

MANAGEMENT OF PATIENTS UNDER ANTI-PLATELET AGENTS' TREATMENT IN ODONTOSTOMATOLOGY

Oral Medecine and Oral Surgery Francophone Society

(Société Francophone de Médecine buccale et Chirurgie buccale or SFMBCB)

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GENERAL METHODOLOGY

Goal

The imprecise literature data concerning the risk of hemorrhage in patients under anti-platelets' treatment in odontostomatology, and more particularly in oral surgery, has lead the Francophone Society of Oral Medicine and Oral Surgery (Société Francophone de Médecine buccale et Chirurgie buccale or SFMBCB) to constitute a work group whose aim is to write, the recommendations concerning the management of patients under anti-platelets treatment.

Bibliographic search

Our definition of a correct practice was based on our systematic assessment and critical analysis of the literature. The definition of these guidelines was established according to the most reliable proofs of such reviews.

The bibliographical research was done based on the pool of information from Medline, Embase, and Bibliodent from the period of january 1960 to february 2005. Selected languages were French and English. Key words used were: (ANTIPLATELETS AGENTS) ; (ACETYLSALICYLIC ACID or ASPIRIN) ; (TICLOPIDINE) ; (CLOPIDOGREL) ; (HEMORRHAGE or BLEEDING) ; (HEMATOMA) ; (THROMBOTIC EVENTS or THROMBOEMBOLIC EVENTS) ; (WITHDRAWAL or DISCONTINUATION) ; (PREDISPOSING FACTORS) ; (DENTAL MANAGEMENT or DENTAL CARE) ; (OPERATIVE DENTISTRY) ; (ORAL SURGERY) ; (TOOTH EXTRACTION or DENTAL EXTRACTION) ; (PERIODONTAL SURGERY) ; (DENTAL IMPLANT) ; (LABORATORY TEST or PLATELET FUNCTION TEST) ; (BLEEDING TIME) ; (PFA-100) ; (DENTAL ANESTHESIA) ; (LOCAL ANESTHESIA) ; (LOCOREGIONAL ANESTHESIA) ; (GENERAL ANESTHESIA).

This bibliographic research was completed by a manuel research and an analysis of the abstracts of English (British Dental Journal, Journal of Cranio-Maxillofacial Surgery, International Journal of Oral Maxillofacial Surgery, Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontology) and French (Annales françaises d'Anesthésiologie et de Réanimation, Annales de Médecine Interne, Revue de Stomatologie et de Chirurgie Maxillofaciale, Sang Thrombose Vaisseaux) general reviews. The already identified references mentioned in the article have already been consulted. Finally, the manually obtained bibliographic search was completed by the lecture of the document of reference and the consultation of the electronic sites.

A total of 265 references were selected and analyzed. Amongst those, 113 were used for the making of the text, 68 of which issued from the automatic research and 45 of the manual research.

Methodology

This work group included a president who directed the group and a reporter, who completed the final document.

The editing and writing of the list of argumentations and guidelines of this work were based on a methodology proposed by the Health National Agency of Accreditation and Evaluation (HNAAS) (Agence Nationale d'Accréditation et d'Evaluation en Santé or ANAES). Each article was analyzed while taking in consideration the methodological entity of these studies, in order to attribute to each one a scientific proof or evidence.

The guidelines were classified and graded (A, B and C), taking into consideration the level of evidence and proof on which they rely (refer to table). The guidelines were defined according to the list of argumentations of the experts, based on their professional experience, and the consensus of the group of experts (professional concordance). In this case, the professional concordance was acquired by the presentation and discussion of these guidelines during the scientific session of the SFMBCB of the 22nd of May 2004 in Montpellier (France).

The text of these guidelines and of the list of argumentations was then submitted to another group of lecture, not involved in our work group, before being finalized. The group of lecture was composed of experts with various specialties (odontology, stomatology, internal medicine, hematology, cardiology, anesthesiology, pharmacology), fields of practice (university, hospital, private practice), and geographical origin. The experts of the group of lecture were assigned to give their opinion on the quality of methodology and the extent of scientific validation of the proposed text. Their comments were submitted to the group of work for modification before validation of the final document.

Level of scientific evidence of the literature and the force of the guidelines according to ANAES

Level of scientific evidence of the studies	Force of guidelines (grade)
Level 1 <ul style="list-style-type: none"> - Comparative and randomized trials of high power - Meta-analysis of comparative, randomized trials - Analysis of the decisions based on well-guided studies 	A Scientific evidence well-established
Level 2 <ul style="list-style-type: none"> - Comparative and randomized trials of low power - Comparative, non-randomized, well-guided studies - Cohort studies 	B Scientific assumption
Level 3 <ul style="list-style-type: none"> - Case-evidence studies 	C Low level of scientific evidence
Level 4 <ul style="list-style-type: none"> - Comparative studies with obvious bias - Retrospective studies - Series of cases - Descriptive epidemiological study (cross-sectional, longitudinal) 	

GUIDELINES

Introduction

Cardiovascular diseases currently represent the primary cause of mortality and morbidity in France. The expanding indications for by anti-platelets' agents (APA) treatment in these diseases has lead the odontostomatologist to be confronted more and more frequently to patients treated by APAs. Patients undergoing APA treatments show alterations in their primary hemostasis, which interferes directly with simple dental treatments or oral surgery. Hence, two treatment modalities come into discussion; the interruption of the APA treatment, with or without a proposal of an alternative treatment, or the continuation of the APA treatment, with absolutely no modification. The interruption of the APA treatment surely reduces the peroperative treatment bleeding. On the other hand, this attitude does not insure the best protection from the risk of thromboembolism. Inversely, continuation of the APA treatment, guaranteeing the

prevention of the thromboembolism risk, is more important than the risk of per and postoperative bleeding.

The goal of these guidelines is to identify a coherent and codified approach for the management of patients treated with APAs when confronted to dental cure, as well as to oral, periodontal and implant surgery.

These guidelines are limited to ambulatory long-term APA treatment. They concern mainly aspirin and clopidogrel. APAs used in operative cardiology, specifically the anti-GP IIb/IIIa, are excluded. Patients with a non-stabilized cardiac pathology, or who suffer from constitutional or acquired hemostasis disorders, are not concerned by these guidelines. These particular cases require hospital care, a multidisciplinary consultation, along with a specific hemostasis control for each particular case.

Aspirin intake in high doses is a specific case which will be treated separately.

These guidelines are intended for odontostomatologists, general practitioners, and specialized physicians (cardiologists, neurologists, anesthesiologists...)

Interruption of the APA treatment

Before undertaking any dental treatment or surgical operation on patients under APA treatment, it might seem logical to interrupt the APA treatment in order to prevent the risk of per or postoperative bleeding. This therapeutic approach insinuates the presence of the thromboembolic risk during a period of 8-10 days. This thromboembolic risk related to the interruption of the APA treatment is very poorly evaluated.

