparing bleeding risk for dental treatment in patients on DOAC therapy (irrespective of continuation, modification or interruption) with patients not on any DOAC therapy. Thirteen observational studies (796 surgical procedures) were included in a qualitative analysis. Meta-analysis for postoperative bleeding risk, carried out on a subset of the studies, found an overall risk ratio (RR) of 3.04 (95% CI = 1.31–7.04; 5 studies) for patients taking any DOAC compared to patients not taking an anticoagulant. Sub-group analysis for the individual DOACs found a RR of 4.13 (95% CI = 1.25–13.69; 3 studies) for rivaroxaban and a RR of 1.00 (95% CI = 0.21–4.82; 2 studies) for dabigatran. There was no meta-analysis for apixaban or edoxaban due to a lack of clinical studies. The SR also assessed post-operative bleeding events in patients taking DOACs compared with patients taking VKAs and found an RR of 0.82 (95% CI = 0.3-2.25; 2 studies).

The review concluded that patients taking DOACs have a three-fold increased risk of postoperative bleeding after oral surgery compared to patients not taking any anticoagulant. According to the meta-analysis, the risk is higher for rivaroxaban than dabigatran, although the data for each was derived from a small number of studies. The SR also concluded that there is a similar bleeding risk for patients taking DOACs compared those taking VKAs.

Surgical procedures included tooth extractions, implant placements, scaling and root planing procedures, soft tissue biopsies, ridge augmentations, implant exposures, alveoplasty, gingivoplasty, gingivectomy, cyst enucleation, abscess drainage, open reduction and internal fixation. More than 70% were extractions.

The evidence is judged to be of very low certainty. The included studies are all observational studies and the evidence certainty is downgraded further due to the high risk of bias in the majority of the studies included in the meta-analysis and the low numbers of participants.

Shi et al. (2017)[25] compared the risk of post-operative bleeding events after minor dental surgery in patients on continuous oral anticoagulant therapy (OAT; VKAs or DOACs) versus patients not taking any anticoagulant drug. The total post-operative bleeding rate for OAT patients was 4.33% (91/2102) compared to 1.10% (25/2271) for the non-OAT patients. Two patients developed severe bleeding but neither were taking a DOAC. Meta-analysis for postoperative bleeding risk for all dental procedures found an overall risk ratio (RR) of 2.794 (95% CI = 1.722–4.532; p=0.000; 12 studies, 4373 participants) indicating a higher post-operative bleeding risk for patients taking a VKA or a DOAC compared with non-OAT patients.

Sub-group analysis for the different drug types found a significant difference in risk of post-operative bleeding for VKAs versus no OAT (RR=3.067, 95% CI: 1.838–5.118, *p* =0.000; 10 studies) but no statistically significant difference for DOACs (rivaroxaban and dabigatran) versus no OAT (RR=1.603, 95% CI: 0.430–5.980, *p* =0.482; 3 studies). The DOAC studies only included implant surgery. The result for the DOACs is in contrast to the finding reported by Bensi et al.[19] of a higher bleeding risk for patients taking a DOAC versus no OAT. However, the meta-analysis carried out by Bensi et al. included 2 additional studies and dental procedures other than implant surgery.

The evidence on DOACs included in Shi et al. is derived from observational studies and is judged to be of very low certainty due to downgrading for imprecision from the small sample sizes.

Two recent SRs specifically assessed bleeding risk associated with dental implant procedures for patients on antithrombotic therapy.[7,9] Both included studies on VKAs and antiplatelet drugs (APs) as well as studies on DOACs.

Miziara et al. (2021)[7] assessed post-operative bleeding following implant procedures including implant reopening, bone grafting, maxillary sinus lifting with lateral window and implant placement. The review found no statistically significant difference in bleeding risk comparing patients on anti-thrombotics (warfarin, antiplatelet drugs or DOACs) with patients not taking antithrombotic drugs (OR=2.19; 95% CI: 0.88–5.44, *p* =0.09; 5 studies, 317 procedures). None of the studies included patients taking edoxaban. The authors judged that there were insufficient studies and participants to allow an individual estimate of bleeding risk for patients taking DOACs.

None of the studies reported major post-operative bleeding and the bleeding was managed with local haemostatic measures. The authors concluded that the absolute risk is low and there is no need to discontinue or alter the dose of the antithrombotic drug for implant placement surgery. The evidence is rated as very low certainty due to the study type (all prospective cohort studies) and the low numbers of participants.

Bajkin et al. (2020)[9] aimed to address a similar question to Miziara et al. but did not carry out meta-analysis or make a direct comparison of bleeding risk for dental implants for patients on antithrombotics versus control groups. This SR included additional studies (9 studies in total) and provides estimates of bleeding risk for each drug type individually.

The review found a bleeding rate of 0.4% (1 event in 253 procedures; 4 studies) for patients taking antiplatelet drugs, including some patients on dual clopidogrel/aspirin, and a bleeding rate for oral anticoagulants of 5.7% (6/105; 4 studies) including some patients taking both OACs and APs. The bleeding rate for patients taking DOACs was 3.3% (3/90; 6 studies) including patients taking rivaroxaban or dabigatran. The overall bleeding incidence for any antithrombotic was 2.2% (10/456). All bleeding incidences were controlled using local measures.

