Dabigatran: A new oral anticoagulant. Guidelines to follow in oral surgery procedures. A systematic review of the literature

Marta Muñoz-Corcuera 1, Lucía Ramírez-Martínez-Acitores 2, Rosa Mª López-Pintor 3, Elisabeth Casañas-Gil 4, Gonzalo Hernández-Vallejo 5

1 DDS, PhD. Assistant professor. Oral medicine specialist, Complutense University, Madrid, Spain
2 DDS. Assistant professor. Oral medicine specialist, Complutense University, Madrid, Spain
3 DDS, PhD. Associate professor. Department of Oral medicine and Orofacial surgery. Faculty of Odontology. Complutense University, Madrid, Spain
4 DDS, PhD Student. Assistant professor. Oral medicine specialist. Complutense University, Madrid, Spain
5 MD, DDS, PhD. Professor. Department of Oral Medicine and Orofacial Surgery. Faculty of Odontology. Complutense University. Madrid, Spain

Correspondence:
Departamento de Medicina y Cirugía Bucofacial
Facultad de Odontología
Universidad Complutense de Madrid
Plaza Ramón y Cajal s/n
28040 Madrid, Spain
martamcorcuera@gmail.com

Received: 21/12/2015
Accepted: 20/07/2016

Abstract
Background: Dabigatran is a newly commercialized drug that is replacing other anticoagulants in the prevention of venous thromboembolism, stroke and systemic arterial valve embolism. It acts directly on thrombin presenting in a dynamic and predictable way, which does not require monitoring these patients. Therefore, we consider the need to assess whether their use increases the risk of bleeding involved before any dental treatment.

Material and Methods: We performed a systematic review with a bibliographic search in PubMed/Medline along with the Cochrane Library. We excluded articles dealing with all anticoagulants other than dabigatran, and works about surgical treatments in anatomical locations other than the oral cavity.

Results: We included a total of 13 papers of which 1 was a randomized clinical trial, 9 narrative literature reviews, 1 case series, 2 clinical cases and 1 expert opinion. Because we did not obtain any properly designed clinical trials, we were unable to conduct a meta-analysis.

Conclusions: Currently, there is no consensus on the procedure to be followed in patients taking dabigatran. However, all authors agree to treat each case individually in accordance to the risk of embolism, postoperative bleeding and renal function. Also, it is necessary to perform minimally invasive interventions, and take the appropriate local anti-hemolytic measures.

Key words: Oral anticoagulants, dabigatran, risk of bleeding, oral surgery, dentistry.
**Introduction**

Atrial fibrillation is the most common cardiac arrhythmia and a major cause of stroke in the United States and Europe. There is an estimated 2.2 million people suffering from this disease in the United States, and 4.5 million in Europe. In patients with atrial fibrillation, 80% of heart attacks cause death or disability, and mortality per year reaches 50%. Vitamin K antagonists such as warfarin and acenocoumarol are very effective in preventing strokes in patients with atrial fibrillation, and have been for many years; thus being the only drugs available for long-term anticoagulant therapy (1,2). Warfarin and acenocoumarol exert its anticoagulant effects by reducing the levels of prothrombin and factor X; whereas heparin acts by binding to antithrombin and enhancing its ability to inhibit thrombin (Fig. 1).

With regards to heparin, its main disadvantage is that it causes an indirect inhibition of thrombin unpredictable, as it is dependent on the availability of antithrombin. On the other hand, warfarin has its drawbacks with a narrow therapeutic window (the range in which a drug can be used without causing toxic or lethal effects on a living organism), the need to monitor the state of anticoagulation of a patient by controlling the International Normalized Ratio (INR), the numerous food and drug interactions, lack of direct action on coagulation proteins and high start activity time and its removal (3-5). This large amount of disadvantages has been the basis for the development of new oral anticoagulants, which act directly inhibiting thrombin (1-6).

Dabigatran etexilate (Pradaxa, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT), is a direct thrombin inhibitor, which was approved by the European Medicines Agency in 2008, and the Food and Drug Administration (FDA) in October 2010 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, as well as, for the prevention of venous thromboembolism after orthopedic surgery for total hip replacement or knee (4).

However, patients taking warfarin or acenocoumarol have a pattern of reduction of the drug and a reference INR values that can be followed without the patient’s risk of bleeding during dental procedures; yet there are no guidelines for managing patients taking dabigatran before dental procedures that can cause bleeding. The aim of this paper is to perform a systematic review and meta-analysis summarizing if the use of dabigatran increases the risk of bleeding before dental procedures that involve bleeding, and if that risk is greater than that produced by conventional anticoagulants.

**Material and Methods**

- Defining the questions:
  - To carry out this systematic review the questions we asked ourselves were as follows:
  - Does the use of dabigatran increases the risk of bleeding when performing dental treatments which involve bleeding?; Is the risk of bleeding before such dental procedures involving bleeding greater than that produced by classic anticoagulant treatments such as heparin and warfarin?, and are there protocols for handling patients who take dabigatran prior to dental procedures that involve bleeding?