Studies have shown that the interruption of the APA treatment, even for a short period of time, could be the cause for thromboembolic events (acute coronary syndromes, cerebral vascular disease, claudication...).

In odontostomatology, the benefit gathered from stopping the APA treatment seems accessory when compared to the seriousness of a thromboembolic recurrence.

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Postoperative studies have shown that the interruption of the APA treatment, even for a short period of time, is the cause of the augmentation of atherothrombotic (acute coronary syndromes, cerebral vascular disease, claudication...)

In odontostomatology, the benefit from stopping the APA treatment seems accessory when compared to the seriousness of a thromboembolic recurrence.

1. The interruption of the APA treatment before dental treatment is not justified (Professional concordance)

2. The interruption of treatment by aspirin at low doses (doses between 75 and 325mg.j⁻¹) before oral, periodontal or implant surgery is not justified (Guideline of grade B).
3. The interruption of treatment by clopidogrel before an oral, periodontal or implant surgery is not justified (Professional concordance).

Continuation of the APA treatment

The continuation of the APA treatment, during dental treatment or oral, periodontal or implant surgery, allows the continued prevention of the thromboembolic risk associated to a cardiovascular disorder. On the other hand, this approach exposes the patient, theoretically, to a greater risk of perioperative bleeding.

Despite the absence of relevant clinical studies, the hemorrhagic risk under APA is considered low, and of favorable prognosis.

4. Patients under APA treatment, and having to undergo dental treatment or oral, periodontal or implant surgery, potentially have a greater risk of perioperative bleeding, but that may be controlled if correct measures of local hemostasis are carried out. Hence, the continuation of the APA treatment is recommended (Guideline of grade C).

Practical application: management of patients under APA treatment when receiving dental treatment or oral, periodontal or implant surgery

5. Preoperative evaluation of the patient has to be global. Its aim is to:
 - search and identify, other than the continuation of the APA treatment, other factors susceptible to enhance bleeding ;
 - evaluate the medical risk ;
 - appreciate the degree of sovereignty and cooperation of the patient (Professional concordance).
6. Until now, no biological test has proved to be sufficiently efficient in order to predict the actual risk of hemorrhage related to APA treatment. It is pointless to describe the bleeding time (BT) prior to the operation or dental treatment. Therefore, the evaluation of the risk of bleeding depends primarily on the medical questioning and clinical examination (Guideline of grade A).
7. The decision of whether to manage such patients in a dental clinic or in a hospital environment should be made depending on the individual examination of the preoperative cardiovascular and hemorrhagic risks, specific to each patient. A systematic ambulatory management of such patients is not justified (Professional concordance).

8. The continuation of an APA treatment does not contra-indicate the use of local anesthesia (LA). A locoregional anesthesia (LRA) of the inferior alveolar nerve is not recommended. It is only recommended to use an LRA in case of impossibility or failure to make an LA. It is advised to use a needle with an external diameter of maximum 27Gauge or 0.4mm. Slow injection is recommended, in order to limit tissue injury (Professional concordance).
9. The continuation of an APA treatment does not contra-indicate the realization of general anesthesia (GA). Naso-tracheal intubation is not recommended because of a higher risk of nasal hemorrhage (Professional concordance).
10. The continuation of an APA treatment does not contra-indicate conservative dental work (restorative dentistry, endodontics, and prosthodontics). Such treatments do not require any particular precautions (Professional concordance).
11. The continuation of an APA treatment does not contra-indicate any non surgical periodontal treatment. In case of persisting postoperative bleeding, a local compression for about 10 min is recommended (Professional concordance).
12. The continuation of treatment by aspirin does not contra-indicate oral, periodontal or implant surgery (Guideline of grade B).
13. The continuation of treatment by clopidogrel does not contra-indicate oral, periodontal or implant surgery (Professional concordance).
14. Both a rigorous surgical technique, along with correct local hemostasis, constitute essential perioperative hemorrhagic prevention attitudes, for patients under APA treatment. Suturing of the wound, along with local compression is crucial. It is also recommended to use resorbable local haemostatic agents (Professional concordance).
15. It is recommended to give to the patient a written copy of postoperative instructions to follow, in case of bleeding (Professional concordance).
16. A control appointment within 24-48 hours, or a simple phone call, to check the correct application and comprehension of the postoperative recommendations, is advised (Professional concordance).
17. Hemorrhagic complications in case of continuation of the APA treatment are rare and most of the times have a good prognosis. Curative treatment of a hemorrhagic complication lies mostly in the surgical revision of the local hemostasis, along with clinical supervision. In case of failure, or affection of the general state of the patient (respiratory distress, asthenia, hypotension...), a hospital transfer is recommended (Guideline of grade C).

Particular cases of high doses of aspirin intake

A daily intake of a total aspirin dose greater than 500mg is indicated for analgic and/or antipyretic and/or anti-inflammatory motives. The therapeutic goal is not the prevention of thromboembolic complications. Therefore, the interruption of aspirin intake could be

envisaged without any danger, all the more as there are various therapeutic alternatives to aspirin when it comes to its antalgic and/or antipyretic and/or anti-inflammatory effects.

18. Conservative dental treatment, as well as non surgical periodontal treatment, is not contra-indicated in the case of intake of aspirin at high doses (Guideline of grade C).
19. As for oral, periodontal or implant surgery, it is advised to stop the aspirin treatment and to postpone the operation for 5 days, in case the haemostatic action is taken into account, or to postpone the surgery for 10 days to insure that the aspirin effect has completely disappeared
20. In case of emergency, when a surgery is required, it could be undertaken without the interruption of aspirin intake at high doses. In order to prevent postoperative complications, the same procedures as those mentioned previously for patients under APA is recommended (Guideline of grade C).

Conclusion

For several years, and in order to reduce hemorrhagic complications, frequent practice opted for the interruption of APA treatment prior to conservative dental treatment or oral, periodontal or implant surgery. This approach is no longer acceptable. Indeed, recent studies have confirmed the occurrence of thromboembolic complications during the postoperative period (1-3 weeks), most likely in consequence to the interruption of the APA treatment, even after their substitution with flurbiprofene. At the same time, no study has actually been able to demonstrate a higher risk of hemorrhagic complications when continuing the APA treatment. Thus, it is currently recommended not to stop the APA treatment for conservative dental treatments, or oral, periodontal or implant surgery, while taking the correct precautions (surgical hemostasis, postoperative advices and supervision). Finally, the hemorrhagic control should not make one neglect the other operative risks. Only a global, multidisciplinary evaluation of the postoperative risk could really guarantee a correct management of patients under APA treatment in odontostomatological practice.

LIST OF ARGUMENTATIONS

Introduction

• Rupture of an atheroma plaque and its consequences

Atherosclerosis is a systemic and multifocal disease, which manifests with either a coronary syndrome (angor, cardiac infarction), or an ischemic vascular cerebral attack (transient cerebral attack, cerebral infarction), or an obliterating chronic arterial disease of the lower limbs (claudication, ulcer, gangrene) ^[72, 77, 80].