The data suggests that the risk of postoperative bleeding events after implant procedures in patients taking antithrombotics is low and the authors concluded that the balance of risk for bleeding versus thromboembolic events supports dental implant placement without interruption of APs, OACs or DOACs, if appropriate haemostatic measures are used. No data on TE events was reported in the

included studies. The evidence is likely to be of very low certainty due to limitations because of the study types and the low numbers of participants.

Additional sources of information:

(i) **NICE Clinical Knowledge Summary - Anticoagulation - oral** (April 2021)[29]

Recommendations for DOACs (the same advice is given for apixaban, dabigatran, rivaroxaban and edoxaban):

For most minor surgical procedures and those associated with a minor bleeding risk (including dental interventions, such as extraction of 1 to 3 teeth, periodontal surgery, incision of abscess, and implant positioning), it is recommended not to interrupt oral anticoagulation.

- *In general, these procedures can be performed 12–24 hours after the last dose of DOAC is taken.*
- *It may be practical to have the intervention scheduled 18–24 hours after the last dose of DOAC is taken, then restart DOAC 6 hours later. This means that one dose of DOAC may be missed.*
  Advise patients they may have to stop DOAC treatment temporarily for certain surgical and dental treatments.

These recommendations are based on the manufacturer's Summaries of Product Characteristics and the 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation.[44] *The European Heart Rhythm Association (EHRA) recommends not to interrupt oral anticoagulation for most minor surgical procedures and those procedures where bleeding is easily controllable.*

(ii) **European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation** (2021)[43]

An updated version of the EHRA guide cited in the NICE CSK was published in 2021 with modified categorisation of bleeding risk for dental procedures.

2018:
Interventions with minor bleeding risk - includes dental interventions, such as extraction of 1 to 3 teeth, periodontal surgery, incision of abscess, and implant positioning.
Advises for procedures with no important bleeding risk and/or adequate local haemostasis possible to perform procedure 12-24 hours after last intake and restart 6 hours later.

2021:
Minor risk interventions (i.e. infrequent bleeding with low clinical impact) - includes dental interventions, such as extraction of 1 to 3 teeth, periodontal surgery, implant positioning and subgingival scaling/cleaning.
Advises for minor risk procedures to perform procedure 12-24 hours after last intake and resume 6 hours later.
Low risk interventions (i.e. infrequent bleeding or with non-severe clinical impact) - includes complex dental procedures.
Advises for low risk procedures to perform procedure 24-48 hours after the last intake of

dabigatran or 24-36 hours for apixaban, edoxaban or rivaroxaban, depending on renal function, and resume 24 hours later.

The EHRA practical guide is a position paper rather than a guideline and does not report the methodology used for development of the advice. The basis for the categorisation of dental procedures is unclear and there is no further detail on how complex dental procedures are defined.

(iii) **American Dental Association – Oral Health Topics - Oral Anticoagulant and Antiplatelet Medications and Dental Procedures** (updated September 2020)[29]

There is no direct evidence from prospective trials comparing different periprocedural management strategies for dental patients receiving the target-specific oral anticoagulants and evaluating effects on patient outcomes. However, based on limited evidence, in most cases, there is no need to alter the anticoagulation regimen prior to most dental interventions.

This is based on a review of articles including several of the SRs discussed above.

(iv) **New South Wales Clinical Excellence Commission Guidelines on Perioperative Management of Anticoagulant and Antiplatelet Agents** (Dec 2018)[31]

In this guideline, minimal bleeding risk procedures include minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings.
The guideline advises:
Withholding of oral direct thrombin inhibitor [dabigatran (Pradaxa®) or factor Xa inhibitor [apixaban (Eliquis®) and rivaroxaban (Xarelto®)] therapy for patients who are having selected minimal or low bleeding risk procedures (see Table 1) may not be required. The treating surgeon should advise whether oral direct thrombin inhibitor or factor Xa inhibitor therapy needs to be withheld. If the decision is made to withhold therapy, it should be withheld according to the guidelines.

The tables included in the guideline do not provide advice for minimal risk procedures. The advice for low risk procedures is for the last dose 24-72 hours before surgery for dabigatran or 24-48 hours for apixaban or rivaroxaban, depending on renal function, with resumption 24 hours later.

No methodology is reported for this guideline.

(v) **American College of Surgeons' Guidelines for the Perioperative Management of Antithrombotic Medication** (2018)[32]

Certain minimally invasive procedures like dental extraction, cataract removal, joint injections, and diagnostic endoscopic procedures have minimal bleeding risk and do not require discontinuation of antithrombotic agents.
No specific advice for DOACs provided.

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

Apixaban (https://www.medicines.org.uk/emc/product/2878/smpc)

- *Apixaban 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.

