SOCIÉTÉ FRANÇAISE DE CHIRURGIE ORALE [FRENCH SOCIETY OF ORAL SURGERY]

IN COLLABORATION WITH THE SOCIÉTÉ FRANÇAISE DE CARDIOLOGIE [FRENCH SOCIETY OF CARDIOLOGY] AND THE PERIOPERATIVE HEMOSTASIS INTEREST GROUP

Perioperative management of patients treated with antithrombotics in oral surgery.

RATIONALE

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Abbreviations

ACS	Acute coronary syndrome(s)
ADP	Adenosine diphosphate
Afib	Atrial Fibrillation
AHT	Arterial hypertension
Anaes	Agence nationale d'accréditation et d'évaluation en santé [National Agency for Accreditation and Health Care Evaluation]
APA	Antiplatelet agent(s)
aPTT	Activated partial thromboplastin time
ASA	Aspirin
BDMP	Blood derived medicinal products
BMI	Body mass index
BT	Bleeding Time
cAMP	Cyclic adenosine monophosphate
COX-1	Cyclooxygenase 1
CVA	Cerebral vascular accident
DIC	Disseminated intravascular coagulation
DOA	Direct oral anticoagulant(s)
DVT	Deep vein thrombosis
GEHT	Study Group on Hemostasis and Thrombosis (groupe d'étude sur l'hémostase et la thrombose)
GIHP	Hemostasis and Thrombosis Interest Group (groupe d'intérêt sur l'hémostase et la thrombose)
HAS	Haute autorité de santé [French Authority for Health]
HIT	Heparin-induced thrombocytopenia
IANB	Inferior alveolar nerve block
INR	International normalized ratio
IV	Intravenous
LMWH	Low-molecular-weight heparin(s)
MA	Marketing Authorization
MI	Myocardial infarction
minC	minimum or residual concentration
NABM	Classification of Biomedical Procedures (nomenclature des actes en biologie médicale)
NSAIDs	Non-steroidal anti-inflammatory drugs
NSTEMI	Non-ST Segment Elevation Myocardial Infarction
PAD	Peripheral obstructive artery disease
PC	Platelet count
PCC	Prothrombin complex concentrate
PCI	Percutaneous Coronary Intervention
PE	Pulmonary embolism
PMSI	Information Systems Medicalization Program (programme de médicalisation des systèmes d'information)
PT	Prothrombin Time
SC	Subcutaneous
SE	Systemic embolism
SMD	Sterile medical device
STEMI	ST Segment Elevation Myocardial Infarction
SVT	Superficial Vein Thrombosis
THR	Total Hip Replacement
TIA	Transient Ischemic Attack(s)
TKR	Total Knee Replacement
t-PA	tissue Plasminogen Activator
TXA2	Thromboxane A2
UFH	Unfractionated heparin(s)
VKA	Vitamin K antagonists or antivitamin K
VTE	Venous thromboembolism

Overview

I. METHODOLOGY

1. Working method for the preparation of recommendations 7
2. Literature search and selection of documents 7

II. RATIONALE

1. Perioperative management of patients treated with antithrombotics in oral surgery (General Information). 15

1.1 Balancing risk in the surgical setting 15

1.2 Preoperative assessment of the risk of surgical bleeding 16
1.2.1 Taking medical history and clinical examination 16
1.2.1.1 Hemostasis disorder(s) related to an associated pathology 16
1.2.1.2 Patient adherence to his (her) antithrombotic therapy 16
1.2.1.3 Type of surgical procedure 17
1.2.1.4 Hemorrhagic risk factors that could increase the risk of surgical bleeding. 18
1.2.2. From laboratory examination(s) 19

1.3 Choice of the management of structure: general practice or in a hospital? 19

1.4 Local hemostasis 20
1.4.1 Surgical hemostatics 20
1.4.1.1 Surgical hemostatics without specific action on the events that occur during hemostasis. 21
1.4.1.2 Surgical hemostatics with specific action on the events that occur during hemostasis. 21
1.4.2 Tranexamic acid 21
1.5.1 Postoperative monitoring and tips 22
1.5.2 Curative treatment of bleeding complications 22

2. Specificities of the management of patients treated with antiplatelet agents(s) 24

2.1 The issues 24

2.2 Antiplatelet agents 25
2.2.1 Conventional antiplatelet agents 25
2.2.2.1 Aspirin 25
2.2.2.2 Dipyridamole 26
2.2.2.3 Ticlopidine 26
2.2.2.4 Clopidogrel 26
2.2.2 Novel antiplatelet agents 27
2.2.2.1 Prasugrel 28
2.2.2.2 Ticagrelor 28

2.3 Discontinuation or maintenance of treatment with antiplatelet agents? 29

2.4 What biological test can be used to evaluate the risk of surgical bleeding in patients on an antiplatelet agent? 31

2.5 Which local hemostasis should be performed to control the risk of surgical bleeding? 31

2.6 Curative treatment of bleeding complications 32

3. Specificities of the management of patients treated with antivitamin K 32

3.1 The issues 32

3.2 Antivitamin K 34
3.2.1 Acenocoumarol 34
3.2.2 Warfarin 35
3.2.3 Fluindione 35
3.3 Discontinuation or maintenance of therapy with VKA? 35
3.3.1 Local anesthesia (LA) and locoregional anesthesia (LRA). 35
3.3.2 Dento-alveolar surgery 36
3.3.2.1 Dental extraction(s) 36
3.3.2.2 Dental implant(s) 37
3.3.3 Surgery with a high risk of bleeding 37
3.3.3.1 Patients at low risk of thrombosis 38
3.3.3.2 Patients at high risk of thrombosis 39

3.4 What biological test should be used to evaluate the surgical risk of bleeding? 40

3.5 Which local hemostasis should be performed to control the risk of surgical bleeding? 41

3.6 What are the drug prescriptions that increase the risk of bleeding? 43

3.7 Curative treatment of bleeding complications 45

4. Specificities of the management of patients treated with direct oral anticoagulants 46

4.1 The issues 46

4.2 Direct oral anticoagulants 47
4.2.1. Dabigatran etexilate 47
4.2.2. Rivaroxaban 47
4.2.3. Apixaban 48

4.3 Discontinuation or maintenance of treatment with direct oral anticoagulants? 49

4.4 What biological test should be used to evaluate the surgical risk of bleeding? 51

4.5 Which local hemostasis should be performed to control the risk of surgical bleeding? 52

4.6 What are the drug prescriptions that increase the risk of bleeding? 52

4.7 Curative treatment of bleeding complications 53

5. Specificities of the management of patients treated with injectable anticoagulants 54

5.1 The issues 54

5.2 Injectable anticoagulants 54

5.2.1. Standard unfractionated heparins....55
5.2.2 Low molecular weight fractionated heparins....55

5.3 Discontinuation or maintenance of therapy with heparin? 56

5.4 What biological test can be used to evaluate the surgical risk of bleeding in patients on heparin?....58

5.5 Which local hemostasis should be performed to control the risk of surgical bleeding in patients on heparin? 58

5.6 Curative treatment of bleeding complications in patients on heparins....59

Conclusion 60

APPENDICES 61
Appendix 1: Antithrombotic agents (antiplatelet agents and anticoagulants) currently marketed in France in 2015....61
Appendix 2: Stratification of the risk of bleeding based on the type of surgery and preventive measures. 63
Appendix 3: Age and comorbidities associated with an increased risk of bleeding events in patients treated with an antithrombotic agent....65
Appendix 4: Evaluation of the risk of bleeding and the postoperative risk of thromboembolism depending on the therapeutic strategy after dento-alveolar surgery. 66
Appendix 5: Patients on antiplatelet agents (aspirin, clopidogrel, ticlopidine) and dento-alveolar surgery (Clinical Studies). 68
Appendix 6: Patients on dual antiplatelet therapy (aspirin and clopidogrel) and dento-alveolar surgery (Clinical Studies). 70
Appendix 7: Patients on VKA (Acenocoumarol, Coumadin, Fluindione Warfarin) and dento-alveolar surgery (Clinical Studies). 72
Appendix 8: Patients on dual antiplatelet therapy + VKA and dento-alveolar surgery (Clinical Studies). 79
Appendix 9: Protocol for discontinuation and resumption of VKA without heparin relay for surgery with a high risk of bleeding....80
Appendix 10: Protocol for discontinuation and resumption of VKA with heparin relay for surgery with a high risk of bleeding....81
Appendix 11: Main pharmacokinetic parameters of DOAs 82
Appendix 12: Protocol for discontinuation and resumption of a DOA without heparin relay for surgery with a high risk of bleeding....83
Appendix 13: Patients on heparins (LMWH, UFH) and dento-alveolar surgery (Clinical Studies). 84
Appendix 14: Systematic algorithm of the management of patients on antiplatelet agents (APAs) during oral surgery. 86
Appendix 15: Systematic algorithm of the management of patients on antivitamin K (VKA) during oral surgery....87
Appendix 16: Systematic algorithm of the management of patients on direct oral anticoagulants (DOAs) during oral surgery. 89
Appendix 17: Systematic algorithm of the management of patients on heparins during oral surgery. 90
REFERENCES 91

METHODOLOGY

1. Working method for the preparation of recommendations

These professional recommendations were developed according to the method of recommendations for clinical practice, published by the Agence nationale d'accréditation et d'évaluation en santé (Anaes) in January 2000 (www.has-sante.fr).

The French Society of Oral Surgery (*Société Française de Chirurgie Orale*, SFCO), sponsor of the project, appointed a chairperson who formed a working group and coordinated all the work. The working group was made up of multidisciplinary professionals in public or private practice, from diverse geographical origins, and members of the French Society of Cardiology (*Société Française de Cardiologie*, SFC) and the French Society of Anesthesia & Intensive Care Medicine (*Société Française d'Anesthésie et Réanimation*, Sfar). A rapporteur was appointed to write the recommendations (short text and rationale), after an analysis of the scientific literature and a summary of the opinions of all the members of the working group.

A peer review group, constituted using the same criteria as the working group was consulted by mail and gave an opinion on the substance and form of the recommendations. The comments from the reading group were analyzed by the working group and taken into account whenever possible when drafting the recommendations.

2. Literature search and selection of documents

An extensive literature search was conducted by searching the Medline® and Cochrane® bibliographic databases.

The following were the restrictions placed on all searches carried out on these automated databases:

- only articles written in English and French were selected;
- the research period defined was from 1985 to 2014. (This search was carried out in January 2014 and Literature monitoring continued until January 2015);
- Only clinical trials, meta-analyses, systematic reviews, clinical practice recommendations, consensus conferences, institutional publications and medical decision-making articles were analyzed.

The keywords used were either words from a thesaurus (MeSH descriptors for Medline) or the title or abstract terms. The following keywords were selected:

“Antithrombotic”, “Antiplatelet”, “Aspirin”, “Dipyridamol”, “Ticlopidin”, “Clopidogrel”, “Prasugrel”, “Ticagrelor”, “Anticoagulant”, “Antivitamin K”, “Warfarin”, “Acenocoumarol”, “Fluindione”, “New oral anticoagulants”, “Novel anticoagulants”, “Direct oral anticoagulants”, “Direct thrombin inhibitor”, “Factor Xa inhibitors”, “Dabigatran”, “Rivaroxaban”, “Apixaban”, “Injectable anticoagulants” “Heparins”, “Low molecular weight heparins”, “Enoxaparin”, “Nadroparin”, “Dalteparin”, “Tinzaparin”, “Fondaripanux”, “Hemorrhage”, “Bleeding”, “Hemostasis”, “Hemostatic agent”, “Topic hemostatic”, “Topic hemostatic agent”, “Surgery hemostatic”, “Tooth extraction”, “Dento-alveolar surgery”, “Dento-alveolar surgery” [*sic*], “Dental implant”.

The keywords were then combined in as many steps as needed using the Boolean search operator operators “AND”, “OR”.

Table 1 shows the details of the research strategy in Medline and the results in terms of the total number of references obtained, as well as those used to answer the questions.

The articles identified were analyzed according to principles of critical reading of the literature using reading grids. Only relevant articles were selected and a level of scientific evidence was assigned for each article selected.

Table 1: Literature search strategy in the Medline database

Subject	*Risk of bleeding in oral surgery for patients on antiplatelet agents*		
	Terms used	**Reference No.**	**Number of references selected**
Step 1	"Antiplatelet" OR "Aspirin" OR "Dipyridamole" OR "Ticlopidine" OR "Clopidogrel" OR "Prasugrel" OR "Ticagrelor"	**17,381**	
Step 2	"Antiplatelet" OR "Aspirin" OR "Dipyridamole" OR "Ticlopidine" OR "Clopidogrel" OR "Prasugrel" OR "Ticagrelor" "**AND"** "Tooth extraction" OR "Dental extraction" OR "Dento-alveolar surgery" OR "Oral surgery"	**28**	Aframian, 2007 [1], Ardekian, 2000 [24], Bajkin, 2012 [35], Bajkin, 2015 [36], Brennan, 2008 [49], Canigral, 2008 [54], Cardona-Tortajada, 2009 [56], Garnier, 2007 [113], Iwabuchi, 2014 [173], Krishman, 2008 [185], Lillis, 2011 [197], Madan, 2010 [204], Medeiros, 2011 [212], Moritomoto, 2008a [223], Morimoto, 2011 [225], Napenas, 2009 [227], Olmos-Carrasco, 2015 [234], Park, 2012 [239], Partridge, 2008 [237], Rai, 2013 [248], van Diermen, 2009 [278], Verma, 2013 [280], Verma, 2014 [281]
Step 3	"Antiplatelet" OR "Aspirin" OR "Dipyridamol" OR "Ticlopidin" OR "Clopidogrel" OR "Prasugrel" OR "Ticagrelor" "**AND"** "Dental implant"	**3**	No reference selected
Step 4	"Antiplatelet" OR "Aspirin" OR "Dipyridamol" OR "Ticlopidin" OR "Clopidogrel" OR "Prasugrel" OR "Ticagrelor" "**AND"** "Osseous graft" OR "Sinus lift" OR "Tumors and cysts of the jaw surgery"	**3**	No reference selected
Subject	*Risk of bleeding in oral surgery for patients on antivitamin K*		
	Terms used	**Reference No.**	**Number of references selected**
Step 1	"Oral anticoagulant" OR "Antivitamin K" OR "Warfarin" OR "Acenocoumarol" OR "Fluindione"	**16,542**	
Step 2	"Oral Anticoagulant" OR "Antivitamin K" OR "Warfarin" OR "Acenocoumarol" OR "Fluindione" "**AND"** "Tooth extraction" OR "Dental extraction" OR "Dento-alveolar surgery" OR "Oral surgery"	**274**	Aframian, 2007 [1], Al-Belasy, 2003 [17], Al-Mubarak, 2006 [19], Al-Mubarak, 2007 [20], Bacci, 2010 [28], Bajkin, 2009 [33], Bajkin, 2010 [10], Bajkin, 2012b [35], Blinder, 1999 [41], Blinder, 2001 [42], Bodner, 1998 [45], Borea, 1993 [46], Broekema, 2014 [51], Cannon, 2003, Carter, 2003a [57], Carter, 2003b [58], Cocero, 2014 [63], Devani, 1998 [82], Evans, 2002 [99], Gaspar, 1997 [114], Gaudy, 2005 [115], Halfpenny, 2001

			[126], Iwabuchi, 2014 [173], Karsh, 2010 [180], Keiani Motlagh, 2003 [181], Martinwitz, 1990 [209], Morimoto, 2008a [223], Morimoto, 2008b [224], Morimoto, 2011 [225], Perry, 2007 [244], Ramström, 1993 [249], Sacco, 2007 [254], Salam, 2007 [255], Sindet-Pedersen, 1989 [263], Souto, 1996 [269], van Diermen, 2009 [278], Wahl, 1998 [283]
Step 3	"Oral anticoagulant" OR "Antivitamin K" OR "Warfarin" OR "Acenocoumarol" OR "Fluindione" "**AND"** "Dental implant"	**58**	Bacci, 2011 [29], Madrid and Sanz, 2009 [205]
Step 4	"Oral anticoagulant" OR "Antivitamin K" OR "Warfarin" OR "Acenocoumarol" OR "Fluindione" "**AND"** "Osseous graft" OR "Sinus lift" OR "Tumors and cysts of the jaw surgery"	**12**	No reference selected
Subject	*Risk of bleeding in oral surgery for patients on dual antiplatelet therapy and VKA*		
Step 1	"Oral anticoagulant" OR "Antivitamin K" OR "Warfarin" **AND** "Antiplatelet" OR "Aspirin" OR "Clopidogrel"	**877**	
Step 2	"Oral anticoagulant" OR "Antivitamin K" OR "Warfarin" **AND** "Antiplatelet" OR "Aspirin" OR "Clopidogrel" **AND** "Tooth extraction" OR "Dental extraction" OR "Dento-alveolar surgery" OR "Oral surgery"	**10**	Bajkin, 2012b [35], Cardona-Tortadaja, 2009 [56], Morimoto, 2008a [223], Morimoto, 2011 [225], Perry, 2007 [144], Pototski, 2007 [247], van Diermen, 2009 [278]
Step 3	"Oral anticoagulant" OR "Antivitamin K" OR "Warfarin" **AND** "Antiplatelet" OR "Aspirin" OR "Clopidogrel" **AND** "Dental implant"	**0**	No reference
Step 4	"Oral anticoagulant" OR "Antivitamin K" OR "Warfarin" **AND**	**0**	No reference

	"Antiplatelet" OR "Aspirin" OR "Clopidogrel" **AND** "Osseous graft" OR "Sinus lift" OR "Tumors and cysts of the jaw surgery"		
Subject	*Risk of bleeding in oral surgery for patients on direct oral anticoagulants*		
	Terms used	**Reference No.**	**Number of references selected**
Step 1	"New oral anticoagulants" OR "Novel anticoagulants" OR "Direct oral anticoagulants" OR "Direct thrombin inhibitor" OR "Factor Xa inhibitors" OR "Dabigatran" OR "Rivaroxaban" OR "Apixaban"	**3,142**	
Step 2	"New oral anticoagulants" OR "Novel anticoagulants" OR "Direct oral anticoagulants" OR "Direct thrombin inhibitor" OR "Factor Xa inhibitors" OR "Dabigatran" OR "Rivaroxaban" OR "Apixaban" "**AND"** "Tooth extraction" OR "Dental extraction" OR "Dento-alveolar surgery" OR "Oral surgery"	**12**	Breik, 2014 [47], Davis, 2013 [77], Firriolo, 2012 [105], Romond, 2013 [293]
Step 3	"New oral anticoagulants" OR "Novel anticoagulants" OR "Direct oral anticoagulants" OR "Direct thrombin inhibitor" OR "Factor Xa inhibitors" OR "Dabigatran" OR "Rivaroxaban" OR "Apixaban" "**AND"** "Dental implant"	**2**	No reference selected
Step 4	"New oral anticoagulants" OR "Novel anticoagulants" OR "Direct oral anticoagulants" OR "Direct thrombin inhibitor" OR "Factor Xa inhibitors" OR "Dabigatran" OR "Rivaroxaban" OR "Apixaban" "**AND"** "Osseous graft" OR "Sinus lift" OR "Tumors and cysts of the jaw surgery"	**0**	No reference selected
Subject	*Risk of bleeding in oral surgery for patients on injectable anticoagulants (heparins, fondaripanux)*		
	Terms used	**Reference**	**Number of references selected**

		No.	
Step 1	"Injectables anticoagulants" OR "Heparins" OR "Low molecular weight heparins" OR "Enoxaparin" OR "Nadroparin" OR "Dalteparin" OR "Tinzaparin" OR "Fondaripanux"	**13,222**	
Step 2	"Injectables anticoagulants" OR "Heparins" OR "Low molecular weight heparins" OR "Enoxaparin" OR "Nadroparin" OR "Dalteparin" OR "Tinzaparin" OR "Fondaripanux" "**AND"** "Tooth extraction" OR "Dental extraction" OR "Dento-alveolar surgery" OR "Oral surgery"	**8**	Bajkin, 2009 [33], Hong, 2010 [167], Karsh, 2011 [180], Morimoto, 2008b [224], Morimoto, 2012 [226]
Step 3	"Injectables anticoagulants" OR "Heparins" OR "Low molecular weight heparins" OR "Enoxaparin" OR "Nadroparin" OR "Dalteparin" OR "Tinzaparin" OR "Fondaripanux" "**AND"** "Dental implant"	**0**	No reference
Subject	*Bleeding and Oral Surgery*		
	Terms used	**Reference No.**	**Number of references selected**
Step 1	"Hemorrhage" OR "Bleeding"	**56,425**	
Step 2	"Hemorrhage" OR "Bleeding" "**AND"** "Tooth extraction" OR "Dental extraction" OR "Dento-alveolar surgery" OR "Oral surgery"	**78**	Czimbireck, 2014 [72], Lockhart, 2003 [199], Chee, 2008 [61], Cosmi, 2009 [70], Iwabucchi, 2014 [173), Moghadam, 2002 [218], Pister, 2010 [246]
Step 3	"Hemorrhage" OR "Bleeding" "**AND"** "Dental implant"	**16**	Bruggenkate, 1993 [53], Darriba, 1997 [75], Givol, 2000 [117], Hong, 2011 [169], Jensen, 2012 [175], Kalpidis, 2005 [179], Laboda, 1990 [186], Masson, 1190 [*sic:* 1990] [211], Mordenfeld, 1997 [220], Niamtu, 2001 [230], Panula, 1999 [235]
Subject	*Local Hemostasis and Oral Surgery in Oral Surgery*		
	Terms used	**Reference No.**	**Number of references selected**
Step 1	"Antithrombotics"	**34,895**	
Step 2	"Antithrombotics"	**116**	Aframian, 2007 [1], Al Belasy, 2003 [17], Al-Mubarak, 2006 [19], Al-

	"AND" "Tooth extraction" OR "Dental extraction" OR "Dento-alveolar surgery" OR "Oral surgery" **"AND"** "Hemostasis" OR "Hemostatic agent" OR "Topic hemostatic" OR "Topic hemostatic agent" OR "Surgery hemostatic"		Mubarak, 2007 [20], Bacci, 2010 [28], Bajkin, 2009 [33] Bajkin, 2012b [35], Beirne, 1996 [39], Blinder, 1999 [41], Borea, 1993 [46], Brennan, 2008 [49], Broekema, 2013 [51], Carter, 2003a [57], Carter, 2003b [58], Evans, 2002 [99], Halpenny, 2001 [126], Kalpidis, 2005 [179], Karsh., 2011 [180], Keiani Motlagh, 2003 [181], Medeiros, 2011 [212], Morimoto, 2008a [223], Patatanian, 2006 [236], Perry, 2007 [244], Pototski, 2007 [247], Ramström, 1993 [249], Sindet-Pedersen., 1989 [263], Souto., 1996 [269], van Diermen, 2009 [278]

During this literature review, it was immediately found that there were few studies and/or a low level of evidence for DOAs, heparins and pre-implant surgery.

Therefore, a second type of search was carried out. The websites of national learned societies (Groupe Etude de l'Hémostase et de la Thrombose (GEHT) de la Société d'Hématologie [Society of Haematology], Société Française de Chirurgie Orale, Société Française d'Anesthésie et de Réanimation) and International learned societies (American Dental Association, American College of Chest Physicians, British Dental Association, British Committee for Standards in Haematology, International Society of Thrombosis and Haemostasis, World Workshop in Oral Medicine), as well as the websites of institutional agencies (HAS, AFSSAPS (*Agence Française de Sécurité Sanitaire des Produits de Santé* [French National Agency for Medicines and Health Products Safety]), ANSM) and books that may be related to the theme were consulted.

The list of sites visited and the documents selected are shown in Table 2.

Depending on the level of evidence from studies, recommendations were made and graded (A to C) according to the scale proposed by the HAS (Table 3). In the absence of studies, the recommendations are based on professional consensus (EO).

Table 2: List of websites of learned societies (national and international) and public institutions under the authority of the Ministry of Health that were consulted.

Learned societies and public institutions	Reference number	References selected
Agence française de sécurité sanitaire des produits de santé (Afssaps)	5	[2], [3], [4], [6], [7]
Agence nationale de la sécurité du médicament (Ansm)	3	[9], [10], [11]
American Dental Association (ADA)	1	[121]
American College of Chest Physicians	7	[12], [61], [85], [86], [91], [111], [125]
American Heart Association (AHA)	1	[121]
British Dental Society (BDS)	1	[244]
British Committee for Standards in Haematology	2	[32], [207]
International Society of Thrombosis and Haemostasis (ISTH)	1	[111]
Groupe Etude de l'Hémostase et de la Thrombose (GEHT) de la Société d'Hématologie	3	[122], [123], [124], [259], [260]
Haute Autorité de Santé (HAS)	34	[130], [131], [132], [133], [134], [135], [136], [137], [138], [139], [140], [141], [142], [143], [144], [145], [146], [147], [148], [149], [150], [151], [152], [153], [154], [155], [156], [157], [158], [159], [160], [161], [162], [163]
Société Française de Chirurgie Orale (SFCO)	2	[266], [267]
Société Française d'Anesthésie et de Réanimation (SFAR)	2	[243],[264], [265]
World Workshop in Oral Medicine (WWOM)	1	[1]

Table 3: Recommendation grades

Recommendation grades	
A	**Established scientific evidence** Based on studies with a high level of evidence (Level of Evidence 1): properly designed randomized controlled trials and free of major bias or meta-analyses of randomized controlled trials, decision analyses based on properly conducted studies.
B	**Scientific presumption** Based on a scientific presumption provided by intermediate level of evidence studies (Level of Evidence 2), such as low level randomized controlled trials, properly conducted non-randomized controlled studies, cohort studies.
C	**Low level of evidence** Based on lower level of evidence studies, such as case-control studies (Level of Evidence 3), retrospective studies, case series, comparative studies involving significant bias (Level of Evidence 4).
EO	**Expert opinion** In the absence of studies, the recommendations are based on consensus between the Working Group experts, after consulting the Peer Review Group. The absence of grading does not mean that the recommendations are not relevant and useful. It should, however, encourage additional studies

RATIONALE

1. Perioperative management of patients treated with antithrombotics in oral surgery (General Information).

1.1 Balancing risk in the surgical setting

The discontinuation of effective antithrombotic therapy that is based on a recognized indication is inconceivable without an increased risk of thrombosis. For anti-platelet agents (APAs), just like for antivitamins (VKA), the analysis of the literature shows that the discontinuation of antithrombotic therapy is accompanied by a significant increase in the number of arterial and/or venous thrombotic events during the postoperative period.[40,64,65,102,283]

Three antithrombotic management strategies: maintain treatment, partial or complete discontinuation (in case of dual therapy) of the treatment and the use of replacement therapy; the preferred therapeutic option as first-line treatment is continuation (non-discontinuation) of antithrombotic therapy.[1,26,48,83,183,228,244,278] It is therefore imperative for the practitioner to identify the risk of bleeding with regard to the planned surgery and its feasibility on an antithrombotic agent.