Rupture or erosion of the atheroma plaque is the trigger mechanism for thrombosis. Loss of the integrity of the endothelium, causing exposition of structures of the fibrous cape, favors adherence and then aggregation of blood platelets, hence forming fibrino-platelet emboli. These emboli may cause the partial or complete obstruction of the artery, but most frequently, might disintegrate and migrate into a distal artery.

Atherosclerosis is the principal cause of mortality and invalidity in France and in most of the developed countries ^[76, 81]. The threat of atherosclerosis is related to its permanent risk of thrombosis and embolism due to the instability of the atheroma plaque ^[85].

• Main APAs and their mode of action

APA are mainly used in order to limit arterial thrombosis which in turn complicates atherosclerosis ^[84, 85, 107]. APAs can be divided into 2 main groups: platelet anti-activators and platelet anti-aggregants. Anti-activators are constituted of acetylsalicylic acid, or aspirin, flurbiprofene, dipyramidol and thienopyrimidines (ticlopidine and clopidogrel). They are given per os and most frequently prescribed for an ambulatory long-term treatment.

Aspirin is the APA of first intention ^[107]. Several studies have proven the efficiency of aspirin in secondary prevention after an ischemic myocardial attack (IMA), or after an ischemic cerebral attack (ICA) ^[77, 99]. Aspirin also diminishes the risk of venous obstruction after an aortocoronary bypass ^[77, 99, 113]. Moreover, despite the absence of indication, some authors recommend replacing some anticoagulants by aspirin, for example in case of an auricular fibrillation, even with the lack of an associated thromboembolic aggravating factor. The antiplatelet action of aspirin lies in its inhibition of the platelet's cyclo-oxygenase (COX). It decreases the platelet's synthesis of thromboxane A₂ (TXA₂) and inhibits in consequence one of the main paths of platelet activation process, the one that is induced by thromboxane A₂ (TXA₂). The result is a partial decrease in platelet aggregation. The fact that the inhibition of the COX by aspirin is irreversible makes the antiplatelet effect persistent ^[92]. A complete recuperation of the platelet aggregation after the interruption of aspirin intake requires a period of 7-10 days – a period that corresponds to the average life time of platelets in the peripheral blood – because circulating platelets, exempt of their nuclei, are not capable of protein synthesis. The posology is comprised between 75 and 325 mg.j⁻¹ ^[45, 86, 95, 96, 106, 113].

Flurbiprofene is equally an inhibitor of the synthesis of TXA₂, but its action is reversible. The antiplatelet efficiency of this NSAID was proven even at low doses (50mg x 2.j⁻¹). Its indication is limited to the secondary prevention of IMA or post myocardial revascularization (coronary angioplasty, aortocoronary bypass) thrombosis, when the treatment by aspirin is momentarily contra-indicated^[95-97, 108, 113].

Dipyridamol slows down recapture of the AMP by platelets. It is also described as the inhibitor of phosphodiesterase of cyclic AMP (AMPC)^[96, 107]. These actions contribute to an augmentation of the intracellular concentration of the AMPC, the platelet's secondary anti-activator messenger^[95-97]. Dipyridamol owns a very weak antiplatelet activity. Clinical efficiency of dipyridamol has never been proven^[95-97, 107].

At last, thienopyridines (ticlopidine and clopidogrel) are specific antagonists for the recapture of adenosine diphosphate (ADP). These molecules inhibit the platelet activation path induced by ADP^[95-97, 107]. As for aspirin, inhibition of platelet aggregation is not complete and their action is equally irreversible. Their antiplatelet action is detectable for a period of 7 to 10 days, after which occurs a renewal of circulating platelets^[74, 107]. Thienopyridines have a superior action to aspirin when coming to reduction of the risk of morbidity due to cardiovascular pathologies^[76], especially in patients with a history of recent myocardial infarction and/or recent ischemic cerebral vascular attack (ICA) and/or an established obliterating arteriopathy of the lower limbs. Prescription of ticlopidine is abandoned and was substituted by that of clopidogrel because of the latter's better pharmacokinetics (one intake daily instead of two), and better hematological tolerance (rare thrombopenia and neutropenia)^[77]. Standard posology of clopidogrel is 75mg. mg.j⁻¹ in one intake^[113].

Antiplatelet anti-aggregants characterize the most powerful APAs. These are antagonists of the Gb IIb/IIIa, where they prevent the formation of an antiplatelet aggregate whichever activation path is used^[95, 96]. Three molecules are actually in use, all administered intravenously, and reserved for hospital usage^[113]. Abciximab is a monoclonal antibody; eptifibatide and tirofiban are synthesis peptides. They are used on patients with an acute coronary syndrome expressing high thrombosis risk or at the time of myocardial revascularization by coronary angioplasty with a stent graft^[13].

The use of anti-GP IIb/IIIa is concerned with the domain of operational cardiology: it is not dealt with in these guidelines.

Only APA that are administered by oral intake in the context of ambulatory treatment are included in these guidelines. The list of these APAs, currently commercialized in France, is illustrated and annexed to the text (Annex 1). The two most prescribed APA currently are aspirin and clopidogrel.

• Association of 2 APAs

The most ancient association is that of aspirin + dipyridamol. It is recommended in the secondary prevention of an ICA^[77, 97]. The association of aspirin + clopidogrel is more recent. It is logic because two different paths of antiplatelet activation are considered. The association of clopidogrel (300mg as a loading dose, then 75mg.j⁻¹) + aspirin (75mg.j⁻¹) correspond to recommended antiplatelet protocol in coronary patients following an acute coronary syndrome with an elevation of the ST interval, with or

without angioplasty with stent graft ^[111] with or without aortocoronary bypass ^[113]. A treatment protocol using clopidogrel and aspirin reduces significantly an ischemic event, which is maximal in the first year. In this context, a continuation of clopidogrel associated with aspirin treatment is particularly recommended for active stents (covered with sirolimus, paclitaxel...), which are slower to re-endothelialise ^[10, 40].

Currently, 1.5 million patients in France are under APA treatment, and the prescription of APA is ceaselessly increasing in the developed countries. Factors such as the ageing of the population, along with the unfavorable environmental factors (tobacco, hypercholesterolemia, HBP, sedentary life style...) lead to an increase of APAs recommendations. Odontostomatologists are hence faced consistently with patients undergoing APA treatment. APA, by altering primary hemostasis, increase the pre and postoperative bleeding risk, during dental treatments and surgical operations. Because of that, we are faced with the problem of the continuation or not of the APA treatment ^[2, 17, 24, 25, 31, 33, 36, 64, 65, 67, 68, 72, 73, 78, 80, 82, 93, 102, 104, 108, 109].

If the interruption of the APA treatment eliminates the hemorrhagic risk, this therapeutic approach however increases a thromboembolic risk. Inversely, a continuation of the APA treatment, despite a greater hemorrhagic risk, limits recurrence of thrombosis.