- *Apixaban 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.*
- *If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.*
- *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 (https://www.medicines.org.uk/emc/product/6402/smpc)

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

Edoxaban (https://www.medicines.org.uk/emc/product/6906/smpc)

- *If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, edoxaban should be stopped as soon as possible and preferably at least 24 hours before the procedure.*
- *In deciding whether a procedure should be delayed until 24 hours after the last dose of edoxaban, the increased risk of bleeding should be weighed against the urgency of the intervention. Edoxaban should be restarted after the surgical or other procedures as soon as adequate haemostasis has been established, noting that the time to onset of the edoxaban anticoagulant therapeutic effect is 1 – 2 hours.*

Dabigatran (https://www.medicines.org.uk/emc/product/6229/smpc)

- *Surgery and interventions:*
  Patients on Pradaxa who undergo surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of Pradaxa.
  Caution should be exercised when treatment is temporarily discontinued for interventions and anticoagulant monitoring is warranted. Clearance of dabigatran in patients with renal insufficiency may take longer. This should be considered in advance of any procedures. In such cases a coagulation test may help to determine whether haemostasis is still impaired.
- *Emergency surgery or urgent procedures:*
  Pradaxa should be temporarily discontinued. When rapid reversal of the anticoagulation effect is required the specific reversal agent (Praxbind, idarucizumab) to Pradaxa is available.
  Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Pradaxa treatment can be re-initiated 24 hours after administration of Praxbind (idarucizumab), if the patient is clinically stable and adequate haemostasis has been achieved.

- *Subacute surgery/interventions:*
  Pradaxa should be temporarily discontinued. A surgery / intervention should be delayed if possible until at least 12 hours after the last dose. If surgery cannot be delayed the risk of bleeding may be increased. This risk of bleeding should be weighed against the urgency of intervention.
- *Elective surgery:*
  If possible, Pradaxa should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required consider stopping Pradaxa 2-4 days before surgery.

Table 6 summarises discontinuation rules before invasive or surgical procedures.

Renal function (CrCL in mL/min)	Estimated half-life (hours)	Stop dabigatran before elective surgery	
		High risk of bleeding or major surgery	Standard risk
≥ 80	~ 13	2 days before	24 hours before
≥ 50-< 80	~ 15	2-3 days before	1-2 days before
≥ 30-< 50	~ 18	4 days before	2-3 days before (> 48 hours)

Postoperative phase:
Pradaxa treatment should be resumed / started after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.
Patients at risk for bleeding or patients at risk of overexposure, notably patients with moderate renal impairment (CrCL 30-50 mL/min), should be treated with caution.

Clinical Question 4

Q4: Should the injectable anticoagulants be continued or interrupted for dental treatment?

(To include dalteparin, enoxaparin and tinzaparin)

Recommendation in 2015 edition of guidance

No key recommendation made.

Basis:
There is a lack of direct clinical evidence regarding the dental treatment of patients taking injectable anticoagulants, including the LMWHs. Furthermore, patients taking these drugs are likely to have varied conditions and drug regimes such that further information is required to make a reasonable judgement on the management of their dental treatment.

The information considered previously is documented in the *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs Guidance Development Methodology (2015)* (available on request).

1. Summary of evidence

*Summarise the evidence for the effects of the intervention on the important outcomes including the ratings for the **certainty** of the evidence. Comment on the degree of **consistency** demonstrated by the available evidence. Note where evidence is lacking.*

There is limited evidence on the risk of bleeding complications for dental surgery in patients taking a LMWH. No recent systematic reviews or meta-analysis that specifically assess bleeding risk for dental patients on LMWHs were identified. A small number of studies including dental patients on LMWH bridging are considered in SRs assessing bleeding risk in patients on any antithrombotic therapy.

Two observational studies[45,46] concluded that bridging with LMWHs is associated with a higher bleeding risk compared to continuing VKA therapy, for implant surgery or extractions. However, this was based on very small sample sizes. In contrast, an older RCT[47] reported no statistically significant difference in bleeding events after dental extractions between patients on continued VKA treatment compared with patients whose VKA had been stopped for 3-4 days and were on LMWH bridging. All cases of bleeding were controlled using local hemostatic measures and none of the patients on LMWH bridging in the 3 studies needed hospitalisation for bleeding events.

Overall, the evidence is rated as **very low certainty** due to the small sample sizes, inconsistency and indirectness with respect to the key question.

Does the evidence differ from previously?

As found previously there is a lack of direct evidence on the risk of bleeding complications for patients on LMWHs. Two more recent studies, and one considered previously, were identified through the systematic reviews. However, it is unclear from these studies whether the risk of bleeding complications from dental treatment is higher or not for patients on LMWH bridging compared to

patients continuing VKA therapy. Evidence relating to dental patients on longer term prophylactic or therapeutic doses of LMWHs, or that directly compares the risks of bleeding and thromboembolic complications for patients continuing versus interrupting LMWHs for dental procedures was not identified.

Additional sources of information

The advice for management of patients taking LMWHs in various other sources of information varies.

Local dental guidelines for NHS Tayside (2013) and NHS Highland (2014), considered previously, provided advice for management of patients on low dose prophylaxis of deep vein thrombosis with dalteparin or enoxaparin, including options to treat as for warfarin or to omit 24 hours prior to an elective extraction if there are particular concerns regarding bleeding. They also advise for patients taking higher therapeutic doses, to delay dental treatment or seek specialist advice.

A 2012 American College of Chest Physicians guideline[48] recommends omitting therapeutic dose LMWH for 24 hours before surgery, but does not specify whether this applies to dental surgery.