- **In dento-alveolar surgery**, low level bleeding can easily be controlled by local hemostasis. The additional cost of a bleeding event is acceptable if antithrombotic therapy is maintained; given that the continuation of antithrombotic therapy also helps ensure optimal antithrombotic safety during the perioperative period.[1,26,48,83,183,228,244,278]

- However, **surgical procedures with a high risk of bleeding** (e.g., osseous graft, tumors and cysts of the jaw surgery) or without the possibility of controlling the induced bleeding (e.g., sinus lift), in the absence of medical contraindications (e.g., prevention of infective endocarditis) are indications for the discontinuation of antithrombotics. Consultation with the prescribing physician is therefore essential in order to assess the risk of thrombosis and determine the therapeutic strategy to be adopted. In all cases, discontinuing antithrombotic therapy is the responsibility of the prescribing physician.

The list of antithrombotic drugs currently marketed in France in 2015, the different proprietary medicinal products and their indications are presented in *Appendix 1*.

1.2 Preoperative assessment of the risk of surgical bleeding

Taking antithrombotic medication(s) and possibly maintaining them during surgery should not overshadow all other factors that may increase the risk of perioperative bleeding. These risk factors are many and must not be neglected under any circumstances.[72,109,199]

The assessment of the risk of surgical bleeding is based primarily on the medical history and preoperative clinical examination. This may, based on clinical data and/or the antithrombotic compound, be completed by ordering laboratory tests.[44]

1.2.1 Taking medical history and clinical examination

The objectives of this preoperative bleeding risk assessment are many. The practitioner must:

- ensure that the patient has no other hemostatic abnormalities (constitutional or acquired) or a co-morbidity (hepatic impairment, renal impairment);
- ensure good patient adherence to his (her) antithrombotic treatment, and that he (she) shows no clinical and/or biological signs of any overdose;
- classify the surgical operation or invasive procedure based on the predictability the of risk of bleeding associated with it (controllable or not by simple mechanical hemostasis measures, critical location or not);
- identify bleeding risk factors (patient-related, surgery-related) that may increase the risk of surgical bleeding.

Taking the medical history and the physical examination should be structured. Many studies have shown that taking the history in a non-structured manner is a predictor of an increased risk of surgical bleeding.[61,70]

1.2.1.1 Hemostasis disorder(s) related to an associated pathology

Many questionnaires with high sensitivity and positive predictive value are used to detect any pathology with associated coagulation. This situation is rare but it should not be ruled out.[61]

1.2.1.2 Patient adherence to his (her) antithrombotic therapy

During the history taking, the name of the antithrombotic medication(s), the dose, the number of daily doses, the indication for antithrombotic therapy, as well as biological monitoring and the value of the last known tests (e.g., INR, platelet count, aPTT) must be reported.

At the time of the physical examination, the clinical signs suggestive of coagulopathy or an overdose should be investigated (epistaxis, gingival bleeding > 3 minutes after brushing, skin and/or mucous membrane bruising, etc.).

1.2.1.3 Type of surgical procedure

In oral surgery, the major factor for assessing the risk of surgical bleeding remains the possibility of controlling bleeding postoperatively by simple mechanical hemostasis measures (pressure + sutures). Therefore, it is legitimate to distinguish, in oral surgery, surgical procedures for which externalized bleeding can easily be controlled by conventional surgical hemostasis from those that are difficult to control by the usual means. The second important factor to be considered is the location of the potential hemorrhage and its consequences on the vital or functional prognosis. In oral surgery, locations referred to as "critical" such as the floor of the mouth, tongue and the maxillary sinus, are anatomical regions in which bleeding can rapidly become uncontrollable in general practice. The other discriminatory factors that could impact the risk of surgical bleeding are the nature of the tissues operated (bone surgery and soft tissue surgery), the surgical technique and procedure (traditional surgery with incisions and large separations versus minimally invasive surgery), the surgical experience of the practitioner, the duration of the procedure (operational time > 1 hour or $\leq$ 1 hour), and the modality of the surgery (elective surgery and emergency surgery that cannot be deferred).[44,109]

In a pragmatic approach, two types of surgical procedures or invasive procedures must be distinguished: the so-called "high risk" procedures where the frequency and/or severity of perioperative bleeding is high, and the so-called "low or moderate risk" procedures where the risk of bleeding is lower. A non-exhaustive list of the main oral surgery procedures, classified in terms of risk of bleeding is presented in *Appendix 2*.

SURGICAL or INVASIVE PROCEDURES WITH A LOW or MODERATE RISK OF BLEEDING

These are cases of dental or periodontal care and surgical procedures where blood loss is small (volume < 50 mL, no cases of platelet transfusion reported)[24,21,239], non-critical by their location and that can easily be controlled by simple mechanical hemostasis measures.

SURGICAL or INVASIVE PROCEDURES WITH A HIGH RISK OF BLEEDING

These are all procedures for which the probability of bleeding is clinically significant (duration of surgery > 1 hour, lowering of the HGB levels, reported platelet transfusion), or critical by their location (maxillary sinus, tongue and floor of the mouth) and/or difficult to control by conventional surgical hemostasis in general practice (compression, sutures, local collagen-based hemostatic agents, gelatin or cellulose).

The need to use a biological glue, a monopolar or bipolar electrocoagulation to ensure the patient's hemostasis, is a criterion used to classify surgeries as surgeries with a high risk of bleeding.

CRITICAL LOCATION

Apart from taking any antithrombotic treatment, anatomical regions point to serious bleeding complications as a result of oral surgery procedures (extraction of the 3rd mandibular molar, implant placement in the symphyseal region, maxillary sinus lift, symphyseal sampling). Thus the following were reported:

- the maxillary sinus with the risk of hemosinus following the injury to the posterior superior or antral alveolar arteries;[169,175]
- the floor of the mouth with the risk of compressive hematoma and/or severe bleeding following injury to the lingual artery or one of its branches (submental artery).[53,75,117,179,186,220,235]

While these events remain exceptional, the literature regularly reports cases of serious life-threatening bleeding,[75,211,218] some of which are fatal.[107,230]

1.2.1.4 Hemorrhagic risk factors that could increase the risk of surgical bleeding.

Several clinical studies have demonstrated predictors of an increased risk of occurrence of perioperative bleeding; they are related either to the patient's age and comorbidities, or to the local conditions of tissues.[72]

AGE and COMORBIDITIES

Phase II and III studies, as well as observational studies reporting severe bleeding that occurred in patients treated with antithrombotics were able to identify risk factors responsible for overdose.[4,122] The HAS-BLED score may be useful in assessing the impact of these factors on the risk of bleeding in case of surgery or an invasive procedure.[246] Among these factors, age and renal impairment as well as co-medications are the most commonly reported.[173,256,261] Note that the frequency of these risk factors is high in the population of patients treated with antithrombotics over the long term. The association or the accumulation of several risk factors requires special vigilance and a prior contact with the cardiologist or the treating physician. *Appendix 3* lists the key factors for risk of bleeding.

MEDICATIONS and FOOD

Drug prescriptions can induce many interactions with all antithrombotics. The list of formally contraindicated medications as well as well as that of medications that increase the risk of the bleeding or thrombosis, likely to be prescribed by the practitioner, will be noted for each antithrombotic family.

Food, fruit juice and herbal remedies can also interact with VKAs, influence their efficacy and also cause an overdose.[81,106,271,285] These interactions should not be ignored or underestimated. The postoperative period is a critical period, because it is often accompanied by a new prescription and/or changes in eating habits. Clinical and/or biological monitoring is required when prescribing anti-infective and/or analgesic agents.[23,38,52,72,79,159,171,187,208,241,268,289,291,292]

LOCAL CONDITIONS

Local inflammation of the gingiva (gingivitis, periodontitis, etc.), the presence of infectious diseases (granuloma, radicular-dental cyst, pericoronitis, etc.), due to vasodilation and increased capillary permeability, potentially increases the risk of hemorrhagic events.[173,221,225,245] Similarly, the absence of attached gingiva makes suturing and traction of soft tissues more difficult.

The accumulation of several risk factors (age and comorbidity, medication and diet, adverse local conditions) may lead to a clinical situation with a high risk of bleeding.

1.2.2. From laboratory examination(s)

In clinical studies, hemostasis tests help demonstrate the *in vitro* efficacy of antithrombotics. When the usefulness of biological monitoring is established (VKA, heparins at curative doses), laboratory tests are used to manage the risk of bleeding (overdose) through dose adjustment. Prescribing them preoperatively to predict the risk of bleeding associated with the surgical procedure depends on the antithrombotic compound and the invasive procedure.[61,70]

At the end of the pre-operative consultation, the practitioner must: - be able to identify patients or clinical situations with a high risk of bleeding complications; - establish all the preventive measures required to optimize hemostatic safety.

1.3 Choice of the management of structure: general practice or in a hospital?

Management can be done in general practice for antithrombotics prescribed over the long term for all elective surgeries or invasive procedures with a low or moderate risk of bleeding.

For clinical situations where there is a high risk of thrombosis and/or surgery with a high risk of bleeding, management will take place in the hospital. The same applies for patients with a non-stabilized cardiovascular pathology and/or having other constitutional or hemostasis-induced anomalies. These

particular cases require hospitalization, multidisciplinary consultation and hemostasis specific to each case.[44,109,199]

1.4 Local hemostasis

Any surgery or invasive bleeding procedure is defined by the shedding of blood outside a vessel. Obtaining hemostasis at the end of the procedure must be controlled. Note that the quality of hemostasis is still influenced primarily by the surgical technique and mastery of the surgical procedure.[160]

- In the case of dental extraction or placement of a dental implant, the bleeding is easily controllable by simple mechanical hemostasis measures (sutures + compression). In the absence of a congenital defect and/or a hemostasis-acquisition abnormality, hemostasis is usually obtained within 10 minutes.
- In the case of a gingival or mucosal wound, these simple mechanical measures (sutures + compression) are normally sufficient. In the case of palatine sampling, the installation of a palatal plate is a simple measure used to ensure effective mechanical compression.
- In the case of substantial mucosal detachment, it is necessary to have a mono- or bipolar electrocoagulation.

When these conventional surgical hemostasis techniques (mechanical and/or thermal) are insufficient, local hemostatics may be used in addition to hemostasis.
In patients on antithrombotics, in order to offset the additional bleeding, the consensus is for the systematic use of hemostatic adjuvants such as local hemostatics and/or tranexamic acid. The time for obtaining hemostasis, the volume of blood loss, and the rate of intra- and postoperative bleeding complications are the most commonly used criteria for evaluating the efficacy of these products.
The local hemostatics used in oral surgery include surgical hemostatics and tranexamic acid.

1.4.1 Surgical hemostatics

By definition, surgical hemostatics are used intraoperatively by the practitioner to prevent the leakage of blood in case of a vascular wound located on the capillaries.
It is important to remember that high-intensity arterial or venous bleeding falls outside of treatment with these products.
Surgical hemostatics are classified into two groups: hemostatics without specific action on the events that occur during hemostasis and hemostatics with a specific action.[231]

1.4.1.1 Surgical hemostatics without specific action on the events that occur during hemostasis.

They include oxycellulose-based products of plant origin (SURGICEL®) collagen-based (PANGEN®) or gelatin-based products of animal origin (CURASPON®). These products have the regulatory status of a sterile medical device (SMD). They are in the form of sponges and sterile gauze. These devices are ready to use and are stored at room temperature. They act primarily by absorbing blood and by compression. They are therefore particularly efficient in the case of an intra-alveolar tamponade. Upon contact with blood, they increase in size, form a gelatinous cap (collagen, gelatin) or a brown mass (oxycellulose), which fills the wound and mechanically opposes the flow of blood.[160]

The use of cyanoacrylate glue (HISTOACRYL®) helps ensure sealing against leakage or to keep in place the surgical hemostatics in case of a gingival wound in the absence of sutures.[17,193]

1.4.1.2 Surgical hemostatics with specific action on the events that occur during hemostasis.

These are biological adhesives also known as “fibrin adhesives”. These products are obtained by fractionation of human plasma and have the special status of blood derived medicinal products (BDMPs). In France, these BDMPs are for hospital use only and given the risk of transmission of conventional infectious agents or not, they are subject to Traceability Decree No. 95-566 dated May 06, 1995.

In the literature, only two adhesives are used in oral surgery.[232] They are TISSUCOL KIT® and BLERIPLAST®.[2] They are used as a liquid gel using an applicator. They contain coagulated proteins of human origin (fibrinogen, factor XIII, fibronectin, thrombin) and aprotinin of bovine origin. They affect hemostasis by reproducing the last step of coagulation. Fibrinogen is converted to fibrin by the action of thrombin. Factor XIII will stabilize the clot and the proteolytic degradation of fibrin is inhibited by aprotinin. Few studies have evaluated the benefit of biological adhesives in dento-alveolar surgery in patients on antithrombotics.[41,45,57,126,209] The available randomized controlled trials have failed to show a possible hemostatic benefit in the prevention of post-operative bleeding compared to conventional methods and/or conventional surgical hemostatics.[41,57,126] However, if intraoperative bleeding is not controlled by these measures, or in case of bleeding complications, the use of these adhesives at the end of the procedure or in case of revision surgery, helps improve hemostatic safety.[232]

1.4.2 Tranexamic acid

Tranexamic acid (EXACYL®) is the only antifibrinolytic agent with an MA in the prevention and treatment of bleeding events maintained by local fibrinolysis as is the case following dental, ENT and gynecological procedures.[151]

Tranexamic acid is a lysine analogue, which binds to lysine binding sites of plasminogen and plasmin. It blocks the binding of plasminogen and plasmin on fibrin and prevents the degradation of the latter. Tranexamic acid is a competitive fibrinolysis inhibitor.[89] Several *in vitro* studies have shown that a concentration of 10 μg/mL of tranexamic acid reduces enzyme activity of t-PA (tissue plasminogen activator) by 80%. In the oral cavity, the t-PA is released in large quantities by the epithelial cells of the oral mucosa and saliva in case of surgical trauma.[118,182] The efficacy of tranexamic acid in the prevention and treatment of post-extraction bleeding has been demonstrated in numerous clinical trials.[46,57,58,236,249,263,269]

The advantage of these local hemostatics and their place in the strategy of the management of perioperative risk of bleeding in case of maintaining antithrombotics will be addressed in a specific paragraph for each family of medicinal products (APA, VKA, DOA, LMWH).

1.5. Postoperative management and monitoring

1.5.1 Postoperative monitoring and tips

Postoperative monitoring is important patient management. Following an oral surgical procedure, verbal and written postoperative advice should be given to patients. Such postoperative monitoring must be particularly strict in case of surgery with a high risk of bleeding.[74] Instructions for oral and dental hygiene and what to do in case of postoperative bleeding should be provided.

The occurrence of postoperative bleeding can occur immediately after surgery or within the following days until D + 6. Monitoring of good mucosal healing via a postoperative check-up on D + 10 is essential. The risk/benefit ratio of continued use of antithrombotics in case of dento-alveolar surgery is dependent on optimal coordination of the course of care and good patient adherence to instructions (information, adherence, patient education).

1.5.2 Curative treatment of bleeding complications

Bleeding complications are defined as uncontrollable bleeding in patients.

They can be classified into two categories: minor bleeding and severe bleeding. Minor bleeding includes permanent bleeding, extra-alveolar clots and bruising. Severe bleeding corresponds to significant post-operative bleeding and expansive hematomas in the deep spaces (submandibular lodge, for example). These bleeding complications may be life threatening conditions and require hospital management.

They are exceptional in oral surgery and are always associated with invasive soft tissue trauma and/or arteriolar or arterial section.

Bleeding complications in patients on antithrombotics after oral surgery are essentially have good prognoses. Their management is always based primarily on a revision of the surgical wound with a resumption of local hemostasis. The search for a local cause of the bleeding is imperative. The operating area is reopened after anesthesia, the intra-alveolar compression material is removed. This procedure allows you to view the source of the bleeding in order to act directly at its source. The follow up is identical to the initial management. An intra-alveolar hemostatic material is replaced, suturing is performed, local compression is introduced and a topical antifibrinolytic agent can be associated during the healing period. The absence of sustainable control of bleeding by conventional local hemostasis measures is considered to be a criterion of severity and hospital management is therefore necessary. The use of general hemostatics and medical monitoring may be indicated.[71,194,207]

2. Specificities of the management of patients treated with antiplatelet agents(s)

2.1 The issues

Cardiovascular diseases related to atherosclerosis are the leading cause of death in the industrialized world and the second leading cause in the world.

In France, the prevalence of **coronary artery disease** is 3.9%. **Acute coronary syndromes** (ACS) are responsible for 150,000 hospitalizations per year and 46,000 deaths per year.[154] **Ischemic cerebrovascular accidents (ischemic CVA)** and **transient ischemic attacks** (TIA) have an estimated incidence of 130,000 cases per year and are responsible for 40,000 deaths per year. This pathology is the leading cause of non-traumatic disability in adults. The risk of recurrence of stroke at 5 years is estimated at between 30 and 43%.[155] **Peripheral obstructive artery disease** (PAD) affects approximately 800,000 patients, and two thirds are symptomatic. The incidence of this pathology is 90,000 new cases per year and is responsible for 60,000 hospitalizations and 10,000 amputations.[31,156]

Antiplatelet agents (APAs) are indicated for secondary prevention in atheromatous disease to prevent the occurrence of cardiovascular events.[8,78]

The prescription of antiplatelet monotherapy for life (aspirin or clopidogrel) is recommended in patients with ACS (in the absence of an indication of an anticoagulant treatment or formal contraindication to aspirin and/or clopidogrel), ischemic CVA or PAD.[8] Dual antiplatelet therapy (aspirin and clopidogrel or prasugrel or ticagrelor) is justified in cases of major risk of thrombosis. It is recommended during the year following ACS, especially myocardial infarction (MI).[13] The optimum duration of dual therapy is controversial because studies report the occurrence of thrombotic events following the early discontinuation of the associated thienopyridine.[251,252] The minimum duration of prescription of dual therapy is 1-3 months after carotid and intracranial angioplasty, 1 month after placement of a bare stent[270] and 6-12 months after placement of a drug-eluting stent.[8,121] Beyond these time frames, the continuation or not of dual therapy is to be adapted on case by case basis, but is not generally recommended.[13,252]

Aspirin alone is recommended for primary prevention when cardiovascular risk is particularly high in patients with diabetes.[8]

In France, the prescription of APAs concerns close to 5% of the population.[27] The number of new patients per year is estimated at between 200,000 and 300,000. In 2010, 81% of patients treated with

APAs were on aspirin and 1 million patients were treated with clopidogrel.[27] The number of patients treated with APAs continues to grow, due to the combined effect of an aging population, the extension of their indications and the rise of interventional therapies. According to national data of the French Information Systems Medicalization Program (PMSI), 125,000 patients underwent percutaneous coronary intervention (PCI) in 2007.[154]

Only oral APAs prescribed as part of outpatient treatment are the subject of recommendations (*see Appendix 1*). GPIIb/IIIa inhibitor antagonists (abciximab, eptifibatide, tirofiban) indicated in the initial management of ACS, will not be considered. The performance of oral surgery is normally not indicated during this period and will be postponed to sometime after stopping antiGPIIb-IIIa.

2.2 Antiplatelet agents

2.2.1 Conventional antiplatelet agents

Conventional APAs include aspirin, dipyridamole, ticlopidine and clopidogrel.

2.2.2.1 Aspirin

Acetylsalicylic acid, or aspirin blocks cyclooxygenase-1 (COX-1) from the platelet, thereby inhibiting the production of thromboxane A2 (TXA2), a potent vasoconstrictor and inducer of platelet aggregation. Given that this inhibition is irreversible, the action of aspirin on platelets is permanent throughout their lifetime. The inhibition of COX-1 is complete under low-dose aspirin (75-160 mg/day) or after a loading dose of 325 mg. Daily doses above 100 mg in clinical practice do not increase the platelet anti-aggregation effect but increase the risk of spontaneous gastrointestinal bleeding. After discontinuation of aspirin, platelet aggregation normalizes within 5-7 days (on average 10% of platelets per day).[78,91]

Aspirin is the most widely used APA. It is marketed either alone (KARDEGIC®, CARDIOSOLUPSAN®),[133,145] or in combination with dipyridamole (ASASANTINE®),[142] clopidogrel (DUOPLAVIN®)[141] or pravastatin (PRAVADUAL®).[143]

Two meta-analyses have evaluated the antithrombotic efficacy of aspirin versus placebo.[21-22] In primary prevention, aspirin can reduce cardiovascular events by 12%, the largest reduction involving non-fatal MI. Its effect is weak and insignificant on coronary disease mortality and on CVA In secondary prevention, aspirin significantly reduces the risk of recurrence of MI by 26% and TIA/ischemic CVA by 25%. It is also associated with a decrease in cardiovascular deaths by 15%. As part of revascularization therapy, the benefits of aspirin after stenting are twofold: significant reduction of cardiovascular events and reduced rates of stent thrombosis.[8]

All patients do not respond to APAs with the same intensity. The rate of low-responders to aspirin is particularly significant in patients with type 1 diabetes and in females.[8] The average rate of non-

responders is around 6% of the population.[69] So called aspirin-resistant individuals often have an effective blocking of the production of thromboxane A2 (TXA2), offset by an increase in the stimulation of other activation pathways (ADP receptor, thrombin receptor). They thus maintain significant platelet aggregation despite the inhibiting activity of aspirin.

In patients on long term nonsteroidal anti-inflammatory drugs (NSAIDs) and who require antiplatelet cardioprotection, it should be noted that ibuprofen combination may decrease cardiovascular protection of aspirin by 70% (OR 1.73, 95% CI 1.05-2.84, $p < 0.05$), by blocking the access of aspirin to COX-1 by the simple phenomenon of competition at the level of the receptor.[203]

2.2.2.2 Dipyridamole

Dipyridamole slows down the reuptake of adenosine monophosphate (AMP) by platelets. It is also described as cyclic AMP (cAMP) inhibitor. These actions contribute to intracellular cAMP elevation, a second anti-platelet activating messenger.

Dipyridamole is marketed in France alone at a dose of 75 mg (CLERIDIUM®, PERSANTINE®),[132] 150 mg (CLERIDIUM®) or at a dose of 200 mg combined with 25 mg of aspirin (ASASANTIN LP®).[142]

The clinical efficacy of monotherapy dipyridamole is low and this APA is therefore not often prescribed.[8] A recent meta-analysis highlighted the value of the aspirin + dipyridamole combination for secondary prevention of ischemic CVA compared to placebo and aspirin (relative risk reduction of 39% and 22%, respectively).[192]

2.2.2.3 Ticlopidine

Ticlopidine was the first thienopyridine synthesized. Like all thienopyridines, it irreversibly inhibits the P2Y12 purinergic ADP receptor, a factor for activation and platelet aggregation triggered by ADP.[91] Ticlopidine has been marketed in France since 1978, at a dose of 250 mg (TICLID®) at two doses per day.[150] A period of 8-11 days is needed to achieve maximal inhibition of platelet aggregation. Its antithrombotic efficacy is certain, but its side effects explain why it has almost completely been abandoned in favor of clopidogrel. Monitoring of complete blood count is recommended because of the high risk, for the first three months of treatment, of agranulocytosis and thrombocytopenia observed in 2.4% of patients.[8]

2.2.2.4 Clopidogrel

Clopidogrel is currently the most prescribed thienopyridine.[8] Clopidgrel is more potent than ticlopidine with better pharmacokinetics (one dose a day instead of two) and a better safety profile (rare cases of leukopenia and thrombocytopenia).[8] Clopidogrel is a prodrug that requires a first pass hepatic

biotransformation at the level of CYP 450. It is an irreversible non-competitive inhibitor of the ADP $P2Y_{12}$ receptor. Although irreversible, inhibition is not complete: the reduction of platelet aggregation is 40-60%.[91] Clopidogrel (PLAVIX®) has been used since 1998, at a dose of 75 mg daily.[135] In monotherapy, clopidogrel has demonstrated superiority over aspirin only in the secondary prevention of TIA/ischemic CVA.[135] The modes of action of aspirin and clopidogrel are different, their combination suggests a high antithrombotic efficacy. The superiority of the dual therapy compared with aspirin alone was demonstrated in two situations: patients with a MI less than 1 year ago and after coronary revascularization. In the CURE trial (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events)[196,213], the clopidogrel + aspirin combination helped reduce the primary endpoint (cardiovascular/MI/CVA deaths) and the number of nonfatal MI by -2.1% and -1.5%, respectively, versus aspirin alone. Dual therapy for 1 month after bare stent placement, without MI, according to the COMMIT (Clopidogrel and metoprolol in Myocardial Infarction Trial)[62] and CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy)[253] trials, makes it possible to obtain a significant decrease from -0.6 to -2.5% of the composite endpoint (cardiovascular death/MI/CVA) compared to aspirin alone. Several randomized studies[8,13,76,222] have shown the benefits of dual therapy during the first 6-12 months after the placement of drug-eluting stents or a venous bypass, with a significant reduction in the rates of stent thrombosis, better maintenance of the permeability of vein graft, as well as reduced mortality. The optimal duration of dual therapy remains controversial.[13]

The antiplatelet activity of clopidogrel is subject to a large individual variability with a rate of non-responders estimated at 12-35%.[91] Several phenomena are involved: a genetic polymorphism, drug interactions, type 1 diabetes, kidney failure and old age.[69] Among the numerous drug interactions, only two have a well-described clinical impact: atorvastatin and omeprazole. Concomitant administration of one of these compounds with clopidogrel reduces the efficacy of the latter by 25% with a significant increase in cardiovascular risk for patients. Note that this effect was not found with other proton-pump inhibitors (lansoprazole, pantoprazole, etc.) and statins.[8,282]

2.2.2 Novel antiplatelet agents

The treatment of ACS and coronary artery disease patients treated by angioplasty receiving aspirin + clopidogrel dual therapy, but heterogeneity in response to these compounds has been demonstrated and hyporesponders have an increased risk of an ischemic event. This is why new compounds allowing faster, more intense and more reproducible inhibition have been developed.[88,127] Among them, two are currently marketed: prasugrel and ticagrelor.