- Search strategy:
To carry out this systematic review we conducted a literature search in PubMed / Medline, and Cochrane Library databases using key words “dabigatran” AND “dentistry” and “dabigatran” AND “oral surgery”. Only papers with human subjects were selected. The titles and abstracts that resulted from the search were reviewed, and full-texts papers that were considered relevant to the review were read. Two authors (MMC and LRM) reviewed the papers selected independently. We compared the lists, and when in disagreement, underwent discussion based on the inclusion and exclusion criteria. We then sought manually for additional papers reviewing the references on selected articles.

- Inclusion and exclusion criteria:

Inclusion criteria:

All articles published in English, that discuss the risk of bleeding from dabigatran after dental treatment, were included. We included narrative reviews, case reports, case series, case-control studies, prospective studies, randomized clinical trials, and systematic reviews. We searched articles published in the last 10 years. The last electronic search was conducted in 15th October 2015. We selected only studies conducted in adult patients.

Exclusion criteria:

Studies were excluded if they were published in a language other than English. Papers that assessed the bleeding caused by other anticoagulants (apart dabigatran) were rejected. We did not include studies realized in animals.

- Quality assessment

In the final selection of eligible studies, we assessed features that could potentially bias following the recommendations by Cochrane for assessing risk of bias. Critical appraisal was conducted by two reviewers (MMC and LRM) independently of each other. The reviewers met to discuss the results of their critical appraisal, if the two reviewers disagreed on the final critical appraisal and could not be resolved through discussion, a third reviewer (RLP) was required.

Results

In figure 2, the search strategy and article selection is discussed. A total of 13 papers were included, 1 randomized clinical trial, 9 narrative literature reviews, 1 case series, 2 clinical cases, and 1 expert opinion (Table 1).

We only found two papers that responded to the question: Does the use of dabigatran increase the risk of bleeding in dental treatments that involve bleeding? The papers selected were two clinical cases, therefore of very poor methodological quality. Regarding the answer to the question: Is the risk of bleeding before dental procedures that involve bleeding in patients taking dabigatran greater than that produced by classical anticoagulants (heparin and warfarin)? We could not find any papers that specifically answers that question; the study by Healy (7) in 2012 includes dental procedures among those evaluated, but does not specify subsequent bleeding complications specific to the type of surgery that the patients underwent. And yes, there are studies that answer the question, are there protocols for handling patients (taking dabigatran) before dental procedures that involve bleeding?

All the studies reviewed provide different protocols for managing these patients, but none of these papers are based on results of methodological, well-designed studies, just mere opinions and recommendations from commercial brands and/or experts.

Because we could not get properly designed clinical studies, we were unable to do a meta-analysis. We will describe in a summarized manner each of the selected papers.

Gómez-Moreno et al. (8) in their review in 2010, mentioned the lack of practical guidelines, as well as a lack of protocol to reduce drug dosage before dental procedures, and the importance of local hemostatic measures. Also, they emphasize among the advantages of dabigatran that it is a drug that does not interfere with antimicrobial antibiotics, most widely used in dentistry nowadays.

In the review by Little et al. (9) in 2012, in light of the revised articles, the authors conclude that patients treated with dabigatran may undergo invasive dental procedures without altering the dose of the medication. The dentist should consult the patient’s physician to plan the procedure, and confirm whether the patient will continue with the same dose after surgery. To manage possible bleeding, local measures should be used. In cases requiring extensive oral surgery, it is important to consult with the patient’s physician to determine an action plan, in order to prevent thromboembolism, as well as, excessive bleeding.

Firriolo and Hupp (10), in 2012 and Davis et al. (11), in 2013 also published reviews and recommendations based on other authors’ recommendations, as well as, the pharmacological properties of dabigatran; and they noted that it does not seem necessary to remove the drug prior to dental treatment, especially if local and adjuvant hemostatic measures are taken (suture, gelatin or cellulose sponges, tranexamic acid rinses at 4.8% for 2-5 days). However, in cases where excessive bleeding or hemostatic problems are expected, dabigatran should be removed at least 24 hours before surgery or more depending on the risk of bleeding, renal function, and the presence of other conditions they could increase the bleeding (Table 2). Due to the anticoagulant effect, that quickly establishes, the drug should not be taken immediately after surgery, instead once the clot is stabilized (24-48 hours after surgery).

Weitz et al. (12) in 2012 published a case study of a patient taking dabigatran which presented bleeding com-
Dabigatran and oral surgery

dilations. In the article, the authors do a systematic reviewed and include recommendations for minor surgical procedures, such as no drug withdrawal in dental cleanings and extractions, and to do such procedures more than 10 hours after taking last dose of the drug.