The SPC sheets for the LMWHs advise that the risk of bleeding (not specifically surgery related) is dependent on the dose and that elderly patients may be at an increased risk for bleeding complications in the therapeutic dosage ranges (dalteparin and enoxaparin) but that no increased bleeding tendency is observed for this patient group with the prophylactic dosage ranges (enoxaparin).

North West Medicines Information have developed a draft advice document for managing dental patients taking LMWHs, with a proposed scheme for judging whether the patient is likely to be on a prophylactic or therapeutic dose (refer to Section 10 of this form for details). The suggested advice is to continue LMWH for patients on a prophylactic dose and to seek specialist advice for patients on therapeutic doses.

See Section 10 of this form for further details of the evidence and additional sources of information.

2. Balance of effects
Comment 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.

There is a lack of clear evidence on the risk of bleeding versus thromboembolic complications for patients continuing or interrupting LMWHs for dental procedures. The bleeding risk is likely to be dose dependent and therefore may be lower for patients taking prophylactic dose LWMH. The thromboembolic risk may be of more concern when interrupting a treatment dose compared to a prophylactic dose.

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

Patients on prophylactic doses of LMWHs may have a lower risk of bleeding complications than those on higher treatment doses. It may be reasonable to consider these subgroups separately, if feasible for dentists to identify patients in each group.
4. Values and preferences *Summarise any evidence or information on values and preferences.*
Although no evidence regarding patient preferences around continuing versus interrupting LMWHs for dental procedures was identified, 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.
6. Acceptability *Is the intervention acceptable to patients, dental team and other stakeholders?*
Either continuing or interrupting a patient's LMWH therapy may not be acceptable to all patients, caregivers or providers.
7. Feasibility *Comment on cost, resource implications and implementation considerations, if applicable.*
Interrupting anticoagulant medication may delay treatment and be less convenient for patient, dentist (and prescribing clinician, if contacted).
8. Other factors *Indicate any other factors taken into account.*
Treatment doses of LMWHs are considered to be equivalent to treatment with warfarin (within therapeutic range) or DOACs. In support of this, indirect (non-dental) evidence suggests that there may be no significant difference in the risk of bleeding events in patients having long-term treatment for venous thromboembolism comparing LMWHs with VKAs.[49,50] See Section 10 of this form for further details. The anticoagulant effect of LMWHs can be incompletely reversed with intravenous protamine.
9. Considered judgment and key recommendation *Summarise the group's judgements for the recommendation including 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.*

The group considered that there was sufficient information and indirect evidence to support a **conditional** recommendation for dental patients taking prophylactic (low) dose LMWHs, to treat without interrupting their medication.

Key recommendation:

- For a patient who is taking a prophylactic (low) dose of a low molecular weight heparin, treat without interrupting their anticoagulant medication.

The bleeding risk is likely to be higher for patients taking treatment (higher doses) of LMWHs and the thromboembolic risk if medication interrupted may also be higher. Patients on treatment doses may have more varied and complex medical conditions so it is more difficult to generalize for these patients. The group agreed not to make a key recommendation for dental treatment for this patient group but to advise consulting with the patient's prescribing clinician for more information about the patient's individual risks.

Acknowledging that it may be unclear what type of dose of LMWH a patient is taking, the group also recommended advising that if uncertain, the dentist should consult with the prescribing clinician.

10. Additional information

Include any further information that is relevant to the considered judgement.

Evidence details

Three systematic reviews[7,11,24] assessing bleeding risk for patients on antithrombotic therapy (AT), compared with interrupted or no AT, included studies with patients on LMWH bridging having interrupted VKAs for dental treatment. A further SR[6] searched for RCTs on dental patients taking any single anticoagulant or antiplatelet, comparing drug interruption with continuation and found none for LMWHs.

One of the SRs[7] found no statistically significant difference in bleeding risk comparing patients on anti-thrombotics (warfarin, antiplatelet drugs, DOACs or LMWHs) with patients not taking antithrombotic drugs (OR=2.19; 95% CI: 0.88–5.44, *p*=0.09; 5 studies, 317 procedures), although only one of the studies included patients on LMWHs. None of the SRs conducted meta-analysis specific for the LMWH groups.

The three dental studies included in the SRs are described individually here:

Clemm et al. (2016)[45] compared the incidence of bleeding events in patients continuing antithrombotic therapy (AT) for implant-related surgery, with a control group of patients not on AT. The AT group included patients on antiplatelets (61), VKAs (32), DOACs (16) or VKAs bridged with LMWH for 3 days (8). The highest frequency of bleeding was seen in the group on LMWH bridging (12.5%; compared to 6.7% for VKAs) but this was based on one event and was not statistically significantly different to the control non-AT group. The authors concluded that bridging with LMWH is associated with higher bleeding risk, but this is very uncertain due to the small sample size

Erden et al. (2016)[46] compared various bleeding outcomes in a small group of patients (36) with prosthetic heart valves who had a first dental extraction while taking warfarin, then a second 15 days later after 5 days of LMWH bridging (enoxaparin) without warfarin. Statistically significant increases in

immediate and early bleeds and bleeding time were observed when the patients were on LMWH bridging. The authors concluded that the risk of bleeding after extractions is higher for LMWH bridging compared to continued warfarin treatment.