2.2.2.1 Prasugrel

Prasugrel is a 3rd generation thienopyridine, which has two essential advantages compared to ticlopidine and clopidogrel: a more rapid onset of action (30 minutes post-dose) and a more potent activity.[275] Prasugrel blocks the $P2Y_{12}$ receptor sensitive to ADP, irreversibly, like ticlopidine and clopidogrel, but with a less variable and more predictive platelet inhibition.[91] Prasugrel (EFIENT®) obtained its MA in 2010 and is used with a 60 mg loading dose and a maintenance dose of 10 mg 1 times/day.[139]

Prasugrel is more effective than clopidogrel in terms of protection against MIs and stent thrombosis, but at the expense of more bleeding episodes. That is why it is contraindicated in patients with CVA and a lower dose (5 mg) is recommended for weight < 60 kg, age > 75 years and with severe renal impairment.[8] The TRITON-TIMI38 trial (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel)[219,286] compared the efficacy and safety of prasugrel (loading dose of 60 mg followed by a maintenance dose of 10 mg/day) to clopidogrel (loading dose of 300 mg followed by a dose of 75 mg/day) in 13,608 patients on dual therapy (aspirin + clopidogrel or prasugrel) admitted for ACS with a high profile risk of myocardial infarction with ST-segment elevation (STEMI) or an intermediate profile risk (unstable angina) who had to undergo PCI. The results show that for 1,000 patients treated with prasugrel, 23 infarctions were avoided for an additional 6 major bleeding complications versus clopidogrel. Prasugrel further reduces the risk of recurrence of MI and stent thrombosis, regardless of the type of stents, compared to clopidogrel. Prasugrel is particularly effective in diabetic patients and in non-responders to clopidogrel. The rate of non-responders to prasugrel is only 3%. However, prasugrel has an increased risk of major bleeding compared to clopidogrel (2.4% instead of 1.8%). The elderly (> 75 years), people of low weight (< 60 kg) and patients with TIA/ischemic CVA (risk of intracranial hemorrhage) are particularly at risk of spontaneous bleeding.[8] Prasugrel is indicated in combination with acetylsalicylic acid for the prevention of atherothrombotic events in patients with ACS treated with primary or delayed PCI.[139,282]

2.2.2.2 Ticagrelor

Ticagrelor is an APA of a new chemical class, the family of cyclo-pentyl-triazolo-pyrimidines. It is a direct and reversible platelet $P2Y_{12}$ ADP receptor inhibitor. This is not a prodrug and it does not need to be metabolized to be active.[91,215] Therefore, these two pharmacological properties distinguish it from thienopyridines.[215] Pharmacodynamic studies have shown that ticagrelor has a more powerful, faster platelet inhibition potency and with less individual variability compared to clopidogrel.[284]

Ticagrelor (BRILIQUE®) has been marketed in France since 2010 and is used at a dose of 90 mg, 2 times/day after a loading dose of 180 mg.[146] Ticagrelor obtained its MA after the results of the PLATO

trial (The Study of Platelet Inhibition and Patients Outcomes)[174] conducted in 18,624 patients admitted for ACS. Ticagrelor was found to be slightly more effective than clopidogrel in reducing the risk of death (RR 0.78, 95% CI 0.69-0.89, p < 0.05), of MI after ACS (RR 0.84, 95% CI 0.75-0.95, p < 0.05), stent thrombosis (RR 0.75, 95% CI 0.59-0.95, p < 0.05), but not in changing the rate of TIA/ischemic CVA (RR 1.18, 95% CI 0.91-1.52, ns). Its efficacy is reduced when combined with high doses of aspirin (> 300 mg/day). It has no preferential effect in diabetic patients. The risk of major bleeding (intracranial or gastrointestinal hemorrhage, loss of 30-50 g/L of hemoglobin) does not differ between ticagrelor (11.6%/year) and clopidogrel (11.2%/year) (p = 0.433). Ticagrelor, in combination with aspirin, is indicated for the prevention of atherothrombotic events in adult patients with ACS (unstable angina, NSTEMI or STEMI) including medically treated patients and those treated with PCI or coronary artery bypass surgery.[146]

2.3 Discontinuation or maintenance of treatment with antiplatelet agents?

- Numerous retrospective studies report the occurrence of ACS, MI, ischemic CVA and death in patients who discontinued aspirin therapy within the immediate postoperative period and within the following month.[25,30,60,64,65,102,103,112,116,1127,214,277]

In a meta-analysis,[40] discontinuation of aspirin in patients taking aspirin over the long term is associated with a three-fold increased risk of thrombotic events (cardiac or neurological) (OR 3.14, 95% CI 1.75-5.61, p < 0.05). This risk of thrombotic adverse events is even higher in patients who had coronary stent implantation (OR 89.78, 95% CI 29.90-269.60, p < 0.01).

In addition, Minassian and coll., 2010[216] report, in a retrospective observational survey of patients with a history of ACS (n=650 patients) or MI (n=525), a significant increase in thrombotic events during the 4 weeks following dental treatment (OR 1.5, 95% CI 1.09-2.06 p < 0.05). Similar observations[165,166] are reported with an early or inappropriate discontinuation of clopidogrel.

All the data in the literature highlight the potential danger with an increased morbidity and mortality in the event of discontinuation of treatment with APA in patients with coronary artery disease or in patients with cerebrovascular pathology with respect to surgery.

Adverse thrombotic complications are not immediate and follow the discontinuation of aspirin and/or clopidogrel within an average period of 8-25 days. The deleterious effect of the discontinuation of treatment with APAs can be explained not only by the suppression of antiplatelet protection, but also by the existence of a rebound effect of platelet activity upon discontinuation of APAs.[201]

The continuation of treatment with APA prior to surgery ensures the prevention of the risk of thrombosis. In return, this therapeutic strategy increases the risk of perioperative bleeding.

The average post-extraction risk of bleeding in case of maintenance of treatment with aspirin or clopidogrel is estimated at less than 2% with extreme values ranging from 0-18% according to studies (*see Appendix 4*). For all of these clinical studies[24,36,48,50,54,56,113,185,197,204,228,234,248,281] no severe bleeding complications not controllable by local hemostasis measures has been reported. Two studies[212,237] evaluated blood loss after dental extraction in patients on aspirin or clopidogrel compared with patients not taking aspirin or who discontinued their treatment with APA 7 days before the dental procedure or on NSAIDs. Although both studies reported a greater blood loss in patients on APA compared to the control groups, there is no significant difference. In addition, no difference in terms of incidence of postoperative bleeding between the groups has been reported.
In case of dual therapy, the incidence of bleeding with the aspirin + dipyridamole combination is similar to that observed with aspirin alone.[228,278] However, in case of the aspirin + clopidogrel combination, the risk of bleeding during the immediate postoperative period is higher in the case of dual therapy compared to aspirin alone (RR 28, $p < 0.001$) and clopidogrel (RR 24, $p < 0.001$),[54,197] but is easily controllable by local hemostasis measures.[36,54,197,227,228,234] No severe or delayed bleeding is reported. A simple surgical hemostasis combining local hemostatic and sutures can be used to effectively control the risk of perioperative bleeding. Furthermore, studies[165,166] have shown the occurrence of thrombotic events within a period of 1-3 months following the discontinuation of the dual therapy (discontinuation of clopidogrel and continuation of aspirin) in stent patients. This raises the question of a possible "prothrombotic rebound" upon discontinuation of clopidogrel,[257] a deleterious effect also mentioned with aspirin,[60,102,103] but whose physiopathology is still unclear.[18]

- All clinical studies show that dental extractions can be performed with aspirin or clopidogrel monotherapy (*see Appendix 5*) and in combination (*see Appendix 6*) without a change in treatment. Scientific data regarding ticlopidine and the aspirin + dipyridamole combination is very poor; it does not show statistically significant differences in terms of the risk of bleeding compared to aspirin and clopidogrel. Regarding prasugrel and ticagrelor, no data has been published, given that these compounds are exceptionally prescribed as monotherapy.

No bibliographic data is currently available regarding the risk of bleeding associated with implant placement in patients receiving APA. In the current state of knowledge, implant placement is a procedure with low to moderate risk of bleeding in the absence of mucoperiosteal detachment beyond the mucogingival junction. Despite the absence of data in the literature, dental implant placement can be performed without discontinuing antiplatelet therapy (monotherapy or dual therapy), given the ease of access to the operating area and the effectiveness of local hemostasis.

• In the event of more invasive oral surgery (e.g., pre implant surgery, benign cysts and tumors of the jaw surgery), there is no bibliographic data available to date. For this type of surgery, since the risk of bleeding is higher or more difficult to control, the maintenance of antiplatelet therapy should be discussed between the practitioner and the prescribing physician on a case by case basis, taking into account the risk/benefit ratio (thrombotic and hemorrhagic). Two dual therapy management strategies can be proposed: maintaining dual therapy or partial discontinuation of dual therapy (discontinuation of clopidogrel or prasugrel or ticagrelor and continuation of aspirin).[8,60,127,162,163]

2.4 What biological test can be used to evaluate the risk of surgical bleeding in patients on an antiplatelet agent?

Historically, bleeding time (BT) was used for the assessment of preoperative hemostasis as well as for the exploration of a hemorrhagic syndrome. Although many studies[24,49,240] have shown prolongation of BT in patients treated with APA, systematic studies dating back to 1990 had shown that the BT had a very low predictive value for risk of bleeding.[198,250] Since 1998, in France, the prescription of a BT test preoperatively is no longer recommended.[161] Many learned societies[61,70,265] have since endorsed this recommendation. BT (regardless of the method of exploration: Duke or Ivy) is not included in the classification of medical biology procedures (NABM) since February 2013.[177] Further tests are proposed at this time to monitor antiplatelet therapies. There are two main families: aggregation tests, which measure platelet reactivity to the stimulation of an agonist (arachidonic acid, adenosine diphosphate ADP), and those that measure more specifically the effect of a drug on its molecular target (urine level of thromboxane B2 for aspirin, VASP test for clopidogrel). In the first case, the tests can be used to identify whether the patient's platelets are more or less reactive upon stimulation by an agonist. In the second case, the tests are used to measure the molecular target inactivation status of drugs prescribed, COX 1 for aspirin, $P2Y_{12}$ receptor for clopidogrel and other inhibitors of this receptor. The value of these platelet inhibition tests is to identify the "poor responders" or "patients resistant to APAs". For now, none of these tests has demonstrated its usefulness in the evaluation of the risk of surgical bleeding in patients receiving APA and they are not recommended in routine practice.

2.5 Which local hemostasis should be performed to control the risk of surgical bleeding?

Conventional measures of hemostasis (sutures, compression, electrocoagulation) are essential.

- In case of simple extraction (single and multiple), conventional hemostatic measures (sutures + mechanical compression of 30 minutes) are effective and sufficient to control postoperative bleeding in patients on aspirin[24,50,185,204,281] or on clopidogrel[54,197] with an acceptable residual postoperative bleeding rate of about 2-3%. For aspirin + clopidogrel dual therapy, local hemostasis combining sutures + compression seems to be insufficient[197] and the use of local hemostatics (collagen sponge, oxycellulose gauze, fibrin glue) is necessary.[36,54,227,234,239,248] In the event of dual therapy, a higher rate of bleeding is observed during the first postoperative hour.[197,234,239] Despite the absence of data from the literature, in case of implant placement, suturing and manual compression are sufficient to ensure the control of hemostasis.
- In case of surgical extraction, the use of surgical hemostatics (gelatin sponge, fibrin, collagen, oxycellulose gauze) in addition to conventional hemostasis measures, is recommended whether the patient is receiving monotherapy[113] or dual antiplatelet therapy[54,197,227] For surgeries with high risk of bleeding with significant mucosal detachment, similar measures should be applied.

All these measures are presented in the form of summary tables *in Appendix 5* and *Appendix 6*.

2.6 Curative treatment of bleeding complications

The management of a bleeding complication is always based on the resumption of local hemostasis. It is most often identical to the initial management. Although the use of preventive surgical hemostatics is not systematic in patients on APA, the use of these products in the presence of bleeding complications is essential. No severe bleeding complications (i.e., not controllable by local hemostasis measures) are reported in the literature. There is no data on prasugrel and ticagrelor.

In the case of a bleeding complication that is exceptionally not controllable by the resumption of local hemostasis, authors recommend the use of desmopressin or platelet transfusion. No clinical studies currently validate such measures.

Although the use of preventive surgical hemostatics is not systematic in patients on APA, the use of these products in the presence of bleeding complications is essential.

3. Specificities of the management of patients treated with antivitamin K

3.1 The issues

Venous thromboembolism (VTE) includes superficial vein thrombosis (SVT), deep vein thrombosis (DVT) and pulmonary embolism (PE). SVT is a benign pathology, whereas DVT and its complication,

PE, by embolic migration of the thrombus into the pulmonary arterial circulation, are associated with morbidity and mortality.[4] VTE is a common disease. In France, the incidence of DVT and PE are estimated at 1.24/1,000 inhabitants/year and 0.6/1,000 inhabitants/year.[233] DVT and PE are responsible for 10,000 deaths/year and 10% of hospital deaths.[4,80,264] Many surgeries are associated with a high risk of DVT in the absence of prophylactic treatment. These primarily include orthopedic and trauma surgery, major abdominal, urological and gynecological surgery.[80,264]

Embolic heart diseases are, in 20% of cases, the cause of ischemic CVA.[155] The main cardiac sources of emboli are: cardiac atrial fibrillation (Afib),[157] valvular heart disease and complicated MI.[158]

Afib is the most common cardiac arrhythmia. Its prevalence is estimated at 1-2% of the population and concerns between 750,000 and 1 million patients in France. It increases with age; two-thirds of patients are between 75 and 85 years old.[157] National data from the 2007 PMSI reported 84,000 hospitalizations per year with a primary diagnosis of Afib and a figure of 349,000 when Afib is coded as a secondary diagnosis.[191] The frequency of occurrence of ischemic CVA in patients with Afib ranges from less than 2% per year (in patients without associated cardiovascular risk) to over 10% per year (in case of a history of TIA/CVA, high blood pressure, heart failure, age > 75 years).[129,210] The risk of thromboembolism is assessed using the CHADS2 and CHA_2DS_2-VASc scores.[190,210] Aspirin is no longer part of the therapeutic options.[210]

Valvular heart diseases (valvulopathies and prosthetic valve disease) have an estimated prevalence of less than 2% of the general population and also increase with age (prevalence between 10 and 15% in patients aged over 75 years).[158] Patients with a tight mitral valve stenosis in Afib or carriers of a valvular prosthesis are at high risk of a thrombotic event.[158] Every year, 100,000 patients have **myocardial infarctions (MI)** and nearly 13% of patients treated die within the first year.[154] The risk of ischemic CVA is major during the first 6 months following MI. Following MI, the risk of CVA is about 1.5% per year. Some situations, such as the persistence of a mural thrombus, the existence of an aneurysm of the ventricular wall or free akinetic area, heart failure and associated rhythm disorder, are particularly thrombogenic (annual thrombotic risk estimated at between 4 and 7%).[158]

VKAs are indicated in the prevention of these thromboembolic events and are usually prescribed as a relay to initial heparin therapy, injectable anticoagulants and more adjusted during the acute phase.[9] Anticoagulants exert no direct action on a thrombus already formed or on ischemic tissue lesions. However, in cases where the thrombus is formed, the administration of anticoagulants aims to prevent the clot from growing and to prevent secondary thromboembolic complications, which could lead to serious after effects and could even be fatal.

More than two thirds of AVK prescriptions fall under cardiology (valvular disease, arrhythmias, coronary syndromes), while less than 20% fall under venous thromboembolic disease. In the indications that fall

under cardiology, treatment is most often prescribed for life. In the indications for VTE, treatment is usually shorter, schematically from 3 months to 1 year.[262]

Four percent of the French population receives anticoagulant therapy. In 2013, over 1 million patients were treated with AVKs.[10]

In the vast majority of cases, the treatment is prescribed by a specialist and monitoring is provided by the general practitioner in collaboration with a medical laboratory. VKAs are characterized by a narrow therapeutic window and therapeutic balance is sometimes difficult to obtain. For each patient, the required dosage of AVKs is variable and must be adjusted according to the results of the INR. Drug interactions, dietary habits and concurrent illnesses must be clearly identified and monitored over time in order to adjust the VKA treatment accordingly.[262]

VKAs involve an increased risk of major bleeding. This is estimated at 3% per year. Such bleeding is 1st among iatrogenic accidents, with 13% of hospitalizations for adverse drug reactions, i.e., approximately 17,000 hospitalizations per year. They are directly responsible for 0.6% of deaths per year recorded in patients on long term treatment with VKA.[122]

3.2 Antivitamin K

The discovery of the first VKA agent, dicoumarol, dates back to 1920; the active ingredient of rodenticides or “rat poison”. It was not until the 40s that the therapeutic dose was determined.

The anticoagulant action of VKA is an indirect action; it is linked to reduced hepatic synthesis of vitamin K-dependent coagulation factors (factors II, VII, IX and X). The degree of anticoagulation obtained is dependent on the dose prescribed and individual susceptibility. It is assessed by the value of prothrombin time expressed in the International Normalized Ratio (INR). Given that the patient’s sensitivity to the drug is unpredictable, the dosage should be adjusted and regularly monitored depending on the INR value.[125]

The target INR values are usually between 2 and 3 when the risk of thrombosis is moderate, between 3 and 4.5 when it is major.[12]

There are two families of VKA: indanediones and coumarins. Three compounds are available in France: acenocoumarol, warfarin and fluindione.[9,10]

3.2.1 Acenocoumarol

Acenocoumarol is a short half-life (8-9 hours) coumarin derivative, marketed since 1990 under the name MINISINTROM® at a dose of 1 mg and SINTROM® at a dose of 4 mg in the form of double-scored

tablets.[130] It is a fast acting and short duration VKA (24 hours). This drug is administered 1-2 times daily. In case of a single dose, it is preferable for the dose to be taken in the evening in order to adjust the dosage as soon as possible after the INR results. However, the use of this VKA is not often prescribed because it has a higher risk of therapeutic instability.[262]

3.2.2 Warfarin

Warfarin is the most frequently prescribed VKA worldwide. It has been marketed in France since 1977 under the name COUMADIN® at a dose of 2 mg and 5 mg, at 1 dose per day. [147] It is a coumarin derivative with a long half-life (35-45 hours). The anticoagulant effect is maximal between 72 and 96 hours following administration. The duration of action of a single dose of warfarin varies among individuals between 2 and 5 days (96-120 hours). [262]

3.2.3 Fluindione

Fluindione is the only indanedione derivative. It has been prescribed since 1988 under the name PREVISCAN® at a dose of 20 mg as double-scored tablet.[144] It is the most widely used VKA in France. It is a long half-life compound (30 hours) with an onset and a prolonged duration of action (48-72 hours).[262]

3.3 Discontinuation or maintenance of therapy with VKA?

Nearly 10% of patients on VKA undergo surgery every year.[9] Three clinical attitudes are possible: to maintain the treatment, discontinue it or relay it with heparin. The choice of the modality of management of VKAs in case of oral surgery depends primarily on the type of surgery envisaged (dento-alveolar or surgery with a high risk of bleeding).[37] The second criterion is the presence or absence of local or general factors that might increase the risk of bleeding. The existence of several risk factors can lead to a situation with high bleeding risk. In the rare case of oral surgery with a high risk of bleeding, two situations can be distinguished based on the risk of thrombosis (*see Appendix 8*). Finally, the special case of the VAK + APA combination will also be addressed.

3.3.1 Local anesthesia (LA) and locoregional anesthesia (LRA).

Bajkin and coll., 2012[34] report the safety of administering local anesthesia in patients receiving VKA regardless of the technique used: submucosal infiltration, inferior alveolar nerve block (IANB). Out of a

total of 560 injections, including 96 IANB, only two minor hematomas are described. No expanding hematoma in the pterygomandibular space is reported.

3.3.2 Dento-alveolar surgery

3.3.2.1 Dental extraction(s)

Wahl, 1998[283] in a systematic review reports that out of 493 patients who discontinued their VKA before a dental procedure, five patients (1%) had severe thrombotic complications including 4 fatal cases. Akopov et coll., 2005[14] in a retrospective study over a period of 12 months report that out of 197 cases of ischemic CVA of cardiac origin, 14 patients (i.e., 7.1%) had discontinued their warfarin treatment 5.4 days on average before the stroke with a view to elective surgery. The initiation or not of a prior relay is not specified in this study.

The discontinuation of a VKA treatment thus involves a significant and unacceptable accident risk of thrombotic events in connection with surgery with a low risk of bleeding. Two comparative, randomized, open-label studies[55,99] also showed that the rate of postoperative bleeding after dental extraction was not statistically different between the patient group for which warfarin was maintained and the group in which it was discontinued two days before the procedure when a surgical hemostasis was achieved.

Karsh et coll., 2011[180]compared blood loss after dental extraction based on the mode of management of the VKA (continuation, discontinuation, replacement) in patients with prosthetic heart valves (with a target INR between 3 and 4). Blood loss was determined by measuring the amount of blood soaked in compresses during the first 20 minutes. The amount of bleeding was 2,486 ± 1,408 mg (warfarin alone), 999 ± 425 mg (warfarin relay - LMWH) 1,288 ± 982 mg (warfarin relay - UFH) and 1,726 ± 876 mg (control). Surgical hemostasis was then performed after 20 minutes of compression using oxycellulose gauze and sutures. No serious bleeding was reported and the number of compresses used did not differ between the groups. The results of this study show that despite significant blood loss when warfarin treatment was maintained, it was mild and easily controlled by local hemostatic measures.

The studies, presented in a summary table *in Appendix 7*, confirm that there is no evidence in favor of the discontinuation of VKAs before dental extractions.

The need for a dose adjustment or replacement therapy (heparin relay) in case of dental extraction(s) and regardless of the value of the INR and/or risk of venous thromboembolism compared to the VKA maintenance strategy could not be demonstrated.[23,33,39,46,66,73,82,104,114,115,174,183,229,244,247,254,269]

Regardless of the risk of thromboembolism for the patient, in case of dento-alveolar surgery, treatment with VKA should not be suspended and heparin relay should no longer be administered.

Out of the 28 controlled studies selected[17,20,21,28,33,41,42,45,46,51,55,57,58,63,82,99,114,126,181,209,223,225,249,254,255,263,269,290] that evaluated the continuation of VKA treatment in case of dental extraction, the important factors to ensure an acceptable safety level of bleeding are a stable preoperative value of INR less than 4 and the systematic use of local hemostasis.

In case of continued treatment with VKA with a stable INR and less than or equal to 4, the risk of severe bleeding complications after dental extraction(s) (recourse to the hospital and repeat surgery) varies between 0 and 2.77% according to these studies. No serious complications (transfusion, death) were reported.

Antiplatelet monotherapy (usually aspirin or clopidogrel) in combination with the VKA treatment does not entail an additional bleeding event.[35,223,225]

This clinical attitude to intervene without preoperative modification of VKA treatment is safer for the patient and also the least onerous compared to the cost of a relay heparin.[66,73,242]

3.3.2.2 Dental implant(s)

Dental implant placement in patients on VKA can be considered unless there is an associated medical risk.[205] It is contraindicated in patients at high risk of infective endocarditis, especially patients with a mechanical or biological valve prosthesis.[5]

In a case-control study, Bacci and coll., 2011[28] compared the effect of warfarin with an INR < 4 (1 hour before surgery) on the occurrence of post-operative bleeding complications after dental implant placement. The same surgical hemostasis procedure that combines sutures + pressure on a compress soaked in tranexamic acid for 10 minutes is applied in the two groups. Two bleeding complications for 50 patients are reported in the group treated (maintenance of VKA) and three complications for 109 patients in the control group (healthy patients not taking VKA). All the bleeding complications were successfully treated by simple mechanical pressure with tranexamic acid. No major bleeding was reported.

3.3.3 Surgery with a high risk of bleeding

In case of surgery with a high risk of bleeding, the goal is to limit the risk of bleeding and/or compressive hematoma related to the procedure. The discontinuation of VKA seems, therefore, to offer the best

protection against the occurrence of postoperative bleeding, but the management of VKAs increases the risk of occurrence of thrombotic events during the postoperative period. Therefore, the risk of thrombosis related to the temporary discontinuation of VKA should be taken into account. Its assessment is the responsibility of the physician who prescribed the VKA.