Van Diermen et al. (13) in 2013 conducted a review aimed at finding dental studies regarding the management of anticoagulated patients, including those taking new anticoagulants; and to propose a patient management guide for general practitioners. Regarding dabigatran in patients subjected to simple dental treatments (up to 3 extractions, up to 3 implants, scaling and root planning, flap surgeries, alveoloplasties and apicectomies), the authors made the following recommendations: To not stop taking dabigatran; Warn patients not to take their medication within 3 hours immediately after surgery; and adopt local, pre and post-operative measures, such as minimizing surgical trauma, suture wounds, the use local hemostatics or apply pressure locally; also providing the patient with written instructions on how the post-operative measures should be, and the steps that the patient should take if he/she experiences bleeding.

Cohen et al. (5) in 2013 conducted a review and developed a small clinical management guide; they advised that the correct clinical care at the dental office should begin by writing a thorough medical history of the patient, collecting any previous episodes of excessive bleeding associated with anticoagulants or diseases of any kind. These authors suggest that basic oral surgery procedures such as few tooth extractions or localized periodontal surgery must be done at the first visit to assess the bleeding, followed by local hemostatic measures such as suture or gelatin sponges. If surgery is more complex or major bleeding is expected, one should consider withdrawing the drug for 48 hours, and after
consulting with the patient’s physician. If the procedure post-operative healing is good, the patient could continue the medication the day after surgery. All these guidelines relate to a healthy patient without kidney or liver disease; in such cases, the drug should be withdrawn 4-5 days depending on the physician’s suggestions. Kerr et al. (14) published in 2013 a letter in which, as experts, proposed a management guide that suggests to not withdraw the medication, requiring the use of atraumatic extraction techniques, limiting the number of teeth extracted in the same procedure to 3-4, and local hemostatic measures (sutures, local pressure and local hemostatics). With this, they consider the treatment will be safe in a regular dental practice. It is also noted that such patients with recently placed stents, liver or kidney failure, alcohol problems, medicated with cytotoxic drugs and with clotting problems, should have the practitioner consult their physician before performing any dental procedures that cause bleeding.

Romond et al. (15) in 2013 published the case report of a patient who had eight dental extractions and preprosthetic surgery (alveoloplasty and remodeling of the tuberosity in the maxilla) who was also taking dabigatran. In this case, the patient withdrew dabigatran 24 hours before the procedure, and surgery was performed under intravenous sedation and local hemostatic measures were taken, such as the use of local anesthesia with vasoconstrictor, gelatin sponges, suture and placement of the immediate prosthesis. There was no excessive bleeding or clotting problems in this case, making the healing process correct. The authors note that having no agent to reverse the action of dabigatran is sufficient reason for withdrawing the medication when the procedure is more invasive than 2-3 extractions.

Breik et al. (16) in 2014 published a guide of recommendations based on a series of cases of 5 patients who had single and multiple extractions. These authors recommended to not removing the dabigatran in pro-

| Author                | Year  | Country of Publication | Type of publication               |
|-----------------------|-------|------------------------|----------------------------------|
| Gómez-Moreno et al. (8) | 2010  | Spain                  | Narrative review                  |
| Little et al. (9)      | 2012  | United States          | Narrative review                  |
| Firriolo and Hupp (10) | 2012  | United States          | Narrative review                  |
| Weitz et al. (12)      | 2012  | United States          | Clinical case and review          |
| Healey et al. (7)      | 2012  | United States          | Randomized clinical trial         |
| Van Diermen et al. (13)| 2013  | United States          | Narrative review                  |
| Coehn et al. (5)       | 2013  | United States          | Narrative review                  |
| Davis et al. (11)      | 2013  | Canada                 | Narrative review                  |
| Kerr et al. (14)       | 2013  | United Kingdom         | Expert’s opinion                  |
| Romond et al. (15)     | 2013  | United States          | Clinical case                     |
| Breik et al. (16)      | 2014  | Australia              | Case series                       |
| Curtin et al. (17)     | 2014  | United Kingdom         | Narrative review                  |
| Sivolella et al. (18)  | 2015  | Japan                  | Narrative review                  |

Table 2. Guide to discontinue use of dabigatran prior to surgical procedures.

| Renal function (creatinine clearance ml/min) | Dabigatran’s half life (h) | Risk of standard bleeding | High risk of bleeding |
|---------------------------------------------|---------------------------|---------------------------|-----------------------|
| >80                                         | 13 (11-22)                | 24h                       | 2-4 days              |
| >50 to <80                                   | 15 (12-34)                | 24h                       | 2-4 days              |
| >30 to <50                                   | 18 (13-23)                | >48h                      | 4 days                |
| <30 *                                        | 27 (22-35)                | 2-5 days                  | >5 days               |

* Dabigatran is contraindicated in these patients.
Dabigatran is administered as a prodrug