These guidelines are above all aimed to discuss the benefit-risk relation when related to the continuation of the APA treatment and to define the pre, per and postoperative modalities enabling to guarantee an optimal management of patients under APA treatment, and having to undergo dental treatments or oral, periodontal or implant surgery.

The intake of aspirin at high doses corresponds to an analgic and/or anti-inflammatory indication and will be dealt with separately.

Patient with a non-stabilized cardiovascular pathology or other congenital or acquired anomalies of hemostasis are not concerned by these guidelines. These specific cases require a hospitalization, along with a multidisciplinary consultation and a specific hemostasis to each case.

The intake of aspirin at high doses corresponds to an analgic and/or anti-inflammatory indication and will be treated separately.

Patient having undergone a non stabilized cardiovascular pathology or other congenital or acquired anomalies of hemostasis are not concerned by these guidelines. These specific cases require a hospitalization, along with a multidisciplinary consultation and a specific hemostasis to each case.

1. Risk related to the interruption of the APA treatment

The APA treatment interruption, although efficient and based on a well-defined recommendation, cannot be conceived without the augmentation of the thromboembolic risk ^[1, 3, 5, 6, 12, 12, 15, 34, 39, 40, 41, 55, 56, 83, 87, 88, 110] more than 70'0000 patients suffering from atherosclerosis in the meta-analysis of the *Antiplatelet trialists* collaboration. This study has shown that a long term treatment by APA allows a reduction of mortality by 16%, a reduction by 31% of the relative risk of the occurrence of IMA and by 18% of the relative risk of occurrence of ICA associated to atherosclerosis. Inversely, the risk of spontaneous hemorrhage is increased by 0.12%. Therefore, the approach that consists of

the interruption of the APA in patients having to undergo surgery, exposes them to a higher risk of recurrence of thrombosis.

There aren't any controlled series evaluating objectively the effects of the transitory interruption of APAs during the perioperative period on coronary or cerebral vascular patients. Nevertheless, separate observations indicated the occurrence of acute thromboembolic attacks (myocardial infarction, cerebral vascular attack, obliterating arthritis of the lower limbs) following interruption of the APAs.

Several recent epidemiological enquiries have brought the attention over the potential danger of the interruption of APA treatment on patients suffering from coronary or cerebral vascular diseases ^[5, 6, 12, 13, 41, 110].

1.1 Interruption of the APA treatment without any particular precautions

A retrospective analysis ^[5, 110] on 475 patients, hospitalized in intensive care for myocardial infarction, has found that, in 11 patients, there was a notion of aspirin interruption 15 days prior to the infarction. These patients had been treated by aspirin for a long time for a coronary insufficiency, perfectly stable until the interruption of aspirin. In 9 out of 11 of these patients, aspirin interruption was prior to a planned surgical operation.

In another retrospective study ^[12, 13] patients hospitalized for acute coronary syndrome from 1999 to 2002, 51 patients were shown to have interrupted their aspirin intake, 10 ± 1.9 days before the occurrence of the coronary attack. This group represented 4.1% of the total number of patients having interrupted aspirin intake, but 13.3% of acute ischemic recurrences. Aspirin was interrupted because of either a minor surgical operation (n=7), a fibroscopy (n=8), a dental surgery (n=13), bleeding (n=3), or finally because of the absence of compliance (n = 20).

These results demonstrate the potential thrombotic risk in case of the interruption of the APA treatment, in perfectly stable coronary patients.

Similar results were revealed for patients with a history of ICA. Bachman ^[3] reported 12 cases with the occurrence of cerebral infarction in the month following aspirin interruption. Michel ^[4] demonstrated in a retrospective study case-testimonies on 618 patients, that the patients with a recurrence of ICA are 3.5 times more susceptible of having stopped their aspirin treatment than those who have not had ICA.

The harmful effect of the interruption of the APA treatment could be explained simply by the suppression of the antiplatelet protection. The thromboembolic risk could also be overridden by a phenomenon of rebound of the platelet activity on the interruption of the APAs ^[87]. Vial and coll ^[66] observed an augmentation of the urinary metabolites of thromboxane B2 after the interruption of aspirin.

Overall, these studies clearly manifest that the interruption of APAs in patients suffering from coronary or cerebral vascular, perfectly stable, pathologies increases significantly the harmfulness of a recurrence of a thromboembolic attack.

For several authors, the frequency of the occurrence of a thromboembolic relapse is proportional to the cardiovascular pathology risk. In high risk patients, an antithromboembolic substitutive treatment is very often proposed in the case of a planned surgery, especially if the latter is associated to an important operational hemorrhagic risk [31, 33, 64, 78, 82, 93, 109].

1.2 Interruption of the APAs and the introduction of a substitutive treatment with another APA

The aim is to continue the antiplatelet treatment to a time very close to the operation and to resume as quickly as possible in order to minimize the risk related to thromboembolic complications, at the same time privileging the bleeding control related to the actual act. A NSAID with a short half-life or a low molecular-weight heparin (LMWH) could theoretically be used in order to replace aspirin or the thienopyridines. Only the flurbiprofene has the market authorization in France for this role of substitution [113]. The procedure of a swap APA-flurbiprofene-APA is the following: interruption of the APA treatment 8 to 10 days before the surgical operation, substitution by flurbiprofene 50mg x 2j⁻¹ along with the inhibition of intake during the surgical act, interruption of flurbiprofene, and then as soon as possible retake of the prior APA postoperatively. According to several authors, it is not necessary to wait till all the platelets are renewed in order to obtain a correct haemostatic management [45, 59, 74, 107]. An interruption of the APA treatment 5 days before the surgical operation seems enough. Since 1/10th of the pool of circulating platelets is renewed each day, this period of 5 days enables the renewal of 50% of circulating platelets, which is sufficient to insure a correct functional primary hemostasis [74, 107].

Unfortunately, this procedure does not guarantee an optimal security against a thromboembolic risk. A recent longitudinal prospective study [6] including 1358 patients hospitalized for an acute coronary syndrome (ACS), has shown that 355 patients (26.1%) were treated by APA, and that 73 patients (5.4%) have stopped their treatment by APAs (aspirin, ticlopidine) in the days prior the thromboembolic attack (11 ± 0.8 days). Amongst these patients, 26 have stopped the treatment in consequence to a minor surgery, and 47 (3.5%), in consequence to a surgical operation. 31 of these 47 patients have benefited of a substitutive antithrombotic treatment : 16 have received an LMWH treatment with 1 (n=6) or 2 (n=10) injections per day, 15 received both LMWH and flurbiprofene. In addition, amongst the 73 patients who stopped their APA treatment, 14 had passed away in the following month.

The death risk is twice greater (RR:2.06) in patients having interrupted APA treatment than those who continued it.