Patients receiving anticoagulants over the long term can be classified based on the risk of thromboembolism into high, moderate or low-risk patients.[39] High-risk patients have an annual risk of arterial thrombosis of 10% or higher (e.g., patient with mechanical valve, recent coronary syndrome < 6 months) and risk of venous thromboembolism at 1 month of over 10% (e.g., venous thrombosis < 6 months). A risk of venous thromboembolism is considered to be low for patients with an annual risk of arterial thrombosis of less than 5% (e.g., Afib) and a risk of venous thrombosis of less than 2% (venous thrombosis > 6 months).[23,39] In a systematic review, Douketis and coll., 2012[86] reported that the average perioperative rate of thrombosis in patients on VKA was estimated at 0.60% in patients with VTE, 0.57% in patients with Afib and 0.80% in patients with mechanical valves with a higher severity. It has been established that the rate of recurrence of thrombosis following the unexpected discontinuation and/or in a surgical context of VKA therapy is higher in the first month and is higher for patients in whom the risk of thrombosis is higher.[264] Therefore, two situations can be distinguished: patients at low risk of thrombosis and patients at high risk of thrombosis.[9,122]

In cases of oral surgery with a high risk of bleeding (e.g., pre-implant surgery), the prescribing physician should be advised to evaluate the risk of thrombosis, determine the therapeutic strategy regarding VKA therapy (total discontinuation of VKAs, relay heparin) and management procedures (in general practice, hospital management).[172]

3.3.3.1 Patients at low risk of thrombosis

In patients treated for Afib with no history of embolism and patients treated for moderate risk VTE, the risk of thrombosis related to one case of discontinuation of the VKA is considered to be low enough (either in terms of frequency or severity) to propose the discontinuation of anticoagulation with VKA without preoperative heparin relay.[85,86,110,122] Discontinuation of VKA preoperatively in case of surgery with a high risk of bleeding in a patient at low risk of thrombosis is the therapeutic strategy recommended by the GEHT and HAS[122]. A summary diagram of the VKA discontinuation protocol is presented in *Appendix 9*. The VKA should be stopped 3-5 days before the procedure. The VKA should be resumed within 24-48 hours postoperatively. The speed of a new state of equilibrium is obtained between 4 and 5 half-lives after any change in dosage.[262] When VKAs cannot be resumed within the 48 hours, postoperative LMWH or UFH relay at curative doses should be initiated.[122]

3.3.3.2 Patients at high risk of thrombosis

Patients with mechanical heart valves (all types), patients treated for Afib with a history of embolism and patients treated for high-risk VTE (proximal DVT and/or PE < 3 months, idiopathic recurrent VTE), the risk of thrombotic complications is considered to be a major risk.[122] To reduce the therapeutic window, i.e., the length of time during which the patient is inadequately anticoagulated (INR value < target INR), a perioperative relay heparin at curative doses is recommended.[122] The use of replacement therapy also aims to better control operative bleeding, while minimizing the risk of thromboembolism.[33,84,108] Three options are possible: unfractionated heparin (UFH) by syringe pump, UFH subcutaneously (2-3 injections per day), and low molecular weight heparin (LMWH) subcutaneously (1-2 injections per day).

The modalities for a preoperative heparin relay with a view to surgery are detailed in the recommendations issued by the GEHT and the HAS published in 2008.[122] First, it is recommended to measure the INR 7-10 days before the procedure. If the INR is in the therapeutic range, it is recommended to discontinue the VKAs 4-5 days before the procedure. The value of 1.5 is retained as the INR threshold below which there is no increased perioperative bleeding complications. In patients at high risk of thromboembolism, relay heparin is to cover the pre- and postoperative period during which VKAs are not effective. For this, heparin should be started at curative doses 48 hours after the last dose of fluindione or warfarin or 24 hours after the last dose of acenocoumarol. It is recommended to perform an INR the day before the procedure. Patients with an INR exceeding 1.5 the day before the procedure should receive 5 mg of oral vitamin K and further monitoring of the INR should be performed on the morning of the procedure. The discontinuation of heparin is recommended as follows: IV UFH by syringe pump (discontinue 4-6 hours before surgery), SC UFH (discontinue 8-12 hours before surgery), LMWH (last dose 24 hours before the procedure). It is not necessary to check the aPTT or anti-Xa activity in the morning of the procedure. After the procedure, VKAs and heparins are resumed as soon as possible depending on the risk of bleeding and thromboembolism. The heparin therapy is discontinued after 2 successive INR tests within the therapeutic range 24 hours apart. A summary diagram of the VKA discontinuation and resumption protocol with perioperative relay heparin is presented in *Appendix 10*. If the relay procedure is not carried out in a course of coordinated care in general practice, the HAS recommends to hospitalize the patient, no later than the day before the surgery, to adapt anticoagulation.

The initiation of a relay heparin generally helps reduce the rate of thrombotic events, but increases the rate of bleeding events (compared to the VKA discontinuation protocol).[272,273,274] Kovacs and coll., 2004[84] in a prospective, multicenter study of patients at high risk of thromboembolism (mechanical prosthetic heart valve and Afib with major risk factors) measured the efficacy and safety profile in case

of relay heparin at a curative dose with a LMWH (dalteparin 200 U/kg/day) as an outpatient. In this study, the frequency of thrombosis and severe bleeding was 3.6 and 6.7%, respectively.

In summary, in case of dento-alveolar surgery, the risk of bleeding is low and easily controllable by a local hemostasis. Dental extractions and dental implants can be performed without interrupting VKAs (after checking the INR and verifying a value ≤ 4).

For operations and invasive procedures with high risk of bleeding, the discontinuation of VKA with or without relay heparin, depending on the risk of thrombosis for the patient, is recommended. The decision to temporarily discontinue VKA therapy should be taken after consultation with the physician who prescribed the VKA, the anesthetist (in case of general anesthesia) and the surgeon. The entire approach adopted should be the subject of a written protocol.

3.4 What biological test should be used to evaluate the surgical risk of bleeding?

The biological examination used to estimate the surgical risk of bleeding in a patient on VKA is the International Normalized Ratio (INR).[49,125] An INR value greater than 6 is associated with a significantly increased risk of spontaneous major bleeding.[59] Patients with a high target INR (at most between 3.5 and 4.5) have a higher risk of spontaneous bleeding (minor, major) than those with a target INR between 2 and 3.[9,10] However, no correlation was found between the risk of bleeding and the VKA compound prescribed or the time elapsed from the start of treatment.[59]

- **In case of dento-alveolar surgery**, 28 observational studies involving 2,150 patients treated with a VKA within usual therapeutic ranges (INR between 2 and 3 and between 3 and 4) show that simple surgical or dental extractions can be performed without interrupting VKAs.

The value of 4 can be retained as the INR threshold below which there is no increased perioperative bleeding complications. Such preoperative biological assessment is used to check the absence of a possible overdose of VKA, a major bleeding risk factor in case of surgery. The INR should be checked within 24 hours before surgery. In case of overdose (INR greater than or equal to 4) the surgical procedure should be postponed and the prescribing physician informed. Corrective measures must be initiated immediately by the prescribing physician to bring the INR within the therapeutic range (skipping a dose, intake of Vitamin K, emergency hospitalization).[122] Within the therapeutic range, the majority of observational studies indicate no positive correlation between preoperative INR value and the rate of incidence of post-extraction bleeding.[42,45,74,223,255] Only one study identifies the preoperative INR value as a postoperative bleeding risk factor.[173] However, in all these studies,[42,45,74,173,223,255] gingival and/or

periapical inflammation was identified as a major factor of the increased risk of bleeding in patients on VKA.

The other condition is to have a stable INR. It is therefore necessary to know the values of the last INR assessments or the treatment monitoring journal. As part of their monitoring of anticoagulant treatment, patients usually undergo an INR exam every 2-4 weeks. An unstable INR is considered to be a factor of severity and the doctor who prescribed the VKA should be contacted. It is recommended to postpone the surgery for 1 month. If surgery cannot be postponed, the choice of a relay heparin and/or hospital management should be discussed with the prescribing physician.[172]

However, it is cautious to maintain this threshold in the presence of comorbidities.[168] In a large prospective case series (n=500), Cocero and coll., 2014[63] recommend lower values with limit values of 2.8 in patients with a mechanical prosthetic heart valve and 2.3 for patients with diabetes, hepatic and renal impairment.

• **In case of surgery with a high risk of bleeding,** it is necessary to interrupt VKAs. Consultation with the physician who prescribed the VKA is imperative in order to assess the risk of thrombosis associated with discontinuation of the VKA. For patients at low risk of thrombosis, discontinuing VKAs without replacement therapy can be proposed. For patients at a high risk of thrombosis, pre- and postoperative relay heparin is recommended. In both cases, it is imperative to perform an INR test the day before the procedure. A hemostatic safety threshold is set at an INR value lower or equal to 1.5.[122]

3.5 Which local hemostasis should be performed to control the risk of surgical bleeding?

A total of 26 randomized prospective observational studies,[17,19,20,28,33,41,42,45,46,51,55,57,58,82,99,114,126,181,209,223,249,254,255,263,269,290] presented in *Appendix 7,* investigated the benefits of using local hemostatics specifically in dento-alveolar surgery.

• **Sutures**

One open-label, randomized, prospective study measured the impact or not of performing sutures on the incidence of postoperative bleeding in case of dental extractions(s) in patients on warfarin with an INR $\leq$ 3.[21] Unexpectedly, patients receiving sutures showed a higher rate of postoperative bleeding. These results, although not significant, showed that suturing, aimed at reducing the rate of postoperative bleeding, is not demonstrated in case of simple extraction and/or the absence of gingival detachment.

- **Surgical hemostatics**

Eight observational or comparative studies[28,33,42,55,82,254,255,223] have shown that the use of gelatin sponge, collagen, or oxycellulose gauze in intra-alveolar tamponade to complement conventional measures (sutures + compression) is used to effectively prevent the risk of post-extraction, postoperative bleeding in patients with an INR $\leq$ 4. However, there is no comparative study between the different surgical hemostatics.

- **Fibrin glue**

Three prospective open-label randomized trials[41,57,126] evaluated the use of a fibrin glue (BLERIPLAST®, FIBRIJET®) as an adjuvant to gelatin sponge, collagen or oxycellulose gauze and sutures. The comparators were the same surgical hemostatics used alone without fibrin glue. No significant reduction in the number of post-operative bleeding events with the use of fibrin glue were reported. To date, the benefit of the use of fibrin glue in the prevention of postoperative bleeding, due to its cost and its limited dispensation (hospital setting, traceability) has not been demonstrated in patients on VKA in case of dental extraction(s).

Although its use in case of revision surgery is widely described in observational studies, its efficacy has not been evaluated or compared to other surgical hemostatics.

- **Cyanoacrylate glue**

Two observational studies[115,193] have yielded favorable results on the efficacy of a cellulose membrane coated with an cyanoacrylate glue in the prevention of the risk of postoperative bleeding in patients on VKA after dental extraction(s). In another prospective study[17] concerning 30 patients for simple extractions, this approach was compared with intra-alveolar tamponade with gelatin sponge. The number of postoperative bleeding events in the group treated (cyanoacrylate glue) was significantly reduced compared to the control group (gelatin sponge). Because of the low level evidence from these three studies, it is difficult to prefer this approach over other local hemostasis measures.

- **Tranexamic acid**

Three comparative, randomized, double-blind placebo-controlled studies[46,249,263] demonstrated the efficacy of topical tranexamic acid (intra-alveolar irrigation then mouthwash 4 times/day for 5-7 days) in the prevention of the risk of bleeding in case of dental extraction(s) and maintenance of VKA therapy with an INR < 4.

A comparative, randomized, double-blind study[58] (5 days vs. 2 days), showed that tranexamic acid mouthwash (4 times daily) for 2 days is as effective as 5 days in the control of postoperative bleeding in patients on VKA.

An observational case-control study[29] (VKA maintenance versus no anticoagulant), evaluated the efficacy of compression with a tranexamic acid-soaked compress in addition to suturing in controlling hemostasis after dental implant placement. The rate of postoperative bleeding was low in the two groups (< 5%). All the bleeding was controlled by simply renewing the procedure (mechanical compression soaked with tranexamic acid).

Overall, in light of data in the literature, the use of local hemostatics (tranexamic acid, gelatin sponge, collagen, oxycellulose gauze) in case of dental extraction(s) in patients on VKA must be systematic. Based on the current state of knowledge, the Working Group could not favor a product or a class of surgical hemostatics. In a preventive context, the relevance of the use of biological adhesives still needs to be demonstrated.

In case of surgery with a high risk of bleeding and in the absence of the possibility of performing mechanical compression or of a critical location, it is imperative to perform the procedure in a situation of hemostatic safety with a pre-operative control of the INR $\leq$ 1.5. In case of a high risk of thrombosis, a relay heparin is necessary.

3.6 What are the drug prescriptions that increase the risk of bleeding?

Many drugs interfere with VKAs. Some contribute to the occurrence of biological overdose (INR $\geq$ 4.0). Many compounds prescribed by professionals of the oral cavity are potentiators of the risk of bleeding from VKAs and may justify temporary increased monitoring of the INR.

- **Prescription of antibiotics**

Any use of antibiotics is a risk factor for imbalance in the intestinal flora and disruption of the endogenous synthesis of vitamin K, with a consequence of an imbalance of VKA therapy and an increased risk of bleeding.[187,289] Macrolides (except spiramycin), doxycycline and metronidazole are not recommended.[282] Regarding the prescription of amoxicillin alone or in combination with clavulanic acid, conflicting data is reported in the literature. Clinical cases,[38,52,79,188,268] one case-control study,[241] and one prospective study[261] reported the incidence of overdoses and bleeding episodes following the introduction of amoxicillin or amoxicillin + clavulanic acid in patients treated with VKA and who were initially perfectly stable. Conversely, in a double-blind, randomized, placebo-controlled study, but in the absence of inflammation and/or infection, prescribing amoxicillin 1 g, 2 times a day for 7 days + clavulanic acid does not significantly change the value of the INR.[292] It should be recalled that an infection with the metabolic changes that accompany it is in itself a risk factor of imbalance of oral anticoagulant therapy. Therefore, it is difficult, in case of infection, to distinguish the part linked to the inflammatory reaction from that which is drug-related.[261] In any event, an established oral infection must be treated in these patients with the appropriate conventional antibiotics with close monitoring of the INR.[159] It should be noted that antibiotic prophylaxis does not change the value of the INR.[208]

- **Prescription of antifungals**

Miconazole is strictly contraindicated regardless of its method of administration, including topical use.[282] No azole antifungals are recommended.[282] In patients treated with VKA, amphotericin B is the recommended antifungal for the treatment of oropharyngeal candidiasis.

- **Prescription of analgesics**

For mild to moderate pain, the prescription of aspirin (at analgesic doses) is strictly contraindicated and that of NSAIDs is strongly discouraged because of the risk of unpredictable severe systemic bleeding (gastrointestinal and intracranial bleeding).[282] The administration of paracetamol is possible, but is subject to precautions when prescribing the maximum dose (4 g per day) for at least 4 days.[282] Studies report a significant increase in the INR following the prescription of paracetamol at therapeutic doses (2-4 g/day)[171,200,206,291] In the elderly, dosage adjustment (< 2 g/day) and the prescription of an INR during the postoperative period are measures used to limit and detect the occurrence of any overdose.[170] For moderate to severe pain, opiate derivatives (codeine, tramadol) may be prescribed, with tramadol being subject to safety precautions.[282].

- **Prescription of anti-inflammatory agents**

If it is necessary to prescribe an anti-inflammatory agent, corticosteroids are recommended.

3.7 Curative treatment of bleeding complications

Their management is always based primarily on surgical revision and on the investigation of a local cause of the bleeding. The absence of sustainable control of bleeding by conventional local hemostasis measures is considered to be a criterion of severity, and hospital management is therefore necessary.

Upon admission of the patient, an emergency measurement of the INR should be performed. Regardless of the value of the INR, surgical revision should be performed immediately. The use of biological glue is clinically relevant. In case of overdose, rapid antagonism with vitamin K or prothrombin complex concentrates (PCC) may be indicated. For further information, refer to the April 2008[122] recommendations of the GEHT regarding “the management of overdoses of antivitamin K, the bleeding risk situations and bleeding events in patients treated with antivitamin K in general practice and hospitals” available at www.has-sante.fr.

4. Specificities of the management of patients treated with direct oral anticoagulants

4.1 The issues

Since 2009, a new class of oral anticoagulants is available. These are selective direct oral anticoagulants (DOAs), either thrombin (anti-IIa) or activated factor X (anti-Xa).[12]

Their indications, limited at first to the prevention of the risk of VTE after orthopedic surgery (total hip and knee replacement)[80,148,149] were extended starting in 2012 to the prevention of thromboembolic events in patients with non-valvular Afib associated with one or more risk factors.[7,9,10,148,149,152] DOAs are contraindicated in patients with mitral stenosis or patients with prosthetic heart valves.

DOAs are mainly used as an alternative to VKAs and/or LMWHs and are intended for a large population. They have modified a number of protocols. The preventive treatment of VTE includes SC heparin for 10-35 days (current standard of care). Similarly, the curative treatment involves a heparin for at least 5 days relayed by a VKA. These conventional therapeutic regimens, widely validated by many clinical trials, however, have drawbacks: the need for frequent laboratory tests, the use of parenteral administration and an overlapping period of two anticoagulants in case of relay which exposes patients to an increased risk of bleeding. The immediate use of a DOA without going through an initial parenteral anticoagulation phase makes this method of treatment very convenient. In the treatment of non-valvular Afib, the DOA should have significant advantages over VKAs (current standard of care): the absence of food interaction, a limited number of drug interactions reflect a “more predictable” anticoagulant activity that makes it possible to administer them at a fixed dose (for each patient) and not to resort to biological monitoring.[7]

This significant development of VKAs appears to be appealing, but the use of DOAs is currently being debated.[15] The absence of biological monitoring is both an advantage and a drawback:

- an advantage because the regular practice of INR and dose adjustment based on results is a constraint for patients treated with VKAs,
- a drawback because the absence of information about the drug effect on anticoagulation exposes patients to the possible risk of an insufficient dose, a source of inefficacy or of an overdose leading to an increased risk of bleeding.

Many cases of bleeding events have been reported. The risk of intracranial hemorrhage will be lower on DOAs than on warfarin. In contrast, that of gastrointestinal bleeding will be higher. Moreover, there is no antidote for overdose and their cost is much higher than conventional treatments.[10] Their use is being closely monitored both at the national level by the Agence française de sécurité sanitaire des produits

de santé (ANSM) and at the European level by the European Medicines Agency (EMA).[10,11] Since their introduction in 2009, the prescription of these DOAs is associated with a high percentage of misuse (non-compliance with indications and/or contraindications) leading to situations of increased or inappropriate risk of bleeding.[11] The absence of a reliable routine biological test for estimating the risk of bleeding and the absence of a specific antidote make the management of these DOAs delicate in case of surgery and bleeding events.

In 2013, 265,000 patients were treated with DOAs in France.[10]

4.2 Direct oral anticoagulants

Three DOA compounds are currently marketed in France: dabigatran etexilate, which inhibits activated factor II (IIa or thrombin); rivaroxaban and apixaban, which inhibit activated factor X (Xa).[9,10]

4.2.1. Dabigatran etexilate

Dabigatran etexilate is a direct thrombin inhibitor (direct anti-IIa) whose inhibition is concentration dependent, competitive, highly selective and reversible.[97,279] This drug is marketed under the name PRADAXA® and is available in three dosages in France: 75 mg, 110 mg and 150 mg. PRADAXA® 75 mg and PRADAXA® 110 mg are indicated in the primary prevention of venous thromboembolic events in adults who underwent elective surgery for total hip replacement (THR) or total knee replacement (TKR) (MA obtained in March 2008).[148] The maximum duration of treatment is limited to 35 days. PRADAXA® 110 mg and PRADAXA® 150 mg are used in the prevention of CVA and systemic embolism (SE) in adult patients with non-valvular Afib associated with one or more risk factors (history of CVA/TIA, SE, LVEF < 40%, symptomatic heart failure (NYHA class ≥II), age≥ 75 years, diabetes, AHT (MA obtained in August 2011). The dosages of 220 mg per day (2 x 110 mg) and 300 mg per day (2 x 150 mg) are recommended in patients in whom there is one or more risk factors.[148,282] Dabigatran etexilate was evaluated and its efficacy compared for each of its indications, either with enoxaparin (40 mg x 1 time/day) (RE-MODEL trial)[94], RE-NOVATE I[95] and II[98]), or with warfarin (with a target INR of 2-3) (RECOVER[258] RE-LY[67,100] trials). During Phases I, II and III clinical studies, risk factors of severe bleeding were identified, namely a high dosage (> 220 mg/day), renal insufficiency (creatinine clearance < 50 mL/min) and the elderly (> 80 years).[67,128,258] Note, however, that there is no difference between dabigatran etexilate and warfarin in terms of overall mortality.

4.2.2. Rivaroxaban

Rivaroxaban is a direct, competitive and highly selective Factor Xa inhibitor (direct anti-Xa). Its selectivity for factor Xa is more than 10,000 times that of other serine proteases (factors Va, IXa, XIa, thrombin and activated protein C).[119] Rivaroxaban can inhibit both the free factor Xa as well as factor Xa within the prothrombinase complex and the factor Xa associated with the clot. The inhibition of factor Xa interrupts the intrinsic and extrinsic pathways of the blood coagulation cascade, thereby inhibiting the generation of thrombin and development of thrombi. Rivaroxaban does not inhibit thrombin (factor IIa) and it has no demonstrated effect on platelets.[217] Rivaroxaban is marketed under the name XARELTO® and is available in three dosages in France: 10 mg, 15 mg and 20 mg. The indications for rivaroxaban differ depending on the dosage used. XARELTO® 10 mg is indicated for the primary prevention of venous thromboembolic events in patients undergoing elective surgery of major orthopedic surgery (THR, TKR) (MA obtained in December 2008).[149] The maximum duration of treatment is usually 35 days and starts 6-10 hours after the procedure. XARELTO® 15 mg and XARELTO® 20 mg are recommended in the prevention of CVA and systemic embolism in case of non-valvular Afib associated with one or more risk factors (same as those cited for dabigatran) and the preventive and curative treatment of DVT and its complications (MA obtained 2012).[282] The RECORD 1[96], 2[178] and 3[189] trials showed the superiority of rivaroxaban (10 mg 1 time/day) compared to enoxaparin (40 mg 1 time/day) in the thromboprophylaxis of elective orthopedic surgery scheduled for a total of 10-14 days for TKR and between 31 and 39 days for THR, respectively. In the prevention and treatment of VTE (EINSTEIN trials)[92,93] and the prevention of ischemic stroke and SE in patients with non-valvular Afib having one or more risk factors (ROCKET-AF trial)[238], rivaroxaban demonstrated non-inferiority in terms of efficacy and safety compared to conventional treatment (enoxaparin, warfarin). There is no significant difference with regard to major bleeding and the overall mortality rate. Note that in the rivaroxaban group, fatal brain hemorrhages were fewer.

4.2.3. Apixaban

Apixaban, like rivaroxaban, is a direct selective inhibitor of factor Xa, with no activity on thrombin.[287] Therefore, it is essentially in their pharmacokinetic characteristics that these two compounds differ. There are no food interactions reported in the literature. Its renal elimination is low (25% in the active form). For this reason, the alteration of the renal function slightly modifies the pharmacokinetics of apixaban, unlike other DOAs (rivaroxaban and especially dabigatran etexilate).[128,288] Apixaban is marketed in France under the name ELIQUIS® and is available in two dosages: 2.5 and 5 mg. ELIQUIS® 2,5 mg is indicated in thromboprophylaxis in case of THR or TKR and ELIQUIS® 5 mg is indicated in the prevention of ischemic CVA and SE in patients with Afib having one or more risk factors

(the same as for dabigatran etixelate and rivaroxaban).[152,282] The efficacy and safety of apixaban (5 mg x 2 times/day) were evaluated in patients with Afib either compared with aspirin (81-324 mg) (AVERROES trial),[68] or with warfarin (with a target INR 2-3) (ARISTOTLE trial).[120] These two studies show results that are generally in favor of apixaban.

4.3 Discontinuation or maintenance of treatment with direct oral anticoagulants?

No study is currently available to evaluate the risk of bleeding in case of dental extraction in a patient on a DOA. A comprehensive analysis of the literature found only five sources of information with low level of evidence: one case report,[293] one series of five case reports,[47] three systematic reviews of the literature[77,101,105] and the retrospective analysis of the RE-LY trial for dabigatran[164] and the ROCKET-AF trial for rivaroxaban.[238]

Romond and coll., 2013[293] report the case of a 67-year-old patient with a history of Afib, Type 2 diabetes, AHT and hyperlipidemia, treated with dual therapy who underwent multiple dental extractions (8 maxillary teeth) associated with alveoloplasty and on dabigatran (2 x 150 mg/day) + aspirin (81 mg/day) dual therapy. Dabigatran was discontinued the evening before the procedure and resumed the day after the procedure (therapeutic window 24-48 hours). Hemostasis combining gelatin sponge, sutures and compression was carried out followed by placement of a complete removable dental prosthesis. No abnormal bleeding was reported. No thrombotic complications were reported during the seven months after surgery.

Breik and coll., 2014[47] based on a small prospective case series (n=5), advise against discontinuing dabigatran in case of simple extraction, given that the risk of bleeding can be controlled by local hemostasis. However, the authors recommend the discontinuation of dabigatran in case of multiple extractions or a complex oral surgical procedure.

Davis and coll., 2013[77] in a systemic review of the literature recommend to follow the same therapeutic approach as the one adopted with warfarin in case of dental extraction, because all the studies show that the risk of bleeding in patients treated with dabigatran was statistically similar to that observed in patients on warfarin with an INR between 2 and 3.

Fahkri and coll., 2013[101] in another systematic review of the literature are in favor of a therapeutic window with a discontinuation of DOAs 3 days before (in case of a high risk of bleeding) or 2 days before (in case of a moderate risk of bleeding) with the resumption of DOAs 24 hours after the procedure. In case of a high risk of thrombosis, a relay heparin is recommended.

For Firriolo and Hupp, 2012,[105] it does not seem to be necessary to suspend dabigatran or rivaroxaban for patients with normal renal function and in the absence of local or systemic factors that may increase the risk of bleeding. The discontinuation of DOAs is only recommended in case of postoperative bleeding that is not controlled by local hemostasis. In case of oral or maxillofacial surgery with a high risk of bleeding, the authors recommend the suspension of dabigatran or rivaroxaban for at least 24 hours before surgery or longer in patients with renal insufficiency (creatinine clearance < 30-50 mL/min). DOAs should be resumed 24-48 hours after the procedure.

During the RE-LY trial,[164] a non-inferiority, open-label, randomized, controlled trial of two doses of dabigatran (110 mg x 2 times/day; 150 mg x 2 times/day) versus warfarin (with a target INR between 2 and 3) of more than 18,000 patients, 4,591 subjects underwent an invasive procedure or surgery. Ten percent underwent a dental procedure. No difference was found between patients taking dabigatran and those receiving warfarin in terms of major bleeding. In this study, patients on dabigatran whose creatinine clearance was normal, were operated between 24 and 72 hours after the last dose (between 2 and 5 half-lives). For rivaroxaban, the only data available are from the ROCKET-AF trial[238], a randomized, controlled study on “non-inferiority” compared to warfarin at an adjusted dose according to INR conducted in 14,264 patients treated for at least 18 months in the indication of the prevention of CVA and SE in patients with non-valvular Afib. In this study, rivaroxaban was stopped for two days before the elective surgical procedure (about 4 half-lives).