Bajkin et al. (2009)[47] compared patients on continued VKA treatment (109) with patients whose VKA had been stopped for 3-4 days and were on LMWH (nadroparin) bridging (105). This RCT found no statistically significant difference in bleeding events after dental extractions between the groups. All cases of bleeding were mild and easily controlled using local hemostatic measures.

None of the patients on LMWH bridging in the 3 studies needed hospitalisation for bleeding events.

Additional indirect evidence

Two Cochrane systematic reviews, not identified through the dental evidence search or formally appraised, provide some very indirect evidence about LMWHs and non-dental bleeding risk. These reviews suggest that there may be no significant difference, comparing LMWHs with VKAs, in the risk of non-dental bleeding events in patients having long-term treatment for venous thromboembolism.[49,50]

Additional sources of information:

Guidelines identified for 2015 edition of guidance

(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:

- *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 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.*

(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 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.*

(iii) **American College of Chest Physicians Evidence-Based Clinical Practice Guidelines - Perioperative Management of Antithrombotic Therapy** (2012)[48]

- *In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we suggest administering the last preoperative dose of LMWH approximately 24 h before surgery instead of 12 h before surgery (Grade 2C).*
  Grade 2C refers to a weak recommendation, based on low or very low quality evidence.

(iv) Extracts from Summary of Product Characteristics (SPC) sheets

Extracts from the drug SPC sheets refer to bleeding but are not necessarily specific to surgical bleeding and certainly not specific to dental surgery.

Dalteparin (https://www.medicines.org.uk/emc/product/4247/smpc)

- *The risk of bleeding is depending on dose. Most bleedings are mild. Severe bleedings have been reported, some cases with fatal outcome.*
- *Caution should be exercised in patients in whom there is an increased risk of bleeding complications, e.g. following surgery or trauma, haemorrhagic stroke, severe liver or renal failure, thrombocytopenia or defective platelet function, uncontrolled hypertension, hypertensive or diabetic retinopathy, patients receiving concurrent anticoagulant/antiplatelet agents. Caution shall also be observed at high-dose treatment with dalteparin (such as those needed to treat acute deep-vein thrombosis, pulmonary embolism, and unstable coronary artery disease).*
- *Elderly patients (especially patients aged eighty years and above) may be at an increased risk for bleeding complications within the therapeutic dosage ranges. Careful clinical monitoring is advised.*

Enoxaparin (https://www.medicines.org.uk/emc/product/1695/smpc)

- *No increased bleeding tendency is observed in the elderly with the prophylactic dosage ranges. Elderly patients (especially patients eighty years of age and older) may be at an increased risk for bleeding complications with the therapeutic dosage ranges.*
- Haemorrhage is listed as a common adverse 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 haemoglobin decrease ≥ 2 g/dL or transfusion of 2 or more units of blood products*.

Tinxaparin (https://www.medicines.org.uk/emc/product/3630/smpc)

No relevant information on bleeding risk

(v) **North West Medicines Information - Draft Dental LMWH FAQ** (June 2021, E. Parker, unpublished)

The draft document summarises relevant information and evidence and provides proposed advice for managing dental patients taking LMWHs based on whether the patient is on a prophylactic or therapeutic dose. The following information is extracted from the draft:

The risk of bleeding associated with LMWHs is dose-dependent. When assessing a patient, it is important to establish the indication and dose of the LMWH in order to assess if it is a prophylactic or

treatment dose. Lower doses are used for prophylaxis of venous thromboembolism, whereas treatment doses tend to be much higher. The dose for prophylactic and treatment doses vary for individuals, mainly depending on their weight and renal function. ***The dose is often adjusted by the specialist team to unlicensed doses for the indication, this is guided by antiXa levels.*** *Therefore what is a prophylactic and treatment dose for individual patients will often lie outside of licensed doses for these indications (with overlap between the two).*

Sometimes it is clear from the indication whether the LMWH is treatment dose or prophylactic dose (e.g. recent DVT or PE will be treatment dose). If not, the guide below can help to judge whether likely on treatment or prophylactic dose. If unsure, contact the specialist:

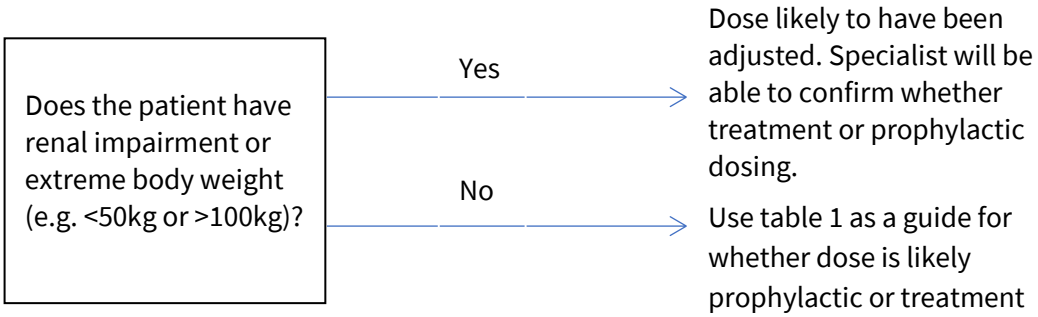

Table 1. Licensed Prophylactic and Treatment Doses of LMWH

LMWH	Prophylactic dose*	Treatment dose*
Dalteparin (Fragmin®)	2,500-5,000 units OD	7,500-18,000 units OD In a 70kg adult expect 15,000 units OD
Enoxaparin (Clexane®)	20-40mg OD 2,000-4,000 units OD	100-150 units/kg OD OR BD (1-1.5mg/kg) In a 70kg adult expect 7,000-10,500 units OD OR BD 70-105mg
Tinzaparin (Innohep®)	3,500-4,500 units OD	175 units/kg OD In a 70kg adult expect 12,250 units OD

*Doses may be reduced in renal impairment

Overall, the evidence for peri-operative management of LMWH is limited.

For patients on ***prophylactic LMWH****, pragmatically, the bleeding risk is likely lower than in those fully anticoagulated on warfarin or a DOAC. Therefore if OACs could be continued it seems reasonable to continue prophylactic LMWH to avoid delays in dental procedures.*

For patients on ***treatment-dose LMWH****, the experience of local secondary care clinicians suggests that it may be reasonable to continue to treat these patients similarly to those on warfarin or DOACs*

using local haemostatic measures, at least for dental procedures with a lower risk of post-operative bleeding. However, other studies suggest added caution with this approach due to a likely higher bleeding risk with LMWH. Further studies are needed in this area to assess whether this potentially higher bleeding risk would affect the risk of dental procedures in primary care; until such a time it is recommended that management of these patients is discussed with the local anticoagulation specialist or dental hospital for further advice on treatment.

Clinical Question 5

Q5: Should other measures be used for dental treatment on patients taking anticoagulants or antiplatelet drugs?

Recommendation in 2015 version of guidance:

No key recommendation made.

Basis:
There is insufficient evidence to indicate any additional benefit of tranexamic acid to minimise bleeding when used in conjunction with other haemostatic measures for dental procedures.

The evidence considered previously is documented in the *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs Guidance Development Methodology (2015)* (available on request).

1. Summary of evidence since 2015 edition of guidance

*Summarise the evidence for the effects of the intervention on the important outcomes including the ratings for the **certainty** of the evidence. Comment on the degree of **consistency** demonstrated by the available evidence. Note where evidence is lacking.*

Several recent systematic reviews (SRs)[8,15,16,20,23] assess the effectiveness of haemostatic measures for reducing the bleeding risk from dental procedures in patients on antithrombotic therapies. Some of these include new studies, in addition to studies considered previously, and report meta-analysis of the data, including a network meta-analysis.

Four SRs[8,15,20,23] compared different haemostatic measures with placebo or with each other and reached similar conclusions. Three of the SRs[8,20,23] found that tranexamic acid (TXA) has a statistically significant beneficial effect in reducing bleeding risk in patients on various antithrombotic therapies having dental treatment, when compared to placebo. The effects included from 3 to7 fold less risk, and 25% reduced risk, depending on the analysis. All of the SRs concluded that there was no significant difference in bleeding outcomes comparing TXA with other haemostatic measures, including N-butyl-2-cyanoacrylate, $CaSO_4$, Ankaferd blood stopper (a herbal product), gelatin sponge, chitosan, sutures or gauze compression. Dental treatments were mostly extractions although other procedures were included in some studies. Patients were most commonly taking VKAs.

A recently published RCT[51], not included in the SRs, found that in patients taking DOACs, TXA appeared to reduce delayed bleeds and postoperative oral bleeding if multiple teeth were extracted but did not seem to reduce the rate of periprocedural or early postoperative oral bleeding compared to placebo.

Overall, there is **moderate certainty** evidence that TXA reduces the risk of bleeding for patients on antithrombotic therapy compared to placebo but it may not have significant benefits compared to other measures including other haemostatic agents or pressure with gauze.

Does the evidence differ from previously?

The conclusions from these SRs are very similar to those from the evidence review carried out for the first edition of the guidance. **Additional sources of information** Some of the guidelines cited for the first edition of the guidance recommended the use of haemostatic agents including TXA to minimize the risk of bleeding for patients on oral anticoagulants. See Section 10 of this form for further details of the evidence.
2. Balance of effects *Comment 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.*
Although the use of TXA may be beneficial compared to placebo in reducing the risk of bleeding complications from dental procedures for patient on antithrombotic therapy, it might not have significant benefits compared to other agents or measures such as pressure with gauze. Adverse events reported in some studies include a bad or sour taste, nausea, tedious treatment or a slight burning feeling, although some of these were also reported in the placebo group.
3. Subgroup considerations *Comment here on any subgroup considerations e.g. should recommendations for patients at high or low risk be considered separately?*
No specific subgroups were identified.
4. Values and preferences *Summarise any evidence or information on values and preferences.*
No information on patient preference about the use of additional haemostatic measures for dental treatment was identified.
6. Acceptability *Is the intervention acceptable to patients, dental team and other stakeholders?*
The use of TXA for dental treatment may be expensive and inconvenient for reasons below.
7. Feasibility *Comment on cost, resource implications and implementation considerations, if applicable.*
Tranexamic acid is not in the dental formulary and cannot be prescribed or dispensed by GDPs (unless privately). A GDP could only request that a GMP prescribes it. In addition, TXA is not available as a mouthwash and would have to be prepared ‘off-label’.
8. Other factors *Indicate any other factors taken into account.*

None

9. Considered judgment and key recommendation

Summarise the group's judgements for the recommendation including 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.