In the meantime, no controlled study has shown that the fact of interrupting the APA treatment before a surgical operation increases the frequency of thromboembolic attacks immediately following the perioperative period. On the other hand, interruption of the APA treatment with or without an APA substitute increases in a significant manner morbidity and mortality in the case of occurrence of a thromboembolic attack during the postoperative period. Consequently, interruption of the APA treatment for dental treatments or oral, periodontal or implant surgery is neither justified, nor recommended.

2. Risk related to the preservation of the APA treatment

The continuation of the APA treatment before a surgical operation insures prevention of the thromboembolic risk associated to the cardiovascular pathology. This therapeutic attitude overrides per and postoperative bleeding risks. Aspirin is the only APA on which studies have been made to analyze its effect on perioperative bleeding in odontostomatology [2, 17, 21, 30, 31, 33, 45, 52, 57, 58, 60, 63, 65, 109]. Argumentation over the bleeding risk associated to the continuation of the APA treatment is very badly evaluated, in terms of frequency or gravity. Postoperative hemorrhagic complications, gravity wise, could be subdivided into 2 groups: severe hemorrhages with functional and/or vital risks, and minor hemorrhages. Severe hemorrhages include significant postoperative bleeding, as well as extensive and active hematomas of the deep regions (mouth floor, submandibular lodge, and lateropharyngeal lodge), in which case hospitalization is required. These events are exceptional in odontostomatology. In such cases a traumatic lesion is almost always in cause, most often a lesion of the lingual artery or one of its branches [4, 7, 18, 20, 26, 29, 38, 42, 44, 53, 89, 101, 103]. Minor hemorrhages include persisting dripping, along with the presence of a hyperplasic clot, and ecchymose. These are by far the most common [23, 70, 79, 91, 105]. APA intake exposes to only a minor risk of hemorrhagic attack. Literature reveals one single case of severe hemorrhage associated to the intake of aspirin as an APA [63]. A male of 30 years, with a renal transplant, under immunosuppressive treatment, antihypertensive treatment and under aspirin at a dose of $150\text{mg}\cdot\text{j}^{-1}$, manifested a persistent bleeding following a gingivectomy operation. Local hemostasis management seemed to be insufficient and a platelet transfusion was necessary. It is however difficult to precisely establish the immutability of aspirin to such an incident, having in mind the other numerous hemorrhagic risk factors.

The incidence of hemorrhagic complications following dental treatment or dental extractions on patients under APA treatment has been very scarcely documented in the literature. One single clinical study has attempted to evaluate the possibility to practice an oral surgery without the interruption of the APA treatment [2]. This concerns a comparative, randomized, single blinded trial, on 39 patients. These were divided into 2 groups: 20 patients stopped the aspirin treatment at a dose of $100\text{mg}\cdot\text{j}^{-1}$, 7 days prior to the dental extractions, and the other 19 pursued it. These patients were grouped according to the complexity of the operation, the number of teeth to be extracted, and lastly the state of the local inflammation. In both groups, a surgical hemostasis comprising sutures and compression were carried out. For both groups, the volume of blood loss was minimal and no persisting postoperative bleeding was observed in the following days. In this particular study, no difference concerning peroperative bleeding between the group under aspirin treatment and the control group was reported. No clinical trial has been undertaken in order to judge the peroperative bleeding risk under thienopyridines treatment (ticlopidine or clopidogrel) following an oral, periodontal or implant surgery. Even though the hemorrhagic risk associated to thienopyridine treatment is theoretically estimated more important, clinical experience has shown that postoperative bleeding risk could be efficiently controlled with surgical hemostasis [33, 78, 104, 109].

Today, not a single clinical study could prove an important increase in hemorrhagic incidents or a surgical revision of hemostasis subsequent to an oral, periodontal, or implant surgery, on patients under APA treatment.

In a definitive manner, and despite the absence of a pertinent study, the augmentation of the risk of preoperative bleeding associated to the continuation of the APA treatment seems low. No recent study in odontostomatology has shown a higher frequency or gravity of the bleeding, in case of the continuation of the APA treatment.

Patients under APA treatment and requiring dental treatments, or oral, periodontal or implant surgery, have a higher potential risk of bleeding, but which is not serious if correct local haemostatic measures are undertaken. Continuation of the APA treatment is thus recommended.

3. Practical conduct: management modalities of patients under APA treatment when undergoing dental treatments or oral, periodontal or implants surgery

Nowadays, odontostomatologists should not interrupt the APA treatment on patients requiring dental treatments or surgical operation. In various cardiovascular pathologies, the pursue of the APA treatment is crucial ^[7, 13, 26].

3.1 Evaluation of the operative risk

The evaluation of the operative risk has to be global. Its goals are to:

- search and identify, in addition to the APA treatment, other factors susceptible of over-increasing the bleeding ;
- evaluate the medical risk ;
- appreciate the degree of autonomy and cooperation of the patient.

• Identification of the other factors representing a hemorrhagic risk

Other than the continuation of the APA treatment, a certain number of other factors could favour the occurrence of hemorrhagic complications. The hemorrhagic attack is most often of a multifactorial source. The principal factors corresponding to a hemorrhagic risk in the literature are: local inflammation, pre-existing infection, delamination of the lingual mucosa, or insufficient surgical experience of the practitioner ^[20, 22, 23, 70, 79, 100]. Surgical operations where the risk of bleeding has shown to be the highest are: multiple dental extractions ^[23, 70], implant placement in the symphysis region ^[4, 7, 18, 26, 29, 38, 42, 44, 103], and extraction of a mandibular third molar ^[20, 79, 89, 91, 101, 105].

Equally, it is important to guarantee the absence of another hemostasis pathology or medical interactions resulting in a hemorrhagic symbiotic potential (association of 2 APAs, association of an APA and another anticoagulant, association of an APA and a NSAID) ^[36, 47, 54, 91, 99]. The association of aspirin and clopidogrel has captured a certain attention lately because they are more and more prescribed, particularly following an acute coronary syndrome without elevation of the ST interval, with or without myocardial revascularization with a stent graft. It is important to point out that the correct evaluation of the risk factors lies mainly on a prior thorough meticulous medical interrogation and examination ^[107]. In no case should these factors be ignored or under-

estimated. The cumulus of several hemorrhagic risk factors could lead to a clinical situation of a high risk of peroperative bleeding, a situation which would require a hospital environment management and extensive preventives procedures.

- **Biological tests**

The main biological tests capable of evaluating the repercussion of the APAs on the hemostasis are: measurement of the bleeding time (BT), PFA (platelet function analyzer), analysis of the platelet functions by aggregametry or by flow cytometry^[11, 19, 27, 28, 37, 43, 61, 94, 107]. Other than the measurement of the BT, all the other biological tests require specialized laboratories; they hence could not be used in a routinely systematic manner^[31, 107]. With the Ivy technique, aspirin increases the BT (1,5 to 2 times the normal value). There exists an important variability in the individual sensitivity to aspirin. The increase of the BT is more important with thienopyridines than with aspirin^[49, 62, 68], and even more important with the association aspirin-clopidogrel than with each APA separately^[47, 107]. Dipyramidol is the only APA that does not modify the BT^[97, 107, 113]. In order to predict the hemorrhagic risk, the BT does not allow us to identify patients with a hemorrhagic risk. An augmentation of the BT is not necessarily related to an increase in the hemorrhagic risk^[8, 9, 32, 48, 51]. An increase of the BT of more than 20 min seems to be associated to a higher frequency of peroperative bleeding^[33]. Inversely, a normal BT does not exclude the possibility of a hemorrhagic complication and risks to induce a false safety. All the studies show that the BT has a weak positive predictive value, and as a screening biological test, represents a negative indicator of the clinical hemorrhagic risk for patients under APAs.