Outside the strict field of oral surgery, proposals and suggestions were made by the Hemostasis and Thrombosis Interest Group (GIHP) and the GEHT.[259,260] In the context of elective surgery, continued treatment with DOA is the rule by establishing a therapeutic window. An interruption of 2 or 4 half-lives is recommended in most cases. It should be longer in case of surgery with a high risk of bleeding and in patients with renal insufficiency. Therefore, for minor surgeries, the administration of DOA is suspended 24 hours before the procedure and resumed 24 hours after (therapeutic window of 48 hours). For procedures with a high risk of bleeding, treatment with DOAs is discontinued 5 days before the procedure and resumed postoperatively as soon as possible once the risk of bleeding is under control. If the risk of thrombosis is high, then a heparin relay is justified. Treatment with heparin should then be initiated 12 hours after the last dose of the DOA if it is administered in two doses per day or 24 hours if it is administered as a single daily dose. Postoperatively, the DOA should be resumed 12 hours after the last dose of LMWH. In all other cases, a postoperative relay heparin is generally not necessary. For DOAs with a very rapid onset of action, there should be no overlap with heparin therapy.[259,260]

In the face of insufficient data in the literature, the Working Group developed recommendations for DOA management in oral surgery from a weaker position than that of VKAs.

In light of efficacy and safety profiles of DOAs in Phase III trials versus reference anticoagulants (warfarin with a target INR between 2 and 3, enoxaparin 40 mg 1-2 times/day), it was legitimate to propose a position similar to that adopted with VKAs. If discontinued, knowledge of pharmacokinetic parameters contributes ton the understanding of the course of action (*see Appendix 11*). A summary diagram of DOA discontinuation and resumption protocol in case of oral surgery with a high risk of bleeding is presented in *Appendix 12*.

- In case of surgery with a low risk of bleeding (in the absence of information at this time in favor of even a one-time preoperative discontinuation), it is recommended to continue DOAs. The procedure should be scheduled far from the last drug dose, ideally just before the next dose corresponding to the residual or minimum concentration (Cmin).

- In case of surgery with a high risk of bleeding, the interruption of DOAs is indicated. The duration of such interruption should be assessed taking into account the time and the dosage of the last dose, as well as the renal function. The elimination half-life of DOAs is about 12 hours in the absence of renal impairment and about 18 hours in patients with moderate renal impairment (creatinine clearance between 30 and 50 ml/min). An interruption of 2 or 4 half-lives is recommended. In practice, the DOA should be stopped before surgery and resumed within 24 hours after surgery (therapeutic window of 24-48 hours). In the rare case of high risk surgery in patients with a high risk of thrombosis, interruption may be longer (therapeutic window of 2-5 days) and a relay with LMWH may be necessary.

In the absence of a comparative study between DOAs and until further information becomes available, there is no distinction to be made between different DOAs (dabigatran, rivaroxaban, apixaban) regarding their perioperative management in oral surgery.

Proper management of patients on DOA in view of surgery or an invasive procedure is mainly based on pharmacological criteria such as the number of daily doses, the product half-life, the time of the last dose, the time and the dosage of the first dose administered after surgery.[16,259,260]

4.4 What biological test should be used to evaluate the surgical risk of bleeding?

If coagulation monitoring is not routinely recommended, there are clinical situations where evaluation can be useful: emergency surgery, thrombotic events, recurrence of thrombosis.

DOAs have effects on routine non-specific coagulation tests (PT or prothrombin time, activated partial thromboplastin time or aPTT). The sensitivity of these tests vary depending on the drug and reagent used. These conventional tests are relatively insensitive to low concentrations and have, depending on

the reagent used, considerable variability at high concentrations.[32,87,123,243,279] Therefore, prescribing these global coagulation tests is not relevant to provide an estimate of the risk of bleeding with respect to surgery and/or an invasive procedure. Finally, the measurement of INR, a mode of expression for PT designed for patients treated with AVK, has no meaning for patients on DOA and so it is totally unnecessary.

Apart from PT and aPTT, there are specific tests:

- modified thrombin time (Hemoclot®, Biophen DTI®) and ecarin time (ECAT-T®) for dabigatran;
- the measurement of anti-Xa activity (Rotachrom® tests, anti-FXa, Hyphen Biomed®, STA Liquid anti-Xa®) for rivaroxaban and apixaban.

All of these tests, although more sensitive and/or specific, are reserved at the moment for specialized centers and/or emergency rooms pending knowledge and validation of a hemostatic safety threshold that would authorize surgery without an increased risk of bleeding for each of these tests. These tests cannot be requested in current practice and are not listed in the NABM.

In the current state of knowledge, there is no biological test routinely available to “screen” the patients on DOAs for risk of bleeding.

4.5 Which local hemostasis should be performed to control the risk of surgical bleeding?

In the absence of data specifically answering the question, the Working Group recommends the systematic use of local hemostatics (gelatin sponge, collagen, fibrin, or oxycellulose gauze) in addition to conventional measures (sutures and compression) in case of dento-alveolar surgery and maintenance of DOAs.

In case of surgery with a high risk of bleeding and in the absence of the possibility of performing mechanical compression or of a critical location, it is imperative to perform the procedure in a situation of hemostatic safety by applying a DOA discontinuation protocol.

4.6 What are the drug prescriptions that increase the risk of bleeding?

In patients treated with DOAs, prescribing aspirin at high doses (1 g per dose or 3 g/day), NSAIDs (all), clarithromycin or azole antifungals (all) via the systemic route is not recommended as this may increase the risk of bleeding.[9,10,282]

4.7 Curative treatment of bleeding complications

Their management is always based primarily on surgical revision and on the investigation of a local cause of the bleeding. The absence of sustainable control of bleeding by conventional local hemostasis measures is considered to be a criterion of severity and hospital management is therefore necessary. In March 2013, the GIHP established proposals on the hospital management of severe uncontrollable bleeding with local hemostasis.[243] Upon admission of the patient, the measurement of exploration of coagulation is essential including a specific dose of dabigatran or rivaroxaban and/or the measurement of PT and aPTT.

In case of overdose, an antagonist will be discussed. In the absence of a specific antidote, possible reversions are non-activated prothrombin complex concentrate factors (e.g., PCC) and activated (e.g., FEIBA®),[131] but efficacy data (stopping bleeding) and safety (risk of thrombosis) are very weak and depend on the compound (dabigatran, rivaroxaban).[90] Idarucizumab, a humanized antibody directed against dabigatran is currently in a Phase III clinical trial.[295]

5. Specificities of the management of patients treated with injectable anticoagulants

5.1 The issues

The prevention of VTE in surgery, medicine and oncology as well as the curative treatment of VTE in the acute phase is based on the prescription of anticoagulants administered by parenteral method.[4,111]

- The incidence and duration of the thromboprophylaxis varies depending on the type of surgery. It is high after THR, neck fracture surgery and abdominal pelvic cancer surgery. Prolonged thromboprophylaxis of 4-6 weeks is recommended. It is reduced after TKR and for other types of gastrointestinal, urological and gynecological surgery. Periods of 7-14 days should be sufficient for these indications.[264] Note that oral and maxillofacial surgery (non-carcinogenic) exposes the patient to a low risk of thrombosis and does not justify thromboprophylaxis.[202]
- The prevention of VTE in medicine depends on the acute medical condition responsible for the hospitalization (heart failure, MI, active cancer, decompensated respiratory failure, CVA, inflammatory diseases, etc.), the risk factors related to the patient (history of VTE, age > 60 years, BMI > 30, varicose veins, pregnancy, oral contraceptives) and the length of bed confinement.[4]
- In oncology, the incidence of VTE varies from 0.5 to 20% depending on the type of cancer. Thromboses are common in pancreatic cancer, lymphomas, cancers of the gastrointestinal tract, ovary and lung. VKAs are less effective and less well tolerated when VTE occurs in the presence of a cancer. LMWHs are recommended for at least 6 months. After 6 months, continued treatment with a LMWH or a VKA is decided depending on the tolerance of the drug and the evolution of the cancer.[294]
- The annual incidence of VTE in France is more than 100,000 cases and is at the root of 5 to 10,000 deaths. This condition is a diagnostic and therapeutic emergency, therefore, curative treatment must be based on quick and effective anticoagulation. For this reason, treatment in the acute phase is a heparin, relayed remotely by VKA treatment.[4,9,10,80]

5.2 Injectable anticoagulants

Injectable anticoagulants include: standard or unfractionated heparin (UFH), LMWHs, and other injectable anticoagulants.[111,124] (*see Appendix 1*)

In these recommendations, only UFHs and LMWHs are addressed. Other injectable anticoagulants which include a group of very heterogeneous compounds: selective Xa inhibitor (fondaparinux ARIXTRA®), recombinant hirudins (Desirudin REVAC®, Bivalirudin ANGIOX®, Lepirudin REFLUDAN®) and danaparoid sodium (ORGARAN®), with indications limited to and reserved for therapeutic niches,

are excluded. There is no data in the literature on the perioperative management of these compounds in oral surgery.

5.2.1. Standard unfractionated heparins

Heparin was discovered in 1916. It potentiates antithrombin (AT), a physiological inhibitor of factors Xa and IIa. Anticoagulation is immediate. UFHs combine anti-IIa and anti-Xa. There are two UFHs: heparin sodium (HEPARIN CHOAY®, HEPARIN PANPHARMA®)[138] for IV bolus injection or continuous administration by syringe pump, and heparin calcium (CALCIPARINE®)[136] for SC injection at 2 doses given every 12 hours or in 3 doses every 8 hours.[9,10] After IV injection, the elimination half-life of heparin is 90 minutes. Heparinemia disappears 4 hours after IV injection and 12 hours after SC injection. Its renal clearance is zero. UFHs can be administered safely in patients with renal impairment and the elderly. There are two main indications for UFHs: the curative treatment of VTE in the acute phase, acute arterial occlusion by embolism and MI in the acute phase and preventive treatment of VTE and arterial thrombosis (anticoagulation of extracorporeal circulation circuits, hemodialysis circuits).[9,10]
In the acute phase, heparin does not dissolve the thrombus but prevents its expansion and the migration of arterial and venous emboli. Thrombolysis is the result of fibrinolysis.
The administration of UFH usually requires hospitalization and a strict protocol. The major side effect, besides the risk of bleeding, is the risk of heparin-induced thrombocytopenia (HIT). HIT is a thrombotic, immuno-allergic, rare but serious complication, involving the vital and functional prognosis, requiring immediate discontinuation of heparin. Its risk for patients on UFH is estimated at between 1 and 5%.[9,10]

5.2.2 Low molecular weight fractionated heparins

LMWHs are obtained by chemical depolymerization, or enzymatic digestion of UFH chains. Decreasing the molecular weight of heparin chains (3-30,000 Da for UFHs and less than 8,000 Da for LMWHs) gives LMWHs, compared with UFH, an anti-Xa activity that is predominant over anti-IIa activity (ratio ranging from 2-4 depending on the compounds) and a longer elimination half-life that makes it possible to reduce the number of daily injections to 1 or 2 injections per day.[111] LMWHs have been marketed in France since 1985 and are four in number:[9,10,282] dalteparin sodium (FRAGMINE®),[134,153] enoxaparin sodium (LOVENOX®),[137] tinzaparin sodium (INNOHEP®)[140] and nadroparin calcium (FRAXIPARINE®, FRAXODI®).[134] Apart from the very specific indication of treatment of certain bleeding disorders, LMWHs have the same indications as UFHs and tend to replace them (better tolerance, reduced number of injections, etc.).[9,10] However, LMWHs are contraindicated in patients with severe renal

impairment (creatinine clearance less than 30 mL/min), while UFHs can be used. The risk of HIT during treatment with LMWHs is less than that with UFHs. It is estimated at less than 1%.[6]

Two contexts of use of LMWHs are typically distinguished: the preventive treatment of VTE (visceral surgery, orthopedic surgery of the hip and knee, bed confinement for acute medical condition) and curative treatment of constituted DVT, pulmonary embolism and unstable angina/non-Q-wave MI. The total duration of injections varies depending on the indications between 8 and 35 days. In situations where the use of LMWHs is not recommended or contraindicated (e.g., acute renal impairment), UFHs can be used.[282]

5.3 Discontinuation or maintenance of therapy with heparin?

The literature on the subject is lean, studies are few and the quality of their methodology is questionable (*see Appendix 13*). These factors contribute to the low level of evidence, thereby leaving a large part to the expert opinion of the Working Group.

Given the immediate and short term anticoagulation (UFHs: 4-6 hours; LMWHs: 12 hours), two strategies can be discussed:

- no discontinuation of heparins;
- discontinuation of heparins prior to the procedure (6-8 hours before for UFHs and the day before for LMWHs and resumption depending on the hemostatic control).

A retrospective study,[168] including 41 patients, evaluated the risk of post-extraction bleeding in patients on enoxaparin sodium in whom the injection preceding the dental procedure was suspended. Local hemostasis in combining intra-alveolar tamponade (oxycellulose, gelatin) with conventional measures of local hemostasis (sutures + compression) was routinely performed. No bleeding complications were reported irrespective of the dose of enoxaparin sodium (doses ranged from 20 mg/day up to 110 mg/day x 2 times/day). However, in case of dual therapy combining antithrombotic enoxaparin sodium and warfarin, 3 in 4 patients had bleeding complications including one severe case that required transfusion of fresh frozen plasma to stop the bleeding. For these three cases, the value of the INR measured during the emergency ranged from 1.6-2.4.

An open-label, randomized, comparative study,[33] comparing relay heparin versus maintenance of VKA therapy, reports in the relay arm (discontinuation of VKA 3-4 days before the procedure, relay nadroparin at a dose of 3,850 to 5,700 IU anti-Xa in 1 or 2 injections per day, suspension of injection before the dental extractions, average preoperative INR of 1.26 $\pm$ 0.11, resumption of VKAs and

LMWHs on the evening of the procedure) a rate of postoperative bleeding of 4.76%. Bleeding was mild and easily controllable by a local hemostasis. No severe bleeding complication or thromboembolic event within 30 postoperative days was reported. The literature review also reported three case reports of relay procedure with an LMWH performed in outpatient care.[43,176,276] Among these 3 cases, severe bleeding complications with repetitive bleeding during the first 24 postoperative hours and requiring neutralization by injection of vitamin K were described.[43] These case reports underscore the importance of strict compliance with the protocol and the importance of biological monitoring (INR) for the entire duration of the relay.[213]

In case of VKA-heparin-VKA relay, the choice will preferentially be for LMWHs given their better tolerance, maneuverability and overall cost of the procedure. The use of UFHs usually requires hospitalization, strict compliance with the protocol and daily biological monitoring. Doubts subsist about the efficacy of antithrombotic protection of LMWHs in patients with a high risk of thrombosis. Studies report the occurrence of thrombotic complications during the perioperative period in patients with mechanical valves.[195] However, a set of studies[85,86,184,272-274] show that the clinical efficacy of a relay with LMWHs at curative doses with twice daily injections (off-label in France) is comparable to that obtained by intravenous UFH by syringe pump or subcutaneous UFH at curative doses (2-3 injections per day). Similarly, Karsh and coll., 2011,[180] showed, in patients with mechanical valves, that there was no significant difference after simple dental extractions, in terms of blood loss or in terms of bleeding or thrombotic complications between the use of LMWHs and UFHs subcutaneously.

Overall in case of heparin relay, establishing a therapeutic window exposes the patient to a 1% risk of thrombosis[274] and temporal overlap of the administration of two anticoagulants (VKA and heparins) presents a severe risk of bleeding of approximately 3%[274] and of moderate bleeding of approximately 7-9%.[33,110,167] The indication of a heparin relay must take account of these risks and the risk/benefit ratio.[85,224]

Only one study[226] evaluated the risk of peri- and postoperative bleeding after dental extraction(s) in case of maintenance of heparin therapy without a therapeutic window. This is a retrospective study that included 31 patients hospitalized and treated with SC UFH (2-3 injections per day) for acute severe medical conditions (cerebral infarction, ACS, intracardiac thrombus, DIC, pregnant woman with PE and DVT). A 28.6% rate of postoperative bleeding (not controlled by a local hemostasis) was reported. Bleeding complications occurred within the first five postoperative days (median 4 days). They were controlled by the resumption of hemostasis and adjustment of aPTT below 57 seconds. In half of the cases, the authors used an electrocoagulation or groove placement and in one case, fibrin glue was used. No severe complication with the use of blood transfusion was reported.

Overall, after a review of the literature, in case of dento-alveolar surgery, it seems to be legitimate to propose the continuation of treatment with heparins (LMWHs, UFHs) in the absence of severe bleeding complications.

In cases of oral surgery with a high risk of bleeding, it is essential to contact the prescribing physician in order to assess the risk-benefit ratio of temporary suspension of heparin. In all cases, the therapeutic window has to be the most narrow with the resumption of heparin as soon as possible.

In the particular case of the relay heparin in patients treated for the long-term with VKA, strict adherence to the protocol is recommended. If the relay procedure is not carried out in a course of coordinated care in general practice, it is recommended to hospitalize the patient, no later than the day before the surgery, to adapt anticoagulation.[122]

5.4 What biological test can be used to evaluate the surgical risk of bleeding in patients on heparin?

- In case of continuation of heparin treatment (LMWH, UFH) and in case of relay heparin, preoperative biological evaluation is useful in order to verify the absence of excessive anti-clotting and to have a reference value. APTT or anti-Xa activity (heparinemia) may be proposed. In the context of biological monitoring, the target values of the aPTT (for UFHs) are between 2 and 3 times the control value for curative treatment, and between 1.5 and 2 times the control value for preventive treatment. The target values of the anti-Xa activity (for UFHs and LMWHs) are between 0.5 and 1 for curative treatment, and between 0.10 and 0.45 for a preventive treatment.
- In the event of discontinuation of heparins prior to surgery (6-8 hours before for UFHs and the day before for LMWHs and resumed depending on the hemostatic control) coagulation tests are useless. It is adherence to the minimum period between the last injection of heparin and the start of the procedure that guarantees hemostatic safety.
- Given the risk of HIT, systematic platelet monitoring is necessary once treatment has been initiated.[4,111,124] It is recommended to perform a blood platelet count at the start of treatment and then twice a week for 1 month and then once a week until the end of treatment.[6]

5.5 Which local hemostasis should be performed to control the risk of surgical bleeding in patients on heparin?

From the outset, it should be noted that no study has had the main objective of evaluating the efficacy of a local hemostasis in patients on heparin or of comparing hemostatic measures with the others.

In case of treatment with long-term maintenance heparins (LMWHs, UFHs), the use of gelatin sponge, collagen or oxycellulose gauze in intra-alveolar tamponade in addition to conventional measures (sutures + compression) is systematic.[167,226]

In case of relay heparin, Bajkin and coll., 2009[33] have shown that when the INR is < 1.5, suturing is not useful for simple dental extraction(s). Mechanical compression for 30 minutes ensures hemostatic control in 95.24% of cases. The management of postoperative bleeding was based on the resumption of hemostasis with the use of collagen sponge in addition to conventional measures (sutures + compression). Similarly, Karsh and coll., 2011[180] reported no postoperative bleeding complications after intra-alveolar tamponade using oxycellulose supplemented by sutures and mechanical compression for 1 hour.

5.6 Curative treatment of bleeding complications in patients on heparins

Their management is always based primarily on surgical revision and on the investigation of a local cause of the bleeding. The absence of sustainable control of bleeding by conventional hemostatic measures is considered to be a criterion of severity and hospital management is therefore necessary.

In case of overdose (for both UFHs and LMWHs), there is an antidote: protamine sulfate. It is a heparin antagonist that is administered intravenously. The neutralization of heparin occurs within less than 5 minutes by forming an inactive complex. One hundred anti-heparin units (AHUs) of protamine sulfate can neutralize the anticoagulant activity of heparin.[9,10]

Conclusion

According to the hemorrhagic potential, the recommendations distinguish between dento-alveolar surgery, oral surgeries with a high risk of bleeding such as pre-implant surgery and benign cysts and tumors of the jaw surgery.

For dento-alveolar surgery, perioperative management of antiplatelets and VKAs is validated and well codified. Continuation of treatment is available for a number of precautions (surgical hemostasis, adapted postoperative monitoring and counseling).

For DOAs and heparins, available data in 2015 is very weak to define the best possible management with regard to the dual risk of bleeding and thrombosis. Therefore, pending specific studies, proposals with less evidence value based on the recommendations established for VKAs were established. They are likely to change depending on the results of necessary future clinical studies.

For surgeries with a high risk of bleeding, regardless of the type of antithrombotic agent (antiplatelet, VKA, DOA, LMWH and UFH), the data available in 2015 is insufficient or inexistent to specify the optimal management. Therefore, the Working Group highlights the need to contact the prescribing physician to determine the best strategy with respect to antithrombotic therapy. A temporary interruption of antithrombotic medication with or without the initiation of replacement therapy and possible hospital management will need be to be discussed**.**

For each family of antithrombotic agents (antiplatelets, AVKs, DOAs and heparins), depending on the potential risk of bleeding based on the type of surgery and the risk of thrombosis associated with the patient's medical condition, an algorithm is proposed *(see Appendix 14, 15, 16, 17)*.

Although many outstanding issues still exist, essentially with DOAs, perioperative management in patients on antiplatelets and VKAs has been considerably simplified. Despite the simplification of procedures, caution is required in very elderly patients who often have a combination of many factors associated with an increased risk of bleeding.

APPENDICES

Appendix 1: Antithrombotic agents (antiplatelet agents and anticoagulants) currently marketed in France in 2015

Antiplatelet agents		
Oral route		Indications (MA)
COX-1 inhibitors	• *Reversible inhibitor* - flurbiprofen (CEBUTID®)	-Secondary preventive treatment following MI after de-obstruction (thrombolysis or transluminal angioplasty) in patients for whom aspirin therapy is temporarily contraindicated (e.g., elective surgery). The medical service rendered in this indication is insufficient.
	• *Irreversible inhibitor* - acetylsalicylic acid (ASPIRIN®, KARDEGIC®, ASPIRINE PROTECT®, ASPIRINE UPSA®, CARDIOSOLUPSAN®, PRAVADUAL®)	-Preventive treatment of thromboembolic events associated with atherosclerosis (MI, CVA)
$P2Y_{12}$ receptor inhibitors of ADP	• *Reversible inhibitors (thienopyridines)* - ticlopidine (TICLOPIDINE®, TICLID®) - clopidogrel (CLOPIDOGREL®, DUOPLAVIN®, PLAVIX®) - prasugrel (EFIENT®) • *Irreversible inhibitor* - ticagrelor (BRILIQUE®)	-Preventive treatment of thromboembolic events associated with atherosclerosis (MI, CVA) - Chronic arterial insufficiency of the lower extremities In dual therapy (aspirin + clopidogrel combination) - ACS without ST segment elevation (unstable angina, Non-Q-wave MI) - ST segment elevation MI - Patient receiving PCI with stent implantation
Phosphodiesterase inhibitors	- dipyridamole (ASASANTINE®, CLERIDIUM®, PERSANTINE®)	-Preventive treatment of CVA after transient or established cerebral ischemic CVA, associated with atherosclerosis, not older than 3 months.
Injection		Indications (MA)
GP IIb/IIIa antagonists	- abciximab (REOPRO®) - eptifibatide (INTEGRILIN®) - tirofiban (AGRASTAT®)	- High risk PCI preoperatively
Prostacyclin analogue (PGI2)	- iloprost (ILOMEDINE®, VENTAVIS®)	-Treatment of idiopathic pulmonary arterial hypertension in patients in functional Class III

Anticoagulants		
Oral route		Indications (MA)
Vitamin K antagonists (Factors II, VII, IX, X inhibition)	- acenocoumarol (MINI-SINTROM®, SINTROM®) - fluindione (PREVISCAN®) - warfarin (COUMADINE®)	- Preventive and curative treatment of VTE Emboligenic heart diseases (prosthetic heart valves, valvular heart diseases, Afib) - Myocardial infarction complicated by heart failure or arrhythmia - Recurrent systemic embolism
Thrombin inhibitors (anti-IIa)	- dabigatran (PRADAXA®)	- Preventive treatment of systemic embolism in Afib without valvular heart disease
Activated factor X inhibitors (anti-Xa)	- apixaban (ELIQUIS®)	- Preventive treatment of venous thromboembolic events following orthopedic surgery - Preventive treatment of systemic embolism in Afib without valvular heart disease
	- rivaroxaban (XARELTO®)	- Preventive treatment of VTE in orthopedic surgery - Curative treatment of DVT and PE - Preventive treatment of systemic embolism in Afib without valvular heart disease
Injection		Indications (MA)
Heparins (Factors IIa and Xa inhibitors)	• *Standard or unfractionated heparins (UFH)* - sodium heparin (HEPARIN CHOAY, PANPHARMA®) - calcium heparin (CALCIPARINE®)	- Preventive treatment of arterial and venous thromboembolic events - Curative treatment: VTE, acute coronary syndrome, extracerebral arterial embolism
	• *Low molecular weight heparins, subcutaneous route (LMWH)* - dalteparin sodium (FRAGMINE®) - enoxaparin sodium (LOVENOX®) - nadroparin calcium (FRAXIPARINE®, FRAXODI®) - tinzaparin sodium (INNOHEP®)	- Preventive treatment of VTE in surgery and in medicine - Curative treatment of DVT and/or PE - Non-ST segment elevation acute coronary syndrome - Renal dialysis in the prevention of clotting in the extracorporeal circuit
Other injectable anticoagulants	• *Pentasaccharide* - fondaparinux (ARIXTRA®)	- Preventive treatment of VTE in orthopedic surgery, abdominal surgery in high risk patients (cancer) or in bedridden patients considered to be at high risk - Curative treatment of DVT and/or PE - Non-ST segment elevation acute coronary syndrome
	• *Heparinoids* - danaparoid (ORGARAN®)	- Preventive and curative treatment of arterial and venous thromboembolic events in patients with a history or with Type II HIT
	• *Recombinant hirudins* - bivalirudin (ANGIOX®)	- Anticoagulants in patients undergoing PCI preoperatively
	- desirudin (REVASC®)	- Preventive treatment of DVT after orthopedic surgery
	- lepirudin (REFLUDAN®)	- Curative treatment of arterial and venous thromboembolic events in patients with a history or with Type II HIT

Appendix 2: Stratification of the risk of bleeding based on the type of surgery and preventive measures.