The group's considered judgement was to not make a recommendation for tranexamic acid as an additional haemostatic measure for dental treatment in patients taking anticoagulant or antiplatelet drugs. This is based on the evidence suggesting a lack of benefit of TXA compared to other measures and the practical issues with its provision in dentistry.

10. Additional information

Include any further information that is relevant to the considered judgement.

Details of Systematic Reviews

Five systematic reviews, one including a network meta-analysis, assessed the effectiveness of haemostatic measures for reducing the bleeding risk from dental procedures in patients on various antithrombotic therapies, comparing different measures with each other or with a placebo control.[8,15,16,20,23] The SRs analysed data from overlapping groups of studies and carried out different comparisons and analysis.

Moreno-Drada et al. (2021)[8] carried out a network meta-analysis of bleeding risk (14 studies, 781 patients) and found a statistically significant reduction when tranexamic acid (TXA) was used as a haemostatic agent before dental procedures in patients taking an oral anticoagulant (Risk Ratio, RR -3.46, 95% CI -7.63, -0.77). This result was rated as moderate certainty according to GRADE criteria. Beneficial effects were also found for N-butyl-2-cyanoacrylate (RR -35.00, 95% CI -107.12, -5.78) and $CaSO_4$ (RR -5.62, 95% CI -11.41, -1.03) compared to placebo, but the evidence was rated as very low certainty due to risk of bias, imprecision and indirectness.

No significant differences in risk of bleeding were found comparing different haemostatic agents with each other. There was also no significant difference detected in mean bleeding time comparing different haemostatic agents (TXA, herbal product Ankaferd blood stopper, chitosan, collagen sponge) with gauze pressure (4 studies, 162 patients).

Most studies reported on dental extractions, some included surgical extractions, periapical surgery, surgery for gingival hyperplasia or cystectomies. The most commonly used haemostatic agent was TXA. All studies were carried out in patients undergoing oral anticoagulation with coumarin derivatives. Studies evaluating DOACs were not found. There was a lack of studies that allowed direct comparisons to be made for agents other than TXA.

Ockerman et al. (2019)[15] carried out a qualitative assessment including many of the studies analysed by Morena-Drada et al. and reached similar conclusions. Six of the studies (5 including patients on

continued anticoagulants and 1 including patients on continued antiplatelets), comparing bleeding outcomes after extractions for TXA (mouthwash, gauzes and sponges) compared to non-TXA haemostatic methods, found that TXA was not significantly better. Seven studies investigated local measures other than TXA but did not find significant differences in bleeding between the treatments. The authors concluded that no local haemostatic agent was superior to another and that TXA mouthwash is an effective haemostatic in patients on anticoagulants.

A Cochrane systematic review (**Engelen et al., 2018**)[20] compared post-operative bleeding and side effects for patients on continuous VKA (within therapeutic INR range) using an antifibrinolytic agent with those using a placebo or having usual care (including gauze compression, sutures, mucosal flap placement). The comparison of TXA with placebo showed a statistically significant beneficial effect regarding the number of post-operative bleeding episodes requiring intervention, with a pooled risk difference (RD) of -0.25 (95% CI -0.36 to -0.14, p <0.0001; 2 RCTs, 128 participants). For the comparison of TXA with either gelatin sponge and sutures or with dry gauze compression, there was no difference between the TXA and the standard care group (RD =0.02, 95% CI -0.07 to 0.11, p =0.7; 2 RCTs, 125 participants). The combined RD of all included trials was -0.13 (95% CI -0.30 to 0.05, p = 0.16). There were no side effects of antifibrinolytic therapy that required treatment withdrawal (128 participants).

The quality of the evidence was rated as moderate for each of the comparisons because of downgrading for imprecision due to relatively small sample sizes. No eligible trials in people on continuous treatment with DOACs undergoing oral or dental procedures were identified.

De Vasconcellos et al. (2017)[23] conducted a similar analysis and reported a combined RR for post-operative bleeding in patients on VKA therapy receiving TXA, in comparison to the control group, of 0.13 (95% CI 0.05-0.36, p < 0.0001; 5 RCTs, 252 participants), indicating a protective effect of topical TXA on bleeding after minor oral surgeries. The evidence considered is judged to be of moderate certainty due to imprecision.

Owattanapanich et al. (2019)[16] carried out a different comparison to assess whether the use of local TXA reduces the bleeding risk in anticoagulated patients to levels for patients not taking any anticoagulant. The review found that the odds of developing post-procedural bleeding, in patients who were taking an oral anticoagulant and received local TXA treatment after a dental procedure, were approximately 2.4 times higher than for individuals who did not take an anticoagulant and underwent similar dental procedures (pooled OR=2.4, 95% CI 0.69-8.12, p =0.17; 4 studies, 1816 patients). The pooled effect estimate was not statistically significant, however, which could be interpreted as suggesting that TXA may be effective, although this is uncertain.