Currently, we do not possess a systematically valid biological test allowing the routine identification of patients under APA treatment and who represent a hemorrhagic risk during a surgical operation. BT does not offer any prognostic valid information. Its preoperative prescription is thus useless^[31, 80]. In the absence of a valid biological test for the prediction of the hemorrhagic risk, the accurate evaluation of the hemorrhagic risk lies mainly on a thorough medical interrogation and clinical examination.

- **Evaluation of the medical status**

The management of patients under APA treatment having to undergo dental treatments or oral surgery should obviously not only be limited to the evaluation of the risk of perioperative bleeding.

As for every patient, a global evaluation of the medical status is crucial. It is essential to be informed specifically about the cardiovascular state of the patient and other associated pathologies. The treating practioner (general practioner or cardiologist), should be consulted in case of doubt on the severity of the current pathologies.

The risk of recurrence of thromboembolic pathology is higher in the following clinical situations: the first year following a first thromboembolic event, or after a coronary stent implantation, patients under aspirin + clopidogrel treatment, and finally patients not stabilized on the cardiovascular level.

- **Choice of management for such patients: in private practice or in a hospital environment**

An important element in the management of patients under APA treatment consists in the determination of the necessity or not of their orientation in a structure of specialized care. In most cases, the odontostomatologist should be able to carry out dental or surgical treatment in a private practice. However, in the case of accumulation of several risk factors for bleeding and/or in the presence of a severe or non-stabilized cardiovascular pathology and/or an altered general status, a hospital management of such patients is recommended ^[36]. Ipso facto, patients who benefit from an association of aspirin + clopidogrel should also be treated in a hospital environment. When dealing with these patients, other than an increased bleeding risk, it is above all the cardiovascular risk which should be considered with care ^[47].

In total, characterization of the operative risk lies mainly on the medical and clinical examination. It could require, if need be, a contact with the treating practitioner. The identification of a patient in the category of high-risk (surgical and/or medical), should incite the practitioner to operate in a hospital environment.

3.2 Operative period

It is important to be aware of the risk of augmentation of bleeding while maintaining the APA treatment during the following clinical acts: anesthesia, conservative treatment and surgical operations.

3.2.1 Anesthesia

- **Local anesthesia (LA)**

The risk of hemorrhage associated to an LA (para-apical, intraligamentary, or intraseptal) is confined to a hematoma at the point of injection ^[90, 98]. These hematomas, apart from an eventual discomfort or a slight delay in the healing process, do not represent any clinical threat. The increase in the risk of hemorrhage by LA is not documented in the literature. Nevertheless, the fact that an important number of patients under NSAID treatment have benefited from an LA without any noticeable danger, renders the operative risk very weak, or non-existent. In conclusion, APAs do not contraindicate the use of LA in odontostomatology.

- **Locoregional anesthesia (LRA)**

The hemorrhagic risk associated with the use of an LRA results in a higher bleeding, secondary to tissue or vascular trauma, thus causing extensive and/or compressive hematoma. Not one single case is reported in the literature where a hemorrhagic incident and an APA treatment are put in parallel, when using a peripheral bloc. Despite the absence of significant argumentation suggesting that the risk of lateropharyngeal hematoma increases with the intake of APAs when using an LRA of the inferior alveolar nerve, several authors do not recommend the latter ^[25, 68, 102]. In addition, in patients under APA treatment, it is recommended to use LRA only in the case of failure or

inconceivability to make an effective LA. As usual, the real problem should be dealt with by the thoughtful evaluation of the benefit/risk relation. Both the choice of a needle with a maximum diameter of 27 Gauge or 0.40mm, along with a slow injection, insures the limitation of tissue traumatism^[90].

- **General anesthesia (GA)**

Tracheal intubation could be the cause of per and/or postoperative bleeding, due to direct trauma by the probe. Most frequent hemorrhagic complications appear following a nasotracheal intubation as a result of a trauma of the conchae^[86]. Intake of APA could result in an important perioperative epistaxis, necessitating a local procedure: anterior and/ posterior gauze plugging and, very rarely, electrocoagulation. Epistaxis can also occur between the 8th and 15th day postoperatively, following the fall of the crust. Thus, the prevention of the nasal hemorrhage lies essentially in the preparation of a non traumatic intubation. Additionally, for patients under APA treatment, Eurin and Fischler^[86] advise orotracheal, as opposed to nasotracheal intubation, due to the fact that the former could be prepared in better condition.

3.2.2 Conservative dental treatments

Not a single incident of hemorrhage secondary to conservative treatments (restorative dentistry, endodontics or prosthodontics) on patients under APAs has been reported. The increase in the perioperative risk of bleeding on patients under APA treatment undergoing conservative dental treatments could be considered as being very low, or even non existent. Consequently, they do not require any supplementary precautions. Similarly, not a single case of perioperative hemorrhagic complication following, non surgical, periodontal treatment secondary to APA intake, has been reported in the literature. In case of a persistent postoperative bleeding, a local compression for 10 min. is recommended.

3.2.3. Oral, periodontal and implant surgery

The hemorrhagic risk related to dental extraction is a rare complication. The incidence of post-extraction hemorrhagic complications, including other risk factors, does not exceed the average of 0.2 and 2.3%^[79, 91, 100, 105]. In oral, periodontal and implant surgery, except in the case subsequent to an arterial trauma, hemorrhagic complications are limited in most cases to persistent, local dripping, along with the occurrence of hyperplasic clot, one that is not able to efficiently seal the vascular lesion, or even worse, more unaesthetic than serious ecchymoses^[23, 70].

Despite the absence of publications comparing the risk of bleeding when continuing the APA treatment, the increase in the associated bleeding risk seems very modest, provided that all the local preventive measure mentioned before are respected (local hemostasis, observation and postoperative advices).

No recent study provides evidence to a greater percentage of frequency or gravity of bleeding in the case of the continuation of the APA treatment during oral, periodontal or implant surgery.

The prevention of preoperative bleeding, during the operative period, lies in the application of general routine preventive measures, along with an adequate local hemostasis [25, 31, 33, 82, 93, 104, 108, 109].