Types of surgeries and invasive procedures	Preventive measures for bleeding complications
Procedures with no risk of bleeding	
● Local anesthesia ● Descaling	- Simple mechanical pressure hemostasis
Surgeries and procedures with low risk of bleeding	
(Surgeries for which externalized bleeding is easily controlled by conventional surgical hemostasis*)	
● Simple avulsion ● Multiple avulsions in the same quadrant ● Endodontic and periapical surgery (lesion ≤ 2 cm) ● Mucogingival surgery (besides gingival graft with palatine sampling) ● Pre-orthodontic surgery of impacted tooth, included ● Single implant ● Implant(s) release (healing abutment) ●Oral mucosa excisional biopsy (≤ 1 cm)	- Oral and descaling hygiene measures - Conventional surgical hemostasis - Tranexamic acid
Surgeries and invasive procedures with a high risk of bleeding	
(Surgeries for which significant blood loss and/or platelet transfusions are reported in the literature, procedures with operating time > 1 hour, critical procedures by their location (maxillary sinus, floor of the mouth) and/or difficult to control with conventional surgical hemostasis*).	
● Multiple avulsions in several quadrants ● Dental avulsion(s) of impacted teeth ● Multiple implants in several quadrants ● Sinus lift (crestal approach, lateral approach) ● Apposition bone graft (in onlay) ● Particulate bone grafting and guided bone regeneration ● Surgery and soft tissue (sialolithiasis) ● Enucleation of cysts and benign tumors (lesion > 2 cm) ● Closing an oral sinus communication ● Excision of pseudo tumors and benign tumors of the oral mucosa (> 1 cm)	- Same preventative measure as for surgery with a low to moderate risk of bleeding - Medicinal products derived from blood, fibrinogen and human thrombin - Mono and bipolar electrocoagulation - Give preference to minimally invasive surgeries (flapless and guided implant surgery, sinus crestal approach, etc.) - Preoperative 3D imaging (sinus, symphyseal region) in case of implant placement
Procedures not recommended	
● Inferior alveolar nerve block: not recommended ● Autologous graft: not recommended due to an additional collection site, give preference to heterologous and synthetic grafts	

Contraindicated procedures
● All procedures contraindicated in case of an associated risk of infective endocarditis ● All procedures with a risk of bleeding in the case where the technical equipment available to the surgeon is inadequate ● Bilateral inferior alveolar nerve block: risk of bilateral lateral pharyngeal hematoma and dyspnea ● Symphyseal sampling: risk of hematoma of the floor of the mouth and dyspnea ● Gingival graft with palatine sampling: risk of injury to the palatine artery

* **conventional surgical hemostasis**: mechanical hemostasis (pressure + sutures) ± local absorbable hemostatics (collagen or gelatin sponge, cellulose gauze) ± synthetic glue (cyanoacrylate glue).

Factors that increase the risk of surgical bleeding: mucoperiosteal detachment beyond the mucogingival line, lingual detachment, avulsion(s) in the inflammation zone, diminished periodontium, duration of surgery > 1 hour (significant blood loss),

Critical locations: floor of the mouth, chin symphysis, maxillary sinus

Appendix 3: Age and comorbidities associated with an increased risk of bleeding events in patients treated with an antithrombotic agent.

Risk factors for spontaneous or induced bleeding
Age: more common after the of age 65 years and worse after 75 years
Low body weight (in adults weight < 50 kg)
Loss of independence and/or lack of cooperation (patient with reduced mobility, disabled, under guardianship, etc.)
Severe renal dysfunction (dialysis, renal transplantation, severe renal impairment: creatinine clearance < 20 mL/min)
Severe heart failure
Poorly controlled arterial hypertension (AHT) (systolic pressure > 160 mmHg)
Anemia
Concurrent disease modifying the metabolism of antithrombotic agents and which could cause an overdose: chronic liver disease (cirrhosis) or biological (bilirubin > 2 times the normal associated with ALT/AST > 3 times the normal) or destruction of the intestinal flora (antibiotics, diarrhea)
Combination with drugs at the origin of potentiation of the antithrombotic agents (NSAIDs, St. John's Wort, azole antifungals, verapamil, etc.)
Unstable INR
Excessive alcohol consumption

Appendix 4: **Evaluation of the risk of bleeding and the postoperative risk of thromboembolism depending on the therapeutic strategy after dento-alveolar surgery.**

Antithrombotic agent(s)	Risk of postoperative bleeding			Postoperative risk of thrombosis (30 days)
Antiplatelet				
Discontinuation of aspirin, clopidogrel	Uncontrolled by sutures and mechanical compression **0%** to **6.5%**[24,54,244,278]			**0.05 % - 5.4%**[13,64,65,102,278] deaths reported[278]
Continuation of aspirin, clopidogrel	Uncontrolled by sutures and mechanical compression **0%** to- **15.7%**[54,185,187,204,212]	Uncontrolled by local hemostasis measures **0%** to **18%**[24,51,54,197]	No severe bleeding complications reported	
Continuation of aspirin + clopidogrel	Uncontrolled by sutures and mechanical compression **1.7%** to **66.7%**[36,54,197,234,239,248]	Uncontrolled by local hemostasis measures **0%**[36,54,197,227,234,239,248]	No severe bleeding complications reported	
Antivitamin K				
Discontinuation of VKA (2-5 days before the procedure)	Uncontrolled by sutures and mechanical compression **14%**[99]		Severe bleeding **0.2%**[283]	**0.5%**[283] 0.4% in case of therapeutic window ≤ 5 days 2.2% in case of therapeutic window ≥ 7 days deaths reported[31,244,278]
Discontinuation of VKA (2 days before the procedure) and UFH relay	Uncontrolled by sutures and mechanical compression **15** to **36%**[226,269]			
Discontinuation of VKA (4-5 days before the procedure) and LMWH relay	Uncontrolled by sutures and mechanical compression **7.3%**[33]	Uncontrolled by local hemostasis measures **4.76%**[33]	Severe bleeding **3.7%**[283]	

Continuation of VKA and INR ≤ 4	Uncontrolled by sutures and mechanical compression **13%** to **40%**[20,46,249,254,263]	Uncontrolled by local hemostasis measures **0%** to **26%**[28,33,41,46,51,55,82,99,114, 115,126,209,249,254,255,263,283]	Severe bleeding, **0%** to **2.77%** [28,33,41,46,51,55,82,99,114,115 ,126,209,249,254, 255,263, 283]
Continuation of VKA (INR < 4) + APA		Uncontrolled by local hemostasis measures **3.9%** to **8.2%**[35,223,225]	
Long-term heparins (inpatients)			
UFH (± VKA ± APA)		Uncontrolled by local hemostasis measures **28.6%**[226]	
LMWH (± VKA or APA)		Uncontrolled by local hemostasis measures **7.1%**[167]	

Patients who are not taking antithrombotic agents: risk of postoperative bleeding: 0 to **2%**[20,28,283]

Appendix 5: Patients on antiplatelet agents (aspirin, clopidogrel, ticlopidine) and dento-alveolar surgery (Clinical Studies).

Comparison of two possible monotherapy methods: maintain therapy versus outright discontinuation of antiplatelet therapy

Study	Type of Study	Dental procedures	Number of patients	Group(s) treated	Control group(s)	Local hemostasis	Bleeding (%)	Results Conclusion by authors	Level of evidence
Ardekian et al., 2000 [24]	Randomized comparative study Open-label	• Single and multiple extraction • Surgical extraction	39	• ASA (75-150 mg)	• Discontinuation of ASA 7 days before the procedure	local hemostatic (unspecified) + sutures ± tranexamic acid (10%) + mechanical compression	• excessive operative bleeding: blood loss (≥50 mL) - ASA: 10% (2/19) - Discontinuation of ASA: 20% (4/20) (p=ns) • Postoperative bleeding (undefined follow-up period) - ASA: 0% (0/19) - Discontinuation of ASA: 0% (0/20) (p=ns) • No severe bleeding complication	There is no data in favor of the discontinuation of ASA.	2
Partridge et al., 2008 [237]	Prospective study (Cohort)	• Single and multiple extraction • Surgical extraction • Biopsy	50	• ASA (unspecified dose) (n=13) • Clopidogrel (n=2) • NSAIDs (n=12)	• Patient who has never taken an APA (n = 23)	Unspecified	• Per-op blood loss p (1 g=1 mL) > ASA: 1.97 ± 1.48 g/blister > Clopidogrel: 0.43 ± 0.18 g/blister > NSAIDs: 1.80 ± 1.28 g/blister (p=ns) • Immediate post-operative bleeding (≤24 hours): none	There is no data in favor of the discontinuation of antiplatelet monotherapy (ASA, clopidogrel).	2
Medeiros et al., 2011 [212]	Randomized double-blind clinical trial	• Simple extraction	63	• ASA 100 mg (n=32)	• Discontinuation of ASA 7 days before the procedure (n=31)	Sutures (n=56) + biological glue (n=7)	• Volume of bleeding - ASA: 16.36 ± 13.54 ml - Discontinuation of ASA: 12.10 ± 9.37 mL (p=ns) • Use of biological glue in case of immediate post op bleeding uncontrolled by sutures - ASA: 15.7% (5/32) - Discontinuation of ASA: 6.5% (2/31) (p=ns) • No severe bleeding complication	There is no data in favor of the discontinuation of ASA.	1
Verma G et al., 2013 [281]	Prospective study (Cohort)	• Simple extraction	90	• ASA (75 mg-325 mg) (n=30)	• Discontinuation of ASA 7 days before the procedure (n=30) • Patients not taking NSAIDs or antithrombotic agent (n = 30)	Mechanical compression (30 min) In case of bleeding > 30 min intra-alveolar tamponade + suture	0 bleeding complications (uncontrolled by local hemostasis measures)	There is no data in favor of the discontinuation of ASA.	2

Comparison of local hemostasis methods

Study	Type of study	Dental procedures	Number of patients	Group(s) treated	Control group(s)	Local hemostasis	Bleeding (%)	Results Conclusion by authors	Level of evidence
Madan et al., 2005 [204]	Case series	• Single and multiple extraction • Surgical extraction • Flap surgery • Implant placement	51	• ASA 75-100 mg	None	sutures + mechanical compression (30 min)	• excessive per-op bleeding: blood loss > 30 mL ASA: 2% (1/51) • Post op bleeding: none • No severe bleeding complication	Local hemostasis combining suturing and mechanical compression is a reliable method for preventing the risk of post-extraction bleeding in patients on aspirin.	4
Garnier et al., 2007 [113]	Retrospective study	• Single and multiple extraction • Cyst enucleation • Implant placement	52	• ASA (unspecified) (n=35) • Clopidogrel (n=16) • Ticlopidine (n=1)	None	sutures + collagen sponge (Curaspon®) + mechanical compression with gauze soaked in tranexamic acid (10 min)	• post-op bleeding (≤24 hours): 1 case • No severe bleeding complication	Local hemostasis combining suturing, collagen sponge and mechanical compression, is a reliable method for preventing the risk of post-extraction bleeding in patients on aspirin.	4
Krishnan et al., 2008 [185}	Prospective study (Cohort)	Multiple simple and multiple extraction	82	• ASA 75-100 mg (n=32)	• Patient who has never taken an APA (n = 25) • Discontinuation of ASA (n=25)	Mechanical compression (30 min.)	• Post op bleeding: none • Emergency consultation for bleeding: none	Mechanical compression (30 min) is an effective local hemostasis measure in case of non-surgical extraction.	2
Brennan et al., 2008 [50]	Randomized double-blind clinical trial	Simple extraction	36	• ASA (325 mg) (n=17)	• Placebo (n=19)	Mechanical compression (5, 8, 11, 14 and 20 min)	• Oral bleeding time - ASA: 7.2 ± 5.9 min. - Placebo: 5.8 ± 6.2 min. (p=ns) • Post-extraction bleeding period - ASA: 3.5 ± 2.9 h - Placebo: 5.2 ± 6.3 h (p=ns) • No severe bleeding complication	• There is no significant difference between the incidence of post-extraction bleeding in patients on aspirin and those who had taken the placebo. • Mechanical compression (30 min) is an effective local hemostasis measure in the case of simple/non-surgical extraction	1
Cardona-Tortajada et al., 2009 [56]	Prospective study (Cohort)	Single and multiple extraction	140	• ASA (100-300 mg) (n=118) • Clopidogrel (n=20) • Ticlopidine (n=2)	None	gelatin sponge (Gelatamp®) + mechanical compression (10 min.)	• Moderate bleeding - within 30 min): 1 case - within 24 hours > ASA: 18% (22/118) > Clopidogrel: 10% (2/20) (p=ns) • No severe bleeding complication.	Local hemostasis combining fibrin sponge and mechanical compression, is a reliable method for preventing the risk of post-extraction bleeding in patients on antiplatelet agents.	2

Appendix 6: Patients on dual antiplatelet therapy (aspirin and clopidogrel) and dento-alveolar surgery (Clinical Studies).

Study	Type of study	Dental procedures	Number of patients	Group(s) treated	Control group(s)	Local hemostasis	Bleeding (%)	Results Conclusion by authors	Level of evidence
Canigral et al., 2008 [54]	Prospective study (Cohort)	• Simple and multiple extraction • Tooth included	36	• Dual therapy - ASA+ clopidogrel (n=10)	• Monotherapy - ASA (n=17) - Clopidogrel (n=10)	• Mechanical compression (≤10 min)=mild bleeding • If bleeding > 10 min, use of a local hemostatic + compression=moderate bleeding • If bleeding (> 60 min), medical treatment and/or surgical revision=severe bleeding	• Mild bleeding: 86% (32/37) • Moderate bleeding: 14% (5/37) - ASA: 5% (1/17) - Clopidogrel: 0% (0/10) - ASA + clopidogrel: 40% (4/10) • No severe bleeding complication	• In case of monotherapy, mild bleeding (97% of cases); No difference between ASA and clopidogrel. • In case of dual therapy (ASA + clopidogrel), moderate bleeding in 40% of cases. • There is no evidence in favor of the discontinuation of APA in case of monotherapy or dual therapy.	4
Napenas et al., 2009 [228]	Retrospective study	• Simple and surgical extraction • Periodontal surgery	43	• Dual therapy - ASA + dipyridamole (n=1) - ASA + ticlopidine (n=1) - ASA + clopidogrel (n=26)	• Monotherapy - Clopidogrel (n=13) - Ticlopidine (n=1)	sutures ± collagen sponge	• Postoperative bleeding (unspecified period): 0% (no cases) • No severe bleeding complication.	The risk of bleeding after oral surgery in patients on mono or dual antiplatelet therapy is low and negligible.	4
Lillis et al., 2011 [197]	Prospective study (Cohort)	• Single and multiple extraction • Surgical extraction	643	• Dual therapy - ASA + clopidogrel (n=33)	• Monotherapy - ASA (n=42) - Clopidogrel (n=36) - Control: patients who have never taken APA (n=532)	• Mechanical compression (30 min) • If bleeding > 30 min, use of a local hemostatic (Surgicel®) + sutures + mechanical compression (30 min)	• Moderate bleeding - within 30 min: > Control: 0.4% (2/532) > ASA: 2.4% (1/42) > Clopidogrel: 2.8% (1/36) > ASA + Clopidogrel: 66.7% (22/33) (p < 0.001) - D + 2: no bleeding	• In the immediate postoperative period (< 30 min), the risk of bleeding is higher in the case of dual therapy compared to aspirin alone (RR=28, 95% CI 4-197, p < 0.001) and to clopidogrel (RR=24, 95% CI 3.4 -168.3, p < 0.001), but is controllable by local hemostasis combining sutures + topical hemostatic + mechanical compression. • There is no evidence in favor of the discontinuation of APA in case of monotherapy or dual therapy.	2

Study	Type of study	Dental procedures	Number of patients	Group(s) treated	Control group(s)	Local hemostasis	Bleeding (%)	Results Conclusion by authors	Level of evidence
Park et al., 2012 [239]	Prospective study (Cohort)	• Extraction (1-6 teeth)	200	• Dual therapy - ASA + clopidogrel (n=59) - ASA + clopidogrel + cilostazol (n=41)	• - Control: patients who have never taken APA (n=100)	sutures + mechanical compression (30 min)	• Excessive operative bleeding: (blood loss ≥ 30 mL) > Control: 0/100 > ASA + clopidogrel: 1.7% (1/59) > ASA + clopidogrel + cilostazol: 2.4% (1/41) (p=ns) • No severe bleeding complication	There is no evidence in favor of the discontinuation of ASA in case of dual therapy.	2
Rai et al. 2013 [248]	Prospective study (Cohort)	• Simple extraction (1-3 teeth)	60	• Dual therapy - ASA + clopidogrel (n=28)	• Monotherapy - ASA (n=32)	• sutures + mechanical compression (30 min) • If bleeding > 30 min, use of a local hemostatic (Surgicel®) + sutures + mechanical compression (30 min)	• 1 postoperative bleeding requiring surgical revision for hemostasis. • No severe bleeding complication	There is no evidence in favor of the discontinuation of ASA in case of dual therapy. The risk of bleeding in case of maintaining dual therapy is not increased.	3
Bajkin et al., 2015 [36]	Prospective study (Cohort)	• Simple extraction (single or multiple) • Lidocaine 2% 1/80,000th	160	• Dual therapy (n=43) - ASA + clopidogrel (n=39) - ASA + ticlopidine (n=2) - ASA + prasugrel (n=2) • Monotherapy (n=117) - ASA I (n= 20) - Clopidogrel (n=20) - Ticlopidine (n=13)	• Control: patients who have never taken APA (n=105)	The same local hemostasis procedure was applied to all patients. Collagen sponge + compression (30 min) in case of bleeding beyond 30 min suturing, of the alveolar wound with silk	• Dual therapy - hemostasis without suturing n=39 - hemostasis with suturing: n=4 (6.8%) - uncontrolled bleeding: n=1 • Monotherapy - hemostasis without suturing n=113 - hemostasis with suturing: n=4 (1.6%) - uncontrolled bleeding: n=0 • Control group - hemostasis without suturing n=105 - hemostasis with suturing: n=0 (0%) - uncontrolled bleeding: 1 (p=ns between the 3 groups) • No severe bleeding complication	The risk of bleeding in case of maintenance of dual therapy is low and easily controllable by local hemostatic measures.	2
Olmos-Carrasco et al., 2015 [234]	Prospective (Cohort) multicenter study	• Simple extraction (1-3 teeth) • mepivacaine 3% without vasoconstrictor	181	• Dual therapy - ASA + clopidogrel (n=176) - ASA + prasugrel (n=5) -	No control group	• mechanical compression (30 min) soaked with tranexamic acid • In case of bleeding > 30 min, mechanical compression (30 min) soaked with tranexamic acid • In case of bleeding > 60 min (alveolar tamponade + sutures)	• Bleeding < 30 min (n=165/181 (91.2%) •Bleeding > 30 min and < 60 min n=15/181 (8.3%) • Bleeding > 60 min (n=1) • No severe bleeding complications (use of general hemostatics and/or hospitalization)	The risk of bleeding in case of maintenance of dual therapy is low and easily controllable since 91.2% patients had hemostasis control within less than 30 minutes and by simple mechanical compression	3

Appendix 7: Patients on VKA (Acenocoumarol, Coumadin, Fluindione Warfarin) and dento-alveolar surgery (Clinical Studies).

Comparison of four possible modalities: outright discontinuation, discontinuation and relay with a heparin, dose reduction and maintenance of VKA therapy

Maintenance versus outright discontinuation of VKA therapy

Study	Type of study	Dental procedures	Number of patients	Pre-op INR (< 72 hours)	Group(s) treated	Control group(s)	Local hemostasis	Results	Conclusion by authors	Level of evidence
Martinowitz et al., 1990 [209]	Case series	• Extraction (type and number of teeth unspecified)	40	2.5 - 4.5	• Maintenance of coumarin	No control group	collagen sponge + fibrin glue (Beriplast®) + sutures	• Moderate bleeding: - Only 1 case (2.5%, 1/40) - occurred on D+3 - associated risk factor: Coumarin + Dipyridamole • No severe bleeding complication	There is no evidence in favor of the discontinuation of VKAs.	4
Evans et al., 2002 [99]	Randomized, comparative study Open-label	• Extraction 1-9 teeth • Surgical extraction • IANB	109	< 4.1	• Maintenance of warfarin (n=52)	• Discontinuation of warfarin 2 days before, Pre-op INR ≤ 2 if INR > 2 surgery postponed to the following day (n=57)	oxycellulose gauze (Surgicel®) + sutures + mechanical compression (10 min +10 min if insufficient)	• Moderate bleeding - Warfarin: 26% (15/57) - Discontinuation of warfarin:14% (7/52) (p =ns) • Management of bleeding - management by the patient at home: 18.3% (20/109) - use of hospital and surgical revision: 1.8% (2/109) • No severe bleeding	There is no evidence in favor of the discontinuation of VKAs.	1
Cannon et al., 2003 [55]	Randomized, comparative, open-label study	• Single or multiple extraction • Surgical extraction • Biopsy • IANB	70	2 – 4	• Maintenance of warfarin (n=35) pre-op INR: 2 - 4	• Discontinuation of warfarin2 days before pre-op INR 1.66 [1.4-1.9] (n=35)	• simple extraction: mechanical compression (20 min) • surgical extraction and soft tissue surgery: oxycellulose (Surgicel®) + sutures + mechanical compression (20 min)	• Moderate bleeding: - within 30 min: none (0%) - within 24 hours > Maintenance of warfarin: 5.71% (2/35) > Discontinuation of warfarin: 8.57% (3/35) (p= ns) • Management of bleeding by simply resuming the hemostasis • No severe bleeding	There is no evidence in favor of the discontinuation of VKAs.	2
Zanon et al., 2003 [290]	Prospective study	• Dental extraction(s)			• Maintenance of warfarin (n=250) Pre-op INR: 1.8 to 4	• Patient not taking an antithrombotic agent (n=250)	fibrin sponge or oxycellulose gauze soaked with tranexamic acid + silk suture	• Moderate bleeding: > Warfarin: 1.6%(4/250) > Control: 1.2% (3/250) (p=ns) No postoperative bleeding required hospitalization. Simple local hemostasis measures were enough to control the bleeding complication.	There is no evidence in favor of the discontinuation of VKAs before dento-alveolar surgery for an INR < 4.	3

Bacci et al., 2010 [28]	Prospective, multicenter study, (Cohort)	• Simple and multiple extraction (≤ 3 teeth)	900	1.8-4	• Maintenance of Warfarin (n=451)	• Patient not taking an antithrombotic agent (n=449)	oxycellulose gauze (Surgicel®) + sutures + mechanical compression (gauze soaked in tranexamic acid	• Moderate bleeding: > warfarin: 1.5% (7/451) > control: 0.9% (4/449) (p=ns) • All the bleeding events were controlled by a simple surgical revision • No severe bleeding complication	There is no evidence in favor of the discontinuation of VKAs before dento-alveolar surgery for an INR < 4	2
Broekema et al., 2014 [51]	Prospective study (Cohort)	• Simple and multiple extraction (≤ 3 teeth) • Surgical extraction • Endodontic Surgery • Implant placement	206	1.8-3.5	• VKA (n=32)	• No anticoagulant (n=103) • APA (n=71)	• Sutures + Mechanical compression (30 min) • Patients on VKA: Tranexamic acid (5%) mouthwash x 4 times/day for 5 days post op.	• moderate bleeding APA: 6% (4/71) VKA: 9% (3/32) Control: 2% (2/103) (APA versus control, p=ns) (VKA versus control, p < 0.05) • all bleeding events were controlled by the patients themselves by simple compression. • no severe bleeding complications (not controlled by the patient himself/surgical revision/hospital)	• There is no evidence in favor of the discontinuation of anti-thrombotic agents in dento-alveolar surgery. • Risk of bleeding statistically higher in patients on VKA compared with patients on APA and control.	3

Maintenance versus dose reduction of treatment with VKA.

Study	Type of study	Dental procedures	Number of patients	Pre-op INR (< 72 hours)	Group(s) treated	Control group(s)	Local hemostasis	Results	Conclusion by authors	Level of evidence
Borea et al., 1993 [46]	Comparative, multicenter, randomized, double blind study	• Extraction (type and number of teeth unspecified)	30	< 4	• Maintenance of VKA Pre-op INR: 3.09 ± 0.2 (n=15)	• VKA dose adjustment with the objective Target pre-op INR ≤2 Pre-op INR: 1.69 ± 0.2 (n=15)	• Group treated: Tranexamic acid 4.8% Socket irrigation, mouthwash, 10 mL, 2 min, x 4 times/day for 7 days • Control group: Placebo (NaCl 0.9%)	• Moderate bleeding - D+1: > Group treated: 6% (1/15) > Control group: 13% (2/15) (p=ns) Easily controlled by the same local hemostatic measures • No severe bleeding complication	There is no evidence in favor of adjusting the target value of INR ≤2.	2
Gaspar et al., 1997 [114]	Prospective study (Cohort)	• Extraction (type and number of teeth unspecified)	47	< 4	• Maintenance of VKA Pre-op INR: 2.50 ± 0.1 [1.90-3.50] (n=15)	• VKA dose adjustment with the objective Target pre-op INR ≤2 Pre-op INR: 1.45 ± 0.15 [1.25-1.90] (n=32)	Tranexamic acid 5% Socket irrigation, 10 mL) + oxycellulose (Surgicel®) + sutures + mechanical compression (30 min) + Tranexamic acid 5% mouthwash, 10 mL, 2 min, x 4 times/day for 7 days	• Moderate bleeding > Group treated: 6% (1/15), D + 2, controlled by gauze soaked with tranexamic acid > Control group: 6% (2/32), 1 on D+2 and 1 on D+7, controlled by gauze soaked with tranexamic acid (D+2) and surgical revision (D+7) (p=ns)	There is no evidence in favor of adjusting the target value of INR ≤2.	2

Devani et al., 1998 [82]	Randomized, comparative study Open-label	• Extraction 1-9 teeth	65	2-4	• Maintenance of Warfarin (n=33) Pre-op INR: 2.7 [2.0-3.9] (n=32)	• Warfarin dose adjustment with the objective: INR between ≤2 Pre-op INR: 1.6 [1.2-2.1] (n=32)	Local hemostatic (Surgicel®) + sutures + mechanical compression (30 min)	• Moderate bleeding - before 30 min and <24 hours: none - D+2: - Group treated: 3% (1/33) - Control group: 3% (1/32) (p=ns), easily controlled by local hemostatic measures.	There is no evidence in favor of adjusting the target value of INR ≤2.	2
Sacco et al., 2007 [254]	Randomized, comparative, open-label study	• Single or multiple extraction (average of 4 teeth) surgical and nonsurgical	131	1.5 - 4	• Maintenance of warfarin Pre-op INR: 2.89 ± 0.42 (n=65)	• Warfarin dose adjustment with the objective: Target INR between 1.5 and 2.0 days before surgery Pre-op INR: 1.77 ± 0.26 (n=66)	• Group treated: Use of local hemostatic (gelatin sponge, oxycellulose gauze) + tranexamic acid (soaked gauze immediate post op), then mouthwash x 6 times/day for 2 days. • Control group: No specific local hemostatic measure.	• Moderate bleeding - within 24 hours: none - D2: > Group treated: 9.2% (6/65) > Control group: 15% (10/66) (P = ns), easily controlled by local hemostatic measures. • No severe bleeding	• There is no evidence in favor of adjusting the target value of INR ≤2.	1

Maintenance versus discontinuation of VKA and heparin relay.