The procedures included were dental extractions and implants. Three studies included patients taking warfarin and one study included patients taking rivaroxaban. The evidence from the 4 observational studies used in the meta-analysis is likely to be of very low certainty due to downgrading for risk of bias and imprecision.

Appendix 5 Environmental Considerations

The guidance specific sustainability considerations for the second edition are reported in the following table.

Sustainability consideration	**Action** *e.g. changes made to the guidance, advice for practitioners and patients, provision of resources etc.*
Travel	
1. The guidance aims to empower dental staff to treat patients taking anticoagulants or antiplatelet drugs in primary care, minimising the need for referral to secondary care. Treatment in local primary care settings might contribute to minimising the distance travelled.	None
2. Establishing the patient's medical history, including their use of anticoagulants or antiplatelet medication, is a key part of the bleeding risk assessment. Incomplete or out-of-date information could result in postponement of the treatment and the patient having to reattend on another occasion.	To avoid extra travel for repeat appointments, practitioners could consider: • Confirming the details of the patient's medical history by phone, in advance of the appointment, to check for any changes that could impact treatment and require postponement. • Consulting with the patient's prescribing clinician, specialist or general medical practitioner, prior to the appointment, if more information or advice is required. A template form is provided with the guidance for recording local contact details for medical, pharmacy, haematology, cardiology and secondary dental care support. Advice points were added in the guidance to note that contacting patients or medical practitioners in advance of the dental appointment could reduce wasted appointments and travel.

Sustainability consideration	**Action** *e.g. changes made to the guidance, advice for practitioners and patients, provision of resources etc.*
3. Patient uncertainty about pre-treatment instructions (e.g. for INR testing or to miss a dose of a DOAC) and failure to carry out required preparation correctly could lead to postponement of treatment and the need to reattend on another occasion.	The second edition of the guidance advises providing the patient with pre-treatment instructions. To facilitate this, treatment advice sheets suitable for recording individual instructions for the patient (e.g. for INR testing or any pre-treatment modification of the drug schedule) were developed and made available with the guidance. These can be provided digitally to patients, or printed if necessary. An advice point was added in the guidance to note that providing pre-treatment instructions could reduce wasted appointments and travel.
4. The guidance strongly encourages suturing and packing for patients taking anticoagulants or antiplatelet drugs, and advises that failure of initial haemostasis will require packing and suturing at a later time. Consequently, in addition to reducing the bleeding risk, suturing and packing at the time of treatment may reduce the need for subsequent travel.	An advice point was added to the guidance to further emphasise that packing and suturing at the time of treatment may reduce the likelihood of the patient having to reattend to manage post-operative bleeding.
5. The guidance advises carrying out procedures with a higher risk of bleeding complications in a staged manner where possible. This will result in additional appointments, with additional travel. Staging is only advised for higher bleeding risk procedures which may be less commonly carried out than the low bleeding risk procedures. Although staging treatment will increase travel, for the higher risk circumstances specified, this is considered to be necessary for patient safety.	No action taken.
6. The guidance advises referring patients who have an INR≥4 and require urgent, invasive treatment, to secondary care. This could result	Advising patients to contact the practice before attending for treatment if their INR≥4 could help to reduce wasted appointments and travel. This advice has been included in the patient pre-treatment advice sheets.

Sustainability consideration	**Action** *e.g. changes made to the guidance, advice for practitioners and patients, provision of resources etc.*
in additional and/or longer distance travel, however, it is considered necessary for patient safety.	
Equipment and supplies (procurement)	
7. Although, the advice on packing and suturing could reduce additional travel required for managing post-operative bleeding complications (discussed above), additional supplies may be required including non-animal-based alternatives as advised by the guidance.	To make most efficient use of, and minimise waste from the additional supplies, practitioners could be advised to: • rotate stock for prolonging shelf life • share between surgeries in practice • audit use to identify when items need to be ordered, to reduce stock and deliveries from suppliers • recycle wrapping materials e.g. carboard and plastic from sutures (if uncontaminated) This general sustainability advice on supplies may be included in SDCEP's *Practice Support Manual*.
8. Staging treatment, as noted in point 5., will lead to additional appointments, involving additional travel, supplies (e.g. PPE), waste, energy use and water (e.g. for instrument decontamination). However, staging higher bleeding risk procedures is considered necessary for patient safety.	No action taken.
Energy	
9. Patient re-attendance for further haemostatic measures will also increase energy use.	Advice points about minimising the need for re-attendance have been added to the guidance, as in point 4. above.

Sustainability consideration	**Action** *e.g. changes made to the guidance, advice for practitioners and patients, provision of resources etc.*
Waste	
10. The guidance advises providing the patient with pre- and post-treatment advice and emergency contact details. If printed, this will obviously use paper, printing consumables and create waste.	The guidance notes that the information could be provided to patients electronically or written. It is recognised that electronic versions might not be suitable for all patients.
Biodiversity and green space	
11. No direct impacts specific to the guidance were identified.	None

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