Therefore, it is recommended to undertake non surgical periodontal treatments before every surgical operation, if necessary, in order to limit as much as possible the preoperative inflammatory state. During the surgical operation, the elimination of all of the granulation, inflammatory tissue is decisive. The curettage of the dental alveolus should be done with care, along with excision of the hyperplasic gingiva. In addition to these general, but imperative precautions, surgical hemostasis is recommended.

- **Surgical hemostasis**

Surgical hemostasis is a validated and quite simple procedure conceived for the prevention of the postoperative bleeding risk for patients under antithrombotic agents.

Its practical modalities on patients under APA treatment are unfortunately not yet well defined. Several therapeutic approaches are suggested: sutures + compression, sutures + resorbable haemostatic buffer + compression, sutures + fibrin glue. A list of the principal haemostatic agents available in France figure in annex to this text (Annex 2). It is important to note that tranexamic acid, in this particular indication of reduction of the bleeding risk in APA patients, undergoing oral, periodontal or implant surgery, has never been evaluated.

Moreover, not one study has compared the efficacy of different techniques of local hemostasis, for patients under APA treatment, having to undergo dental extractions. The only clinical study having dealt with this issue concludes that the hemorrhagic risk related to the pursue of treatment by aspirin could be controlled by the application of a resorbable haemostatic gauze, along with sutures and a local compression [2, 17]. There doesn't exist any equivalent study for thienopyridines and the other APAs.

Conclusively, despite the absence of pertinent clinical studies, it seems logical to propose the following imperative recommendations: suturing of the surgical wound, along with local compression. The application of resorbable local haemostatic buffer is highly recommended.

3.3 Postoperative period

Postoperative period represents one of the most important steps in the management of APA patients. It should not be neglected. It includes supervision, postoperative advices, and specific instructions on what the patient should do in case of postoperative bleeding.

3.3.1 Supervision and postoperative advices

The postoperative advices and instructions should be adapted to each patient's level of comprehension, and to the organization of the emergency services in a given region. A written form of information and postoperative advices could be prepared and given to the patient at the end of the operation, this is figured in annex to this text (Annex 3).

The initial postoperative period (the first 3 days) is the one with the most serious postoperative bleeding risk [23, 70, 107]. A clinical follow up within 24-48 h of the

operation, or simply a phone call, is recommended in order to insure the correct compliance of the postoperative recommendations.

3.3.2 Curative treatment of postoperative hemorrhagic complications

Hemorrhagic complications following an oral, periodontal or implant surgery, for patients under APA treatment, are most of the time of local origin and have a good prognosis. An incorrect surgical technique, the absence of a well-adapted surgical hemostasis, along with the non-respect of the postoperative recommendations all constitute the main causes of postoperative hemorrhages^[23, 70]. It is exceptional that a patient is addressed to an emergency service for an APA-related bleeding. Literature reports only two cases of serious hemorrhagic complications on patients under APA treatment, following an oral surgery^[30, 63].

Curative treatment of a postoperative hemorrhage lies in a surgical revision of local hemostasis, along with a clinical follow up. In case of failure of this revision of local hemostasis, or an affection of the general state of the patient, a hospital transfer is recommended. A hemostasis analysis is thus conducted in order to eliminate a haemostatic, non screened cause (liver disease, coagulation pathology...). There does not exist any known antidote to the pharmacological activity of aspirin, or clopidogrel^[68, 99, 113]. Some authors suggest desmopressine, or platelet transfusion^[30, 63], in order to correct the effects of the APAs. No present clinical study validates these findings.

4. Particular cases of aspirin at high doses

The intake of aspirin at daily doses superior to 500 mg corresponds to antalgic and /or antipyretic and/ or anti-inflammatory indications^[86, 99, 112, 113]. In such clinical situations, the therapeutic objective is no longer the prevention of thromboembolic complications. Hence, the interruption of aspirin intake could be envisaged without taking any risk, because there exists numerous alternatives to aspirin, for its antalgic and/or antipyretic and/ or anti-inflammatory indications.

At high doses, aspirin inhibits the synthesis of the platelet's TXA₂ (proaggregant), but also the synthesis of endothelial prostacycline (antiaggregant). Experimental studies seem to demonstrate equally that aspirin at high doses possesses both weak anticoagulant and fibrolytic properties^[27, 35, 45, 61, 106, 112].

Literature reports one single case of severe, hardly controllable, hemorrhage associated with the intake of aspirin at high doses. It concerns a male of 62 years, without a history of hemorrhage in particular, and who presented a severe and persistent bleeding, 24 hours following the extraction of 18 teeth. Platelet transfusion was necessary in order to stop the bleeding. The imputability of the aspirin has been cited by authors but was never established (existence of numerous risk factors for local hemorrhage).

Two double blinded trials have evaluated the risk of per and postoperative bleeding, associated with the intake of aspirin at antalgic doses during dental extractions. In both clinical trials, the number of patients is very small, 23 and 32 patients respectively. The first trial^[21], aspirin versus placebo, shows that the risk of peroperative bleeding is moderate with intake of 1g of aspirin the night before the operation and 2g.j⁻¹ in the

following 3 days. The second trial ^[57], aspirin versus paracetamol, concludes that the perioperative bleeding risk after the intake of 500 mg of aspirin the day before the operation and 2g.j⁻¹ in the following 3 days, is not more significant than in the paracetamol group.

Overall, conservative dental treatments are not contra-indicated when the patient is under aspirin at high doses. In the case of a planned surgical operation it is advised to stop the aspirin treatment and to postpone the operation for 5 days ^[74, 107], in case the haemostatic action is taken into account, or to postpone the surgery for 10 days to insure that the aspirin effect has completely disappeared ^[106, 109].

In an emergency context, and if an oral or periodontal operation is essential, it could be accomplished without prior interruption of the aspirin at high doses. When it comes to postoperative bleeding, the same attitude as that adopted for APA should be undertaken.

CONCLUSION

Management of patients under APA treatment has considerably evolved in a very little period of time. Until the year 2000, practically all authors have recommended the interruption of APA treatment prior to a surgical operation in order to limit the augmentation of the associated bleeding risk. The truth is, there was a tendency to underestimate the thromboembolic risk when compared to the hemorrhagic risk. Unluckily, retrospective studies have illustrated the occurrence of serious thromboembolic complications in the postoperative period (1-3 weeks), most probably resulting from the interruption of the APA treatment, even though in some cases flurbiprofene was used as a substitute. On the other hand, not a single study could provide evidence for a greater relative risk of hemorrhagic complications in the case of continuation of the APA treatment.

Consequently, it is now recommended not to interrupt APA treatment before undertaking either dental conservative treatment, or oral, periodontal or implant surgery. The continuation of APA treatment could be envisaged for the totality of the clinical situations faced with in odontostomatology, while keeping in mind a certain number of precautions (surgical hemostasis, recommendations and adequate postoperative follow up).