Study	Type of study	Dental procedures	Number of patients	Pre-op INR (< 72 hours)	Group(s) treated	Control group(s)	Local hemostasis	Results	Conclusion by authors	Level of evidence
Souto et al., 1996 [269]	Randomized, comparative study Open-label	• Extraction (type and number of teeth unspecified)	92	1-5	• Maintenance of acenocoumarol	• Discontinuation of VKA and relay with calcium UFH	Use of aminocaproic acid or tranexamic acid mouthwash (2 minutes every 6 hours, for 2 days)	• No significant difference between the groups in terms of postoperative bleeding. • No severe bleeding complication.	• There is no evidence in favor of initiating a VKA-UFH relay in case of dento-alveolar surgery.	4
Bajkin et al., 2009 [33]	Prospective, randomized study	• Nonsurgical extraction (1-5)	214	< 4	• Maintenance of VKA Pre-op INR (1 hour before): 2.45 ± 0.54 (n=109)	• Discontinuation of VKA and relay with a LMWH (nadroparin calcium) (n=105) Pre-op INR (1 hour before): 1.26 ± 0.11	• VKA: local hemostatic (collagen sponge) <u>without suturing</u> + mechanical compression (30 min) • Discontinuation of VKA and relay with a LMWH: with no suturing or local hemostatic agent, only mechanical compression (30 min)	• Moderate bleeding VKA: 7.34% (8/109) LMWH relay: 4.76% (5/105) (p=ns) • All the bleeding events occurred on the day of the procedure (D+1) • All the bleeding events were controlled by a Level 2 hemostasis (collagen sponge + sutures) • No severe bleeding complication	• Maintenance treatment with VKA and heparin relay with LMWH are two therapeutic modalities that expose patients to a moderately low risk of bleeding (<10%) that is controllable by a simple local hemostatic measure. • No thromboembolic complications within 30 days after surgery.	2

Comparison of local hemostasis methods

Study	Type of study	Dental procedures	Number of patients	Pre-op INR (< 72 hours)	Group(s) treated	Control group(s)	Local hemostasis	Results	Conclusion by authors	Level of evidence
Sindet-Pedersen et al., 1989 [263]	Comparative, randomized, double blind study	• Extraction (1-20 teeth) Surgical and nonsurgical	39	PT < 20%	• Maintenance of VKA - Group 1 (n=19) - Group 2 (n=20)	No control group	• Group 1: Tranexamic acid 4.8% Socket irrigation, then mouthwash, 10 ml, 2 min, x 4 times/day for 7 days • Group 2: Placebo (NaCl 0.9%)	• Moderate bleeding (duration > 20 min) - Group 1: 6% (1/19) - Group 2: 40% (8/20) (p < 0.01) • One severe bleeding complication (placebo group) (fresh plasma transfusion)	Tranexamic acid is an effective topical hemostatic in the prevention of the risk of bleeding in oral surgery in patients on VKA.	1
Ramström et al,1993 [249]	Comparative, multicenter, randomized, double blind study	• Extraction (1-5 teeth)	90	< 4	• Maintenance of VKA - Group 1 (n=46) - Group 2 (n=47)	No control group	• Group 1: Tranexamic acid 4.8% Socket irrigation, then mouthwash, 10 ml, 2 min, x 4 times/day for 7 days • Group 2: Placebo (NaCl 0.9%)	• Moderate bleeding - Tranexamic acid 0% (0/44) - Placebo: 22% (10/45) (p < 0.01) • Management of bleeding - compression with gauze soaked in tranexamic acid (n=3) revision surgery (n=6) - Vitamin K injection 5 mg (n=1)	Tranexamic acid is an effective topical hemostatic in the prevention of the risk of bleeding in case of dental extraction and maintenance of VKA therapy and INR < 4.	1
Blinder et al., 1999 [41]	Randomized, comparative, open-label study	• Simple and multiple extraction (not detailed)	150	1.5 - 4	• Maintenance of coumarin - Group 1 (n=50) - Group 2 (n=50) - Group 3 (n=50)	No control group	• Group 1: gelatin sponge + sutures • Group 2: gelatin sponge + sutures + Tranexamic acid 500 mg mouthwash, 2 min, x 4 times/day for 4 days • Group 3: fibrin glue + gelatin sponge + sutures	• Moderate bleeding - Group 1: 6% (3/50) - Group 2: 12% (6/50) - Group 3: 8% (4/50) (p=ns) • Management of bleeding revision surgery and local hemostatic measure combining gelatin sponge + fibrin glue + sutures + tranexamic acid	• Local hemostasis combining gelatin sponge + sutures is sufficient to effectively prevent the risk of post-extraction bleeding in patients on VKA with an INR < 4. • The benefit of the use of fibrin glue is unproven in patients on VKA in the case of dental extraction(s).	2
Halfpenny et al., 2001 [126]	Randomized, comparative, open-label study	• Extraction (1-6 teeth)	50	2-4	• Maintenance of warfarin - Group 1 (n=20) - Group 2 (n=20)	No control group	• Group 1: fibrin glue (Beriplast®) + sutures • Group 2: oxycellulose gauze (Surgicel®) + sutures	• Moderate bleeding (< 30 min): none • Moderate bleeding at D+1 - Group 1: 5% (1/20) - Group 2: 10% (2/20) (p=ns), easily controlled by local hemostatic measures • risk of bleeding not related to the value of the pre-op INR	No difference in terms of efficacy between Beriplast® and Surgicel® in the prevention of the risk of bleeding in the case of dento-alveolar surgery.	2
Keiani Motlagh et	Case series	• Extraction (simple and	40	2 - 4	• Maintenance of acenocoumarol	No control group	Socket irrigation (10 mL tranexamic acid 5% per	No post-operative bleeding reported	The administration of tranexamic acid (irrigation + mouthwash)	4

al., 2003 [181]		multiple) • Surgical extraction • endodontic surgery					socket) + sutures + mouthwash (tranexamic acid 5%, 2 min, x 4 times/day (after meals and at bedtime) for 4 days		provides reliable and economical surgical hemostasis in the prevention of post-extraction bleeding in patients on VKA.	
Al-Belasy and Amer, 2003 [17]	Prospective study (Cohort)	• Extraction (5-7 teeth) • Surgical extraction	40	1 - 4	• Maintenance of warfarin - Group 1 (n=15) - Group 2 (n=15)	• Patients who have never taken a VKA - Group 3 (n=10)	• Group 1: gelatin sponge • Group 2: *n*-Butyl-2-cyanoacrylate glue (Histoacryl®) • Group 3: gelatin sponge	• Moderate bleeding (unspecified period) - Group 1: 33% (5/10) - Group 2: 0% (0/15) - Group 3: 0% (0/10) (p <0.05)	Cyanoacrylate glue (Histoacryl®) is an effective topical hemostatic in the prevention of the risk of post-extraction bleeding in patients on VKA.	2
Carter et al., 2003a [57]	Randomized, comparative, open-label study	• Extraction (1-18 teeth)	49	2 - 4	• Maintenance of warfarin - Group 1 (n=26) - Group 2 (n=23)	No control group	• Group 1: Socket irrigation (tranexamic acid 4.8%) + oxycellulose gauze (Surgicel®) + sutures+ mouthwash (tranexamic acid 4.8%, 10 mL, 2 min, x 4 times/day for 7 days. • Group 2: oxycellulose gauze (Surgicel®) (1/3 apical to the socket) + fibrin glue (Fibrijet®) + sutures	• Moderate bleeding within the first 48 hours post op - Group 1: 0% (0/26) - Group 2: 8.7% (2/23) (p=ns) The two cases of bleeding complications involve maxillary molars with severe periodontal infection.	The benefit of the use of fibrin glue in terms of efficacy and cost (local hemostasis of Group 1 is 20 times more expensive than group 2) is not demonstrated in patients on VKA in the case of dental extractions.	2
Carter et al., 2003b [58]	Comparative, randomized, double blind study	• Simple extraction (single and multiple)	85	2 - 4	• Maintenance of warfarin - Group A (n=43) - Group B (n=42)	No control group	• Group A Oxycellulose gauze (Surgicel®) + sutures + mouthwash (tranexamic acid 4.8%, 10 mL, 2 min, x 4 times/day for 2 days. • Group B: Oxycellulose gauze (Surgicel®) + sutures + mouthwash (tranexamic acid 4.8%, 10 mL, 2 min, x 4 times/day for 5 days.	• Moderate bleeding within the first 48 hours post op - Group A: 5% (2/43) - Group B: 2.5% (2/42) (p=ns) •The three cases of bleeding complications involve maxillary molars with severe periodontal infection. The INR value measured in patients on the day of the bleeding complication were within the therapeutic range (3.4 -2.4 -3.7)	Tranexamic acid 4.8% mouthwash for 2 days is just as effective as 5 days in postoperative bleeding control in patients on oral anticoagulants.	1
Al-Mubarak et al., 2006 et 2007 [19,20]	Randomized, comparative, open-label study	• Extraction (number of teeth unspecified)	214	1.5 - 4	• Maintenance of warfarin Group 2: W+ S- Group 4: W+ S+	• Discontinuation of warfarin: Group 1: W- S- Group 3: W- S+ • Discontinuation modalities: 2 days before the surgical procedure and start again 12 hours after	4 subgroups: - Sutures (S+) Group 3 and 4 - No sutures (S-) Group 1 and 2 For all the groups, mechanical compression (6-10 min)	• Moderate bleeding: G 1: D1: 12%, D3: 4%, D7: 0% G 2: D1: 23%, D3: 3%, D7: 0% G 3: D1: 18%, D3: 3%, D7: 4% G 4: D1: 31%, D3: 6%, D7: 0% (p= ns)	When pre-op INR ≤ 3, the suturing of the peri-alveolar gum is not always necessary. Assessment on a case by case basis. Suturing can be avoided in case of simple extractions	2

Risk factors affecting the incidence of post-extraction bleeding in patients on VKA

Value of preoperative INR

Study	Type of study	Dental procedures	Number of patients	Pre-op INR (< 72 hours)	Group(s) treated	Control group(s)	Local hemostasis	Results	Conclusion by authors	Level of evidence
Bodner et al., 1998 [45]	Case series	• Simple and multiple extraction (not detailed) • Surgical extraction	69	1 - 5	• Maintenance of VKA - Stratification based on the intensity of anticoagulation (INR value) and the degree of surgical trauma (score). • Intensity of anti-coagulability: - low: INR ≤ 2 - average: 2 < INR ≤3 - high: 3 < INR ≤ 5 • Surgical Trauma Score: 1. Single-rooted tooth extraction with forceps 2. Double-rooted tooth extraction with forceps 3. Multi-rooted tooth extraction with forceps 4. Surgical extraction	No control group	Gelatin sponge (Gelfoam®) + fibrin glue (Tissucol®) + sutures	• Moderate bleeding depending on the INR value - INR≤ 2: 0% (0/22) - 2 < INR≤3: 3.8% (1/26) - 3 < INR≤5: 4.3% (1/23) (p=ns) • Moderate bleeding depending on the surgical trauma - Score from 1 to 3: 2.5% (1/39) - Score from 4 to 12: 6.6% (2/30) (p=ns)	• There is no correlation between the incidence of postoperative bleeding and the INR value and the degree of surgical trauma.	4
Blinder et al., 2001 [41]	Prospective study (Cohort)	• Simple and multiple non-surgical extraction	249	1.5 - 4	• Coumarin (n=249) 5 subgroups: 1.5 < INR < 1.99, n=59 2.0 < INR < 2.49, n=78 2.5 < INR < 2.99, n=59 3.0 < INR < 3.7, n=30 INR > 3.5, n=23	No control group	gelatin sponge + sutures + mechanical compression (30 min)	• Moderate bleeding depending on the INR value 1.5 < INR < 1[.]99: 5% (3/59) 2.0 < INR < 2.49:12.8% (10/78) 2.5 < INR < 2.99: 15.2% (9/59) 3.0 < INR < 3.7: 16.6% (5/30) INR > 3.5: 13% (3/23) (p=ns) • *Risk factors identified: gingival inflammation*	• The value of the INR has no significant influence on the incidence of postoperative bleeding.	2
Salam et al., 2007 [255]	Case series	• Surgical and nonsurgical simple and multiple extraction	150	< 4	• Maintenance of VKA Group 1: INR ≤2.5 (n=101) Group 2: INR > 2.5 (n= 49)	No control group	oxycellulose (Surgicel®) + sutures + mechanical compression (30 min)	• Moderate bleeding - Group 1: 4.95% (5/101) - Group 2: 10% (5/49) (p=ns).	Within the therapeutic range (INR between 1.5 and 4) in dento-alveolar surgery, the risk of bleeding is not correlated to the pre-op value of INR.	4
Morimoto et al., 2008a [223]	Prospective study (Cohort)	• Simple and multiple extraction (≤ 3 teeth) • Surgical extraction	270	1.5 - 4	• Warfarin (n=134) 4 subgroups: 1.5 < INR < 1[.]99; n=67 2.0 < INR < 2.49;n=42 2.5 < INR < 2.99; n=21 3.0 < INR < 3.7; n=4	• Warfarin + APA (n=49) 3 subgroups: 1.5 < INR < 1.99, n=23 2.0 <I NR < 2.49, n=22 2.5 < INR < 2.99, n=4	oxycellulose (Surgicel®) + sutures + mechanical compression (30 min)	• Moderate bleeding depending on the INR value (Group 1 and 2) -INR < 2: 3.3% (2+1/67+23) -INR ≥ 2: 6.4% (5+1/67+26) (p=ns)	• No difference between the groups in terms of bleeding between patients with an INR < 2.0 and those with an INR of ≥ 2.0.	2

Comorbidities and VKA therapy

Study	Type of study	Dental procedures	Number of teeth extracted	Pre-op INR (< 72 hours)	Group(s) treated	Control group(s)	Local hemostasis	Results	Conclusion by authors	Level of evidence
Cocero et al., 2014 [63]	Prospective study	• Simple extraction (single and multiple)	500	1.5 - 4	• INR < 3 Maintenance of VKA	• INR > 3 Discontinuation of VKA and relay heparin	Fibrin sponge (Spongostanl®) + sutures + mechanical compression (30 min)	Comorbidities identified in both groups with a significant difference between the patient group that experienced a bleeding event and those who had no bleeding complication: - diabetes, - liver diseases, - renal impairment	In case of diabetes, liver disease and associated renal impairment, the safety value (to reduce the incidence of postoperative bleeding) of INR is 2.8 (in case of mechanical prosthesis) and 2.3 (for other indications) or consider a VKA-LMWH relay.	3

Assessment of the risk of hematoma and anesthetic technique

Study	Type of study	Dental procedures	Number of teeth extracted	Pre-op INR (< 72 hours)	Group(s) treated	Control group(s)	Local hemostasis	Results	Conclusion by authors	Level of evidence
Bajkin et al., 2012a [34]	Prospective study	• Local infiltration (LI) • Inferior alveolar nerve block (IANB)	352	2 - 4	• VKA -LI=340 injections -IANB=96 injections (n=279)	• No anticoagulant, INR < 2 - LI=99 injections -IANB=23 injections (n=73)	• 25G, 27G needle	•VKA: 0 hematomas • Control: 2 hematomas after multiple lingual LI, not severe (p=ns)	The practice of IANB in patients on VKA is safe.	2

Dental implants and VKA therapy

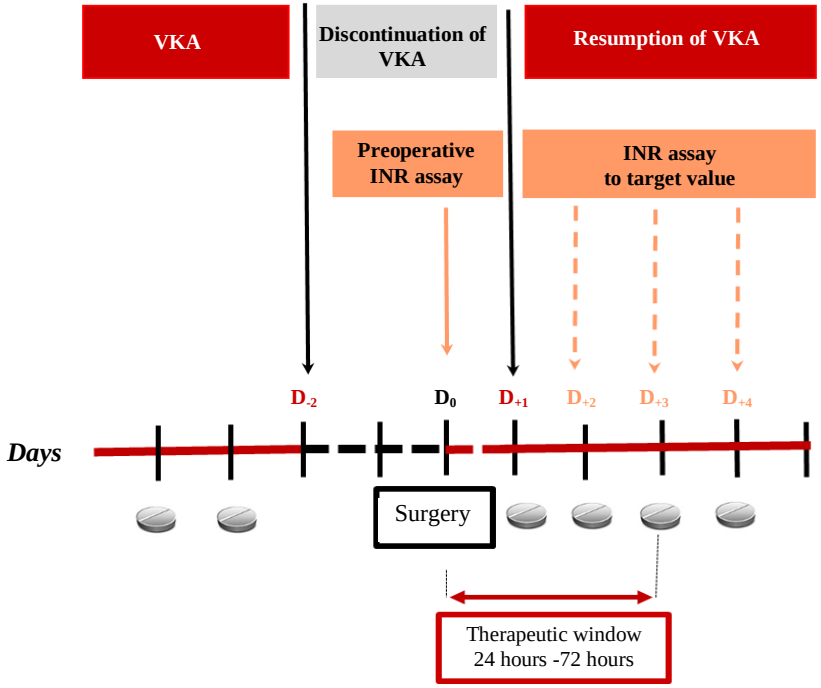
Study	Type of study	Dental procedures	Number of patients	Pre-op INR (< 72 hours)	Group(s) treated	Control group(s)	Local hemostasis	Results	Conclusion by authors	Level of evidence
Bacci et al., 2011 [29]	Study Case-control	• Implant placement	161	< 4	• Maintenance of warfarin (n=52)	• No anticoagulant (n=109)	Sutures + mechanical compression with gauze soaked in tranexamic acid	• Moderate bleeding at D+2 - warfarin: 4% (2/50) - control: 2.7% (3/109) (p=ns) • All bleeding was controlled by simple mechanical compression with gauze soaked with tranexamic acid.	Taking VKA does not increase the risk of bleeding after implant placement.	3

Appendix 8: Patients on dual antiplatelet therapy + VKA and dento-alveolar surgery (Clinical Studies).

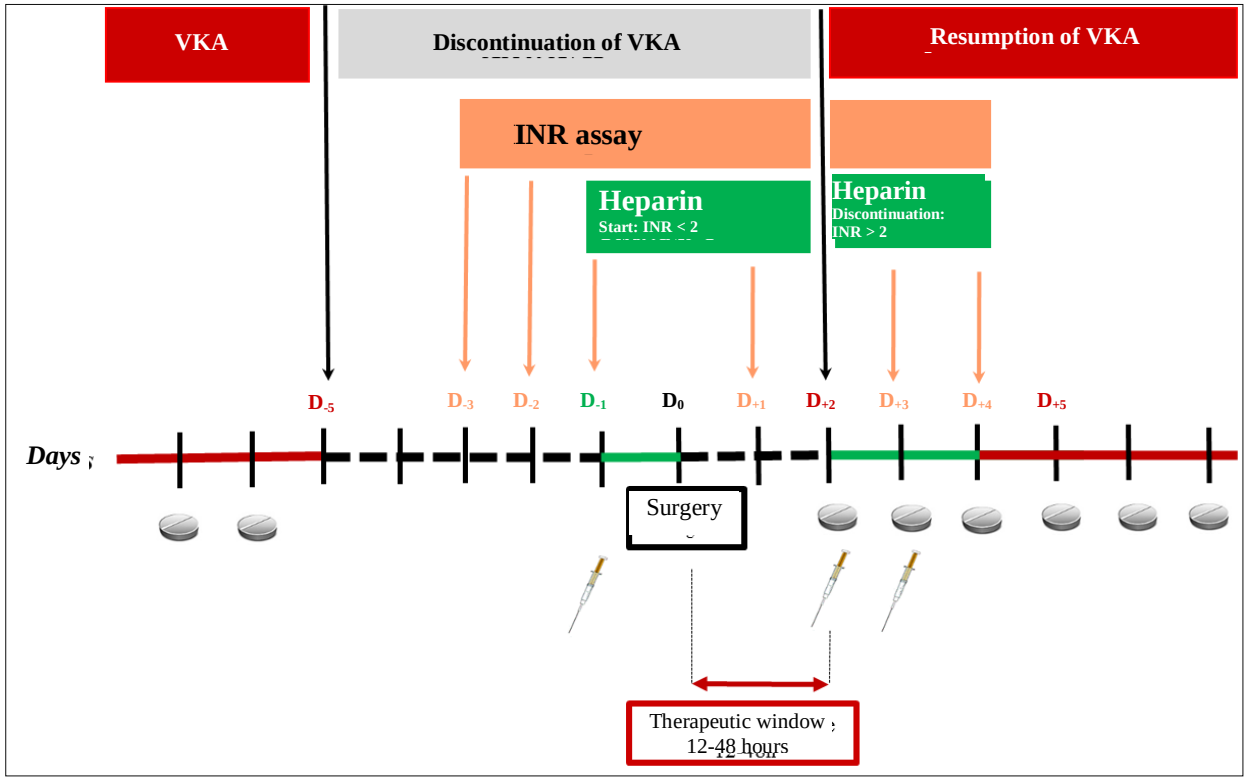
VKA + APA combination

Study	Type of study	Dental procedures	Number of patients	Pre-op INR (<72 hours)	Group(s) treated	Control group(s)	Local hemostasis	Results	Conclusion by authors	Level of evidence
Morimoto et al., 2008a [223]	Prospective study (Cohort)	• Simple and multiple extraction (≤ 3 teeth) • Surgical extraction	270	1.5 - 4	• Dual therapy: warfarin + APA 1.5 < INR < 2.99 (n=49)	• Monotherapy APA (n=87) - warfarin 1.5 < INR < 3.7 (n=134)	Oxycellulose (Surgicel®) + sutures + mechanical compression (30 min)	• Moderate bleeding - APA: 2.2% (2/87) - warfarin: 4.4% (7/134) - warfarin + APP [*sic*: APA]: 3.9% (2/134) (p=ns) • Risk factors identified: inflammation and periodontal infection	• No difference in bleeding between the groups of patients receiving warfarin or APA monotherapy and the warfarin + APA combination.	2
Morimoto et al., 2011 [225]	Prospective study (Cohort)	• Simple extraction (single and multiple) • Surgical extraction	392	1.5 - 4	• Dual therapy: warfarin + APA (n=66)	• Monotherapy - warfarin (n=188) - APA (n=128)	Oxycellulose (Surgicel®) + sutures + Mechanical compression (30 min) Management of postoperative bleeding: - revision surgery - suture + Surgicel® ± acrylic splint ± electrocoagulation	• Moderate bleeding (n=17) - warfarin + APA: 8.2% (6/66) - warfarin: 9% (9/188) - APA: 1.4% (2/128) (p=ns) • No bleeding beyond 6 days. • No severe bleeding complication.	• No difference in bleeding between the groups of patients receiving warfarin or APA (monotherapy) and warfarin + APA • Local hemostasis combining hemostatic + suture necessary in case of VKA + Aspirin dual therapy • Risk factors identified: - surgical extraction, - acute inflammation.	2
Bajkin et al., 2012 [35]	Prospective study (Cohort)	• Single and multiple extraction (1-4)	213	1 - 4	• Dual therapy: acenocoumarol + ASA INR = 2.43 ± 0.61 (n=71)	• Monotherapy - ASA (100 mg) (n=71) - acenocoumarol INR = 2.45 ± 0.60 (n=71)	Collagen Sponge + Mechanical compression (30 min.)	• Moderate bleeding (< 24 hours) - ASA: 0% (0/71) - Acenocoumarol: 2.8% (2/71) - Acenocoumarol + ASA: 4.2 % (3/71) (p=ns) • Simple bleeding complication treated with sutures + Surgicel® + compression • Risk of bleeding factors identified: - Multiple extractions, - Acute inflammation, - INR > 3. -	• There is no evidence in favor of the discontinuation of VKA and dual therapy in case of dento-alveolar surgery. • Local hemostasis combining topical hemostatic + suture necessary in case of VKA + ASA dual therapy.	2

Appendix 9: Protocol for discontinuation and resumption of VKA without heparin relay for surgery with a high risk of bleeding In a patient at low risk of thrombosis.



Appendix 10: Protocol for discontinuation and resumption of VKA with heparin relay for surgery with a high risk of bleeding In a patient at high risk of thrombosis.