Finally, the control of the hemorrhagic risk should not make the practitioner disregard the other operative risks. Both a meticulous medical interrogation, along with a thorough clinical examination are crucial. Consultation of the opinion of the general practitioner or the specialist (neurologist, cardiologist...) is highly recommended for the correct evaluation of the cardiovascular risk. According to the act envisaged (dental cure, surgical operation), and to the severity of the cardiovascular pathology (recent ischemic complication, arrhythmia, rhythm and/or associated cardiac insufficiency), the practitioner should decide whether or not the treatment should be done in hospital environment. Only a global evaluation of the operative risk could guarantee an optimal management of patients under APA treatment in odontostomatology.

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Annex 1: A list of the APAs prescribed via oral intake, actually commercialized in France

Common international denomination	Specialty name	Use
Aspirin and salicylates		
Lysine acetylsalicylate	KARDEGIC 75 mg, 160 mg, 300 mg CARDIOSOLUPSAN 100 mg, 160 mg	<ul style="list-style-type: none"> • Alone - following an ischemic myocardial accident (angor, myocardial infarction) - following an aortocoronary bypass - following an ischemic cerebral attack (transitory or constituted ischemic attack)
Acetylsalicylic acid	ASPIRINE Project 300 mg ASPIRINE Upsa 325 mg CATALGINE 250 mg	
Aspirin + dipyramidol	ASASANTINE LP	<ul style="list-style-type: none"> • In association with dipyramidol - following an ischemic cerebral accident (transitory or constituted ischemic attack)

Thienopyridines		
Clopidogrel	PLAVIX 75 mg	<ul style="list-style-type: none"> • Alone <ul style="list-style-type: none"> - following a recent myocardial infarction - following a recent constituted ischemic cerebral accident - in case of an established obliterating arteriopathy of the lower limb • In association with aspirin <ul style="list-style-type: none"> - following an acute coronary syndrome without an elevation of the ST interval (instable angor or myocardial infarction without the Q wave)
Ticlopidine	TICLID 250 mg TICLOPIDINE Gé 250 mg	<ul style="list-style-type: none"> • Alone <ul style="list-style-type: none"> - following an ischemic cerebral accident - in case of a symptomatic chronic obliterating arteriopathy of the lower limbs - chronic hemodialysis (arterio-venous access) • In association with aspirin <ul style="list-style-type: none"> - following a myocardial revascularization with a stent graft

<i>Others</i>		
Dipyramidol	CLERIDIUM 150 mg PERSANTINE 75 mg + numerous generics	<ul style="list-style-type: none"> • In association with AVK - mechanical valvular prosthesis
Flurbiprofene	CEBUTIDE	<ul style="list-style-type: none"> • Alone - following myocardial infarction or myocardial revascularization, when the treatment by aspirin is momentarily contra-indicated

Annex 2: A list of the haemostatic medicaments that are active following local placement, available in France

Nomination	Composition	Forms and presentations	Acting mechanism	Use
<i>Local resorbable haemostatic</i>				
GELFOAM	Gelatinous	sponge	- these molecules stimulate platelet adhesion as well as the contact system of coagulation (activation of the XII factor, keniogen of low molecular weight)	- place in the alveolus and keep in place using sutures
PANGEN	Collagen* of bovine origin	compress reserved for hospital use		
SURGICEL	Oxidized regenerated cellulose	gauze		

Antifibrinolytics				
EXACYL drinkable solution SPOTOF Gé drinkable solution	Tranexamic acid	vial of 10ml	- tranexamic acid inhibits fibrinolysis (inactivation of the plasmin following its irreversible fixation to plasminogen)	
Biological glue (fibrin glue)				
BERIPLAST BIOCOLL TISSUCOL	<ul style="list-style-type: none"> • Solution A (tissucol): - fibrinogen - fibronectine - aprotinine of bovine origin - factor XIII - human plasminogen • Solution B (thrombin) - human thrombin 	<ul style="list-style-type: none"> - kit of 1- 2mL - after mixture of both solution, it results a viscous mixture which rapidly transforms into an elastic gel, of a whitish colour, strongly adherent to tissues - reserved for hospital use only. 	- fibrin glue reproduces the final phase of coagulation (transformation of fibrinogen to fibrin under the action of thrombin, and stabilization of the clot by the XIII factor), and inhibit fibrinolysis (aprotinin)	- place in the alveolus and maintain in place using sutures.

Miscellaneous (therapeutic effects not evaluated by controlled studies)				
ARHEMAPECTINE	Pectine	vial of 20ml	- non defined	- as a mouth rinse - by blotting using a compress
REPTILASE	Hemocoagulase	vial of 1ml	- extract of a snake venom with pro-coagulation properties	- by blotting using a compress

*There exists numerous dental product containing collagen:

- of bovine origin: COLLAGEN Z (Atozine Laboratory), CURACOLL (Curaspon Healthcare Laboratory), BIOCLOGEN (Biodica Laboratory), ETIK COLLAGEN (Pierre Roland Laboratory), HEMOCOLLAGEN (Septodont Laboratory), HERMACOL (Spad Laboratory)
- of equine origin: ANTEMA (Odopharm Laboratory)
- of synthetic origin: BLEED-X (Dentsply Laboratory).

Annex 3: Example of postoperative recommendations that could be handed to the patient

This document is destined to inform you about the continuation of your antiplatelet treatment, its advantages and risks. We thus invite you to read it carefully.

What are the advantages of the continuation of your antiplatelet treatment?

Daily intake of your antiplatelet treatment limits the risk of recurrence of a thromboembolic accident (angina pain, myocardial infarctus, cerebral vascular accident, inferior limb claudication). Its interruption even for a couple of days, for a dental extraction for example, cannot be estimated free of risk. Its preservation is hence justified and recommended.

What are the inconveniences and risks related to its continuation?

The continuation of your antiplatelet treatment increases the risk of postoperative bleeding. This risk is easily controllable during extraction by the execution of local hemostasis. On the other hand, the preservation of the blood clot in its place requires additional precautions from your side.

What are the postoperative measures to be respected?

You must:

- Take the medication prescribed to you.
- Apply an ice bag against the operated region, as soon as the treatment is over.
- Privilege a soft and cold or half-cold diet during the first week following the operation (for example: eggs, pasta, puree, ham, dried meat, jam, yogurt, cream, ice-cream...)
- In case of prescription of antiseptic mouth rinses, you should do them in a passive manner, without any gargling or tightening of the cheeks, in order not to provoke bleeding.
- Brush your teeth normally while avoiding to disturb the operated region.

What one should not do:

- smoke or drink alcohol because both delay healing
- carry out antiseptic mouth rinses on the day of the operation
- carry out antiseptic mouth rinses in order to stop bleeding.
- use the tongue to touch the wound, suck or spit.

Don't worry if:

- you see the first days blood stains on your pillow
- you spit during the first days small quantities of blood.
- you develop a blue stain, a hematoma.
- you bleed: in this case, bite hard on a sterile compress for about 20 min, to renew if necessary

In case of incontrollable bleeding:

- you should contact the following phone number...
- in case of absence, do not hesitate to show up at the hospital emergency service (public, private), or consult your own physician.