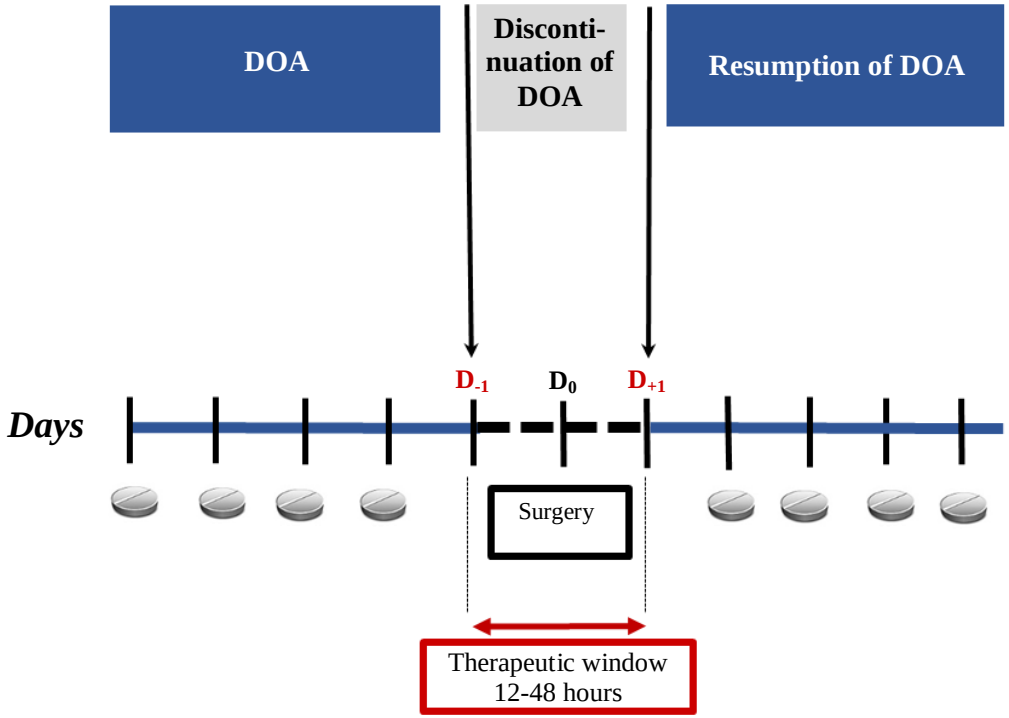
This therapeutic strategy applies only in cases of elective surgery.

1. Discontinuation of VKA 5 days before surgical procedure.
2. INR monitoring, every 24-48 hours.
3. The heparin therapy is started once the INR is less than 2, at 1 to 2 injection (s) per day depending on the risk of thromboembolism.
4. The surgical procedure is scheduled. Discontinuation of heparin 12 hours before the surgical procedure. In practice, the morning injection is canceled.
5. Resumption of heparin and VKA as soon as possible depending on the hemostatic control. In practice, resumption of heparin and VKA on D+1 or D+2.
6. INR monitoring every two days; discontinuation of heparin as soon as the target INR is reached.

Appendix 11: Main pharmacokinetic parameters of DOAs

Pharmacokinetic parameters	Dabigatran	Rivaroxaban	Apixaban
$t_{1/2}$ (elimination half-life)	12-14 hours Prolonged in case of renal impairment	5-9 hours in young subjects 11-13 hours in elderly subjects	12 hours
T_{max}	0.5-2 hours after the dose	2-4 hours after the dose	3-4 hours after the dose
T_{min}	12-24 hours after the dose	16-24 hours after the dose	12-24 hours after the dose
Main factors of the increase in the area under the curve	Renal impairment Age Low weight	Renal impairment Age Hepatic impairment	Renal impairment Age Low weight

Appendix 12: Protocol for discontinuation and resumption of a DOA without heparin relay for surgery with a high risk of bleeding.



Appendix 13: Patients on heparins (LMWH, UFH) and dento-alveolar surgery (Clinical Studies).

Discontinuation of VKA and relay heparin (LMWH, UFH)

Study	Type of study	Dental procedures	Number of patients	Group(s) treated	Control group	Local hemostasis	Results	Conclusion by authors	Level of evidence
Bajkin et al., 2009 [33]	Randomized, comparative, open-label study	• Simple extraction (single and multiple) • IANB	214	• Group B Discontinuation of VKA 3-4 days before the procedure and relay with LMWH (nadroparin) with 1 or 2 SC injections per day, the relay is stopped 12 hours before, check compliance with the target INR < 1.5, and resumption of LMWH and VKA as soon as possible, discontinuation of LMWH once the INR target is reached.) Pre-op INR = 1.26 ± 0.11 (n=105)	• Group A Maintenance of VKA Pre-op INR = 2.45 ± 0.54 (n=109)	• Group treated: neither collagen sponge nor sutures, mechanical compression (30 min). • Control group: collagen sponge (without sutures) + mechanical compression (30 min).	• Moderate bleeding: - Group A: 7.3% (8/109) - Group B: 4.7% (5/105) (p=ns) • Management of bleeding by simply resuming the hemostasis (collagen sponge + sutures) • No severe bleeding complication • No thromboembolic complications.	• **Incidence of risk of bleeding after relay VKA-LMWH = 4.7%** • There no evidence in favor of relay heparin in case of dento-alveolar surgery; however, this procedure may be indicated in case of surgery with a high risk of bleeding. • Suturing of the alveolar wound is not essential in all patients and should be reserved for more invasive surgery or in case of hemostasis after insufficient compression.	2
Karsh et al., 2011 [180]	Comparative, open-label study	• Simple extraction (single and multiple)	40	• Group B patients with a mechanical valve (= 27) • Subgroup 1 Maintenance of warfarin with an INR <4 • Subgroup 2 Discontinuation of warfarin and relay with LMWH (discontinuation 12 hours before surgery) • Subgroup 3 Discontinuation of warfarin and relay with UFH (discontinuation 4 hours before surgery, pre-op aPTT)	• Group A (=13) Patients who have never taken anticoagulants	Mechanical compression for 20 minutes and measurement of blood loss. Then intra-alveolar tamponade using Surgicel® + sutures + mechanical compression (1 hour).	• Quantification of blood loss by measuring the weight of the gauze used to achieve hemostasis • Maintenance of warfarin: 2,486-± 1,408 mg, relay with LMWH: 999 ± 425 mg, UFH relay: 1,288 ± 982 mg, healthy patient: 1,736 ± 876 mg (p= ns) • After completion of the surgical hemostasis: no bleeding event was reported (for the 4 groups)	• There is no significant difference in terms of blood loss after dental extraction between healthy patients and patients treated with anticoagulants. • In patients with a prosthetic valve, surgical hemostasis comprising oxycellulose, sutures and mechanical compression for 1 hour is effective in case of maintaining treatment with VKA. • Low potency.	2

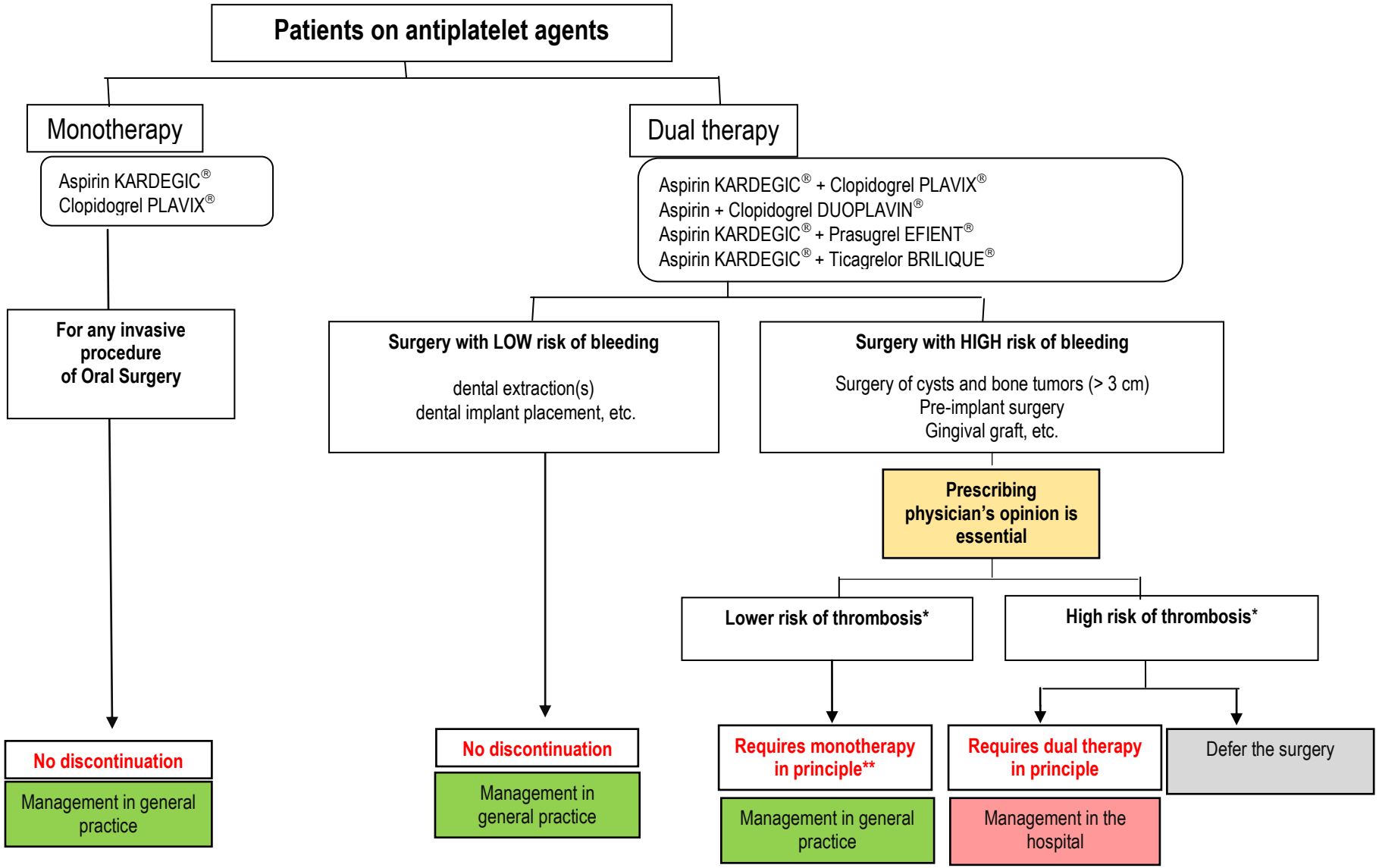
Patients on long-term LMWH.

Study	Type of study	Dental procedures	Number of patients	Treatment	Indication	Local hemostasis	Results	Conclusion by authors	Level of evidence
Hong et al., 2010 [167]	Retrospective study	• Simple and surgical extraction (1-14) • Mucosal biopsy	41	• Enoxaparin (28/41) • Enoxaparin + ASA: (9/41) • Enoxaparin + warfarin: (4/41)	• Patients hospitalized	• Gelatin sponge + sutures + compression (30 min) (n=9) • Sutures + compression (30 min) (n=15) • Electrocoagulation (biopsy) (=2)	• Post-op bleeding: 7.1% (3/41), the 3 cases belong to the enoxaparin + warfarin group: 1st case: bleeding on D0 4 maxillary teeth/enoxaparin 50 mg + warfarin 10 mg (INR=1.6), controlled by local hemostasis + fresh plasma transfusion + Vit K 2nd case: bleeding on D+4, 1 maxillary premolar, enoxaparin 90 mg + warfarin 2 mg (INR=1.6), controlled by local hemostasis 3rd case: bleeding on D13, 1 maxillary premolar, enoxaparin 110 mg x 2 times/day + warfarin 5 mg/day controlled by local hemostasis	• Incidence of post-op risk of bleeding for patients on LMWH (enoxaparin 30 and 40 mg administered 1-2 times/day) = 7.1% • There is no evidence in favor of stopping or adjusting the dosage for patients treated with LMWH (the risk of bleeding is low to negligible and hemostatic measures are effective). • Bleeding risk factors identified ($p < 0.05$): - enoxaparin + warfarin; - maxillary cusps.	4

Patients on long-term UFH.

Study	Type of study	Dental procedures	Number of patients	Treatment	Indications	Local hemostasis	Results	Conclusion by authors	Level of evidence
Morimoto et al., 2012 [226]	Retrospective study	• Simple and surgical extraction (1-14)	31	• Heparin (14/31) • Heparin + warfarin: (11/31) • Heparin + APA: (4/31) • Heparin + warfarin + APA: (2/31)	• Patients hospitalized - Cerebral infarction - Acute coronary syndrome - Intracardiac thrombus - DIC - Pregnant women with PE, DVT	• Oxycellulose gauze + sutures + compression (30 min)	• Post-op bleeding: 28.6 % (10/31) • The only bleeding risk factor identified: Pre-op aPTT value ($p < 0.05$) Mean aPTT 62 sec. [49.75-75.75] (Group with bleeding) versus mean aPTT 42 sec. [35.5-45.0] (Group with no bleeding) • Post-op bleeding controlled by revision surgery (oxycellulose gauze + fibrin glue) • No blood transfusion reported	• Incidence of risk of bleeding on UFH is high (=28.6%). • To limit the risk of bleeding, it is necessary to adjust the pre-op aPTT below 57 sec.	4

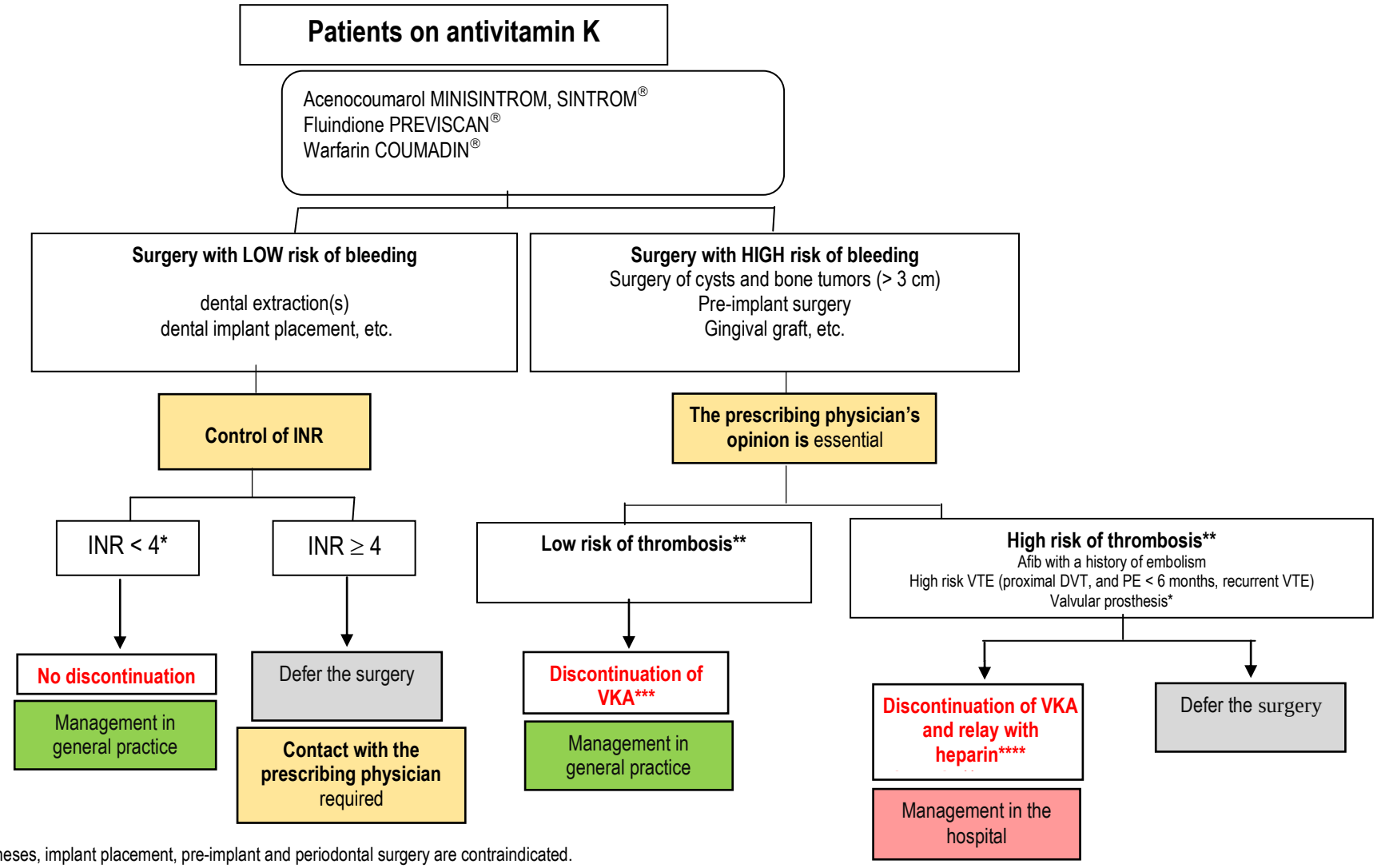
Appendix 14: Systematic algorithm of the management of patients on antiplatelet agents (APAs) during oral surgery.



* Determination of the level of risk of thrombosis available at: website www.has-sante.fr, « Recommandations : Antiagregants-plaquettaires : prise en compte des risques thrombotiques et hémorragique pour les gestes percutanés chez le coronarien » ["Recommendations: Platelet antiaggregants: consideration of risks of thrombosis and bleeding for percutaneous procedures in coronary patients"] (HAS November 2013).

** Monotherapy: continue prescribing aspirin, interruption time: clopidogrel: 5 days, prasugrel: 7 days, ticagrelor 3-5 days

Appendix 15: Systematic algorithm of the management of patients on antivitamin K (VKA) during oral surgery.



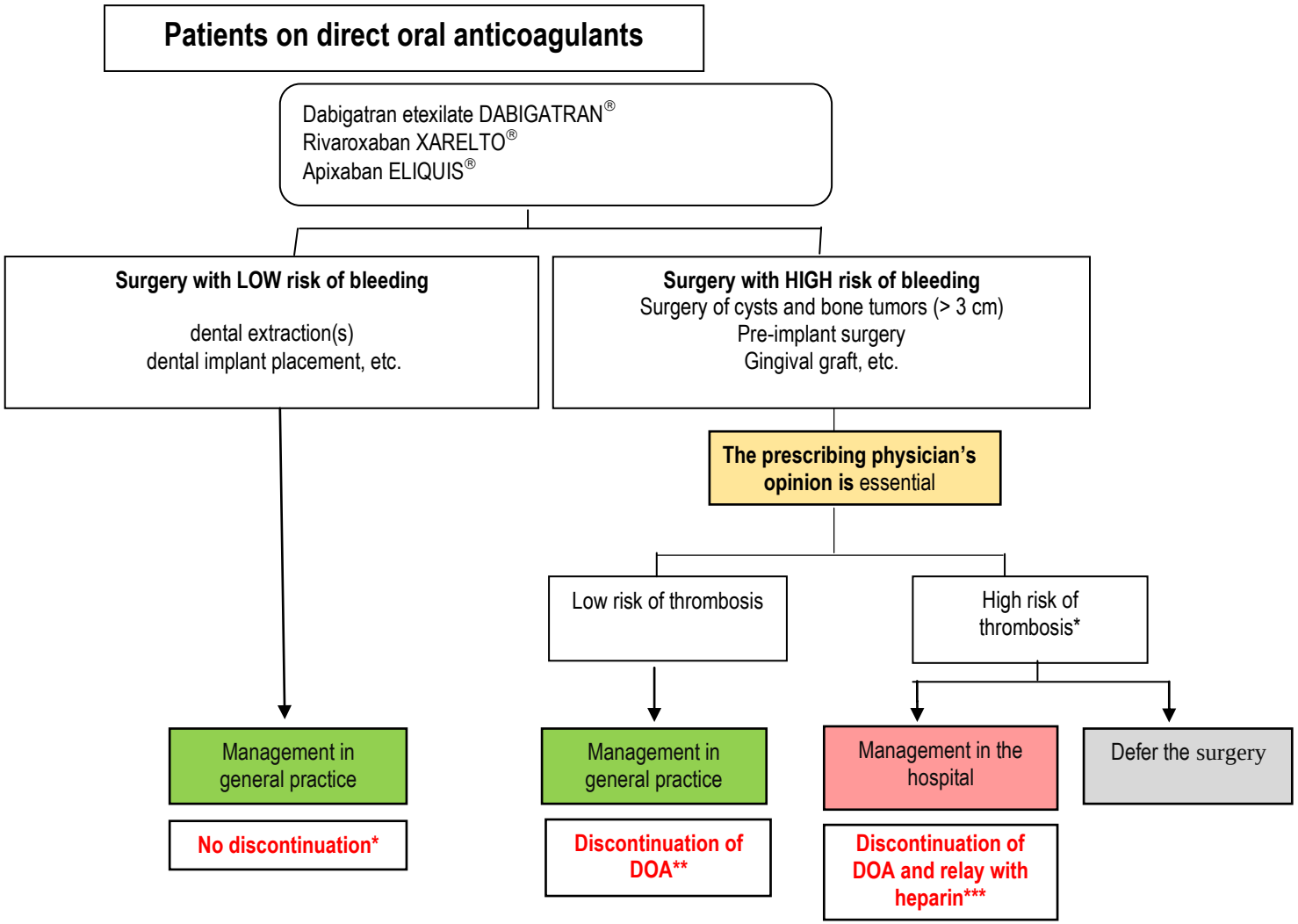
* For patients with valvular prostheses, implant placement, pre-implant and periodontal surgery are contraindicated.

** Determination of the level of risk of thrombosis is available at the website www.has-sante.fr « Recommandations : Prise en charge des surdosages en antivitamines K, des situations à risque hémorragique et des accidents hémorragiques chez les patients traités par antivitamines K en ville et en milieu hospitalier » ["Recommendations: Management of overdose of antivitamin K, situations at risk of bleeding and bleeding events in patients treated with antivitamin K in general practice and in hospitals"] (GEHT, HAS April 2008).

*** Discontinuation of VKA: Discontinue VKA 4-5 days before the procedure, resumption of VKA in the evening or the day after surgery, perform an INR test after 48 hours (HAS 2008)

**** Discontinuation of VKA and relay with heparin: on D-5 discontinuation of VKA, D-3 relay with LMWH (or UFH) with a curative dose, D-1 last injection of HPBM in the morning, UFH in the evening on D0 of the procedure, D+1 resumption of VKA and heparin (to be adjusted depending on the risk of bleeding), discontinuation of heparin once the INR target is reached.

Appendix 16: Systematic algorithm of the management of patients on direct oral anticoagulants (DOAs) during oral surgery.

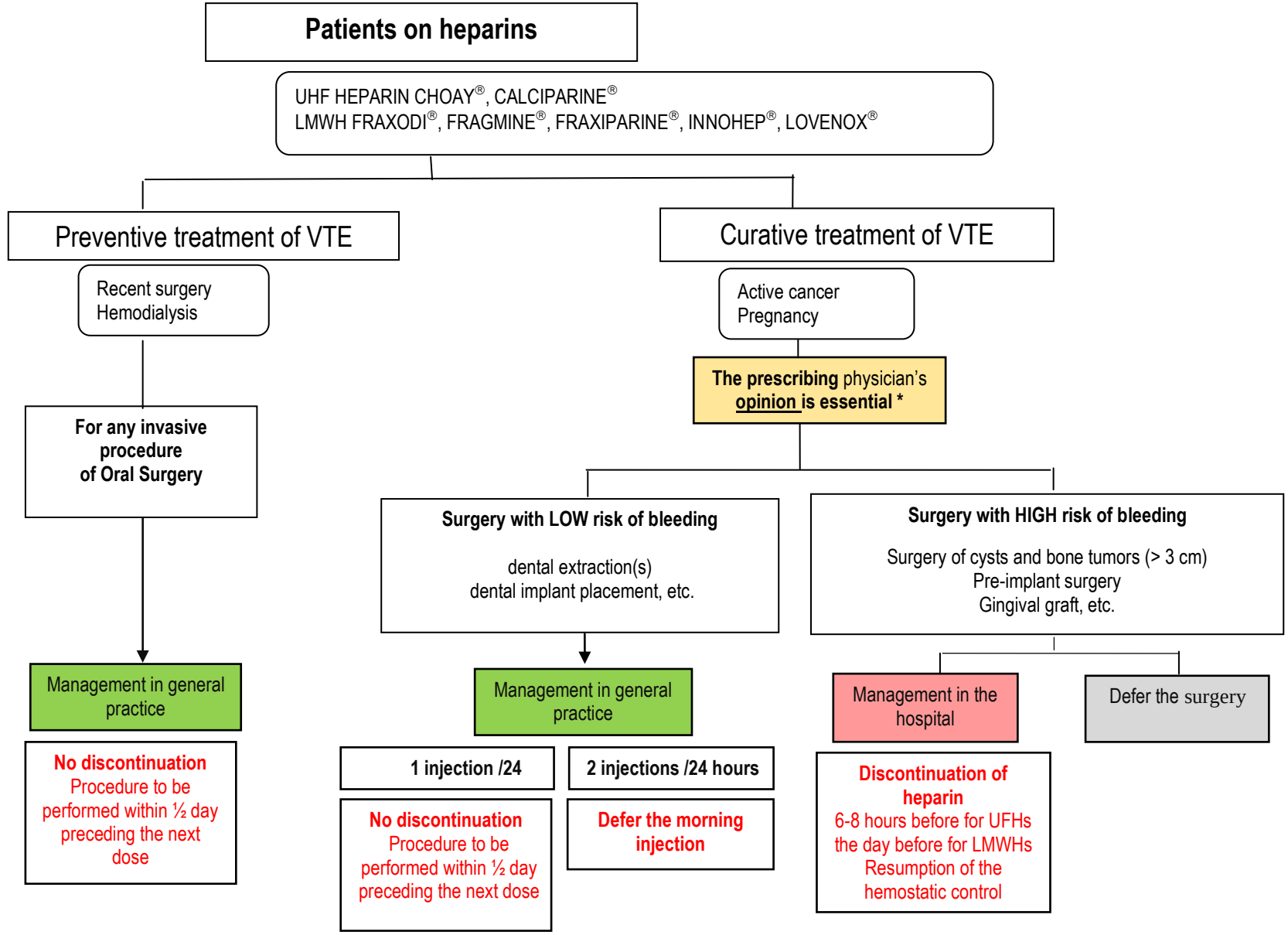


*** No discontinuation**: it is important to specify the age, indication (curative regimen or prevention in orthopedic surgery), the dose and number of doses per day, the time of the last dose, procedure to be performed within the half day preceding the next dose

**** Discontinuation of DOA**: discontinue DOA on the day before and on the day of the procedure (therapeutic window of 48 hours).

***** Discontinuation of DOA and relay with heparin**: discontinuation of DOA 5 days before surgery.

Appendix 17: Systematic algorithm of the management of patients on heparins during oral surgery.



*** check whether there are no other risks and precautions.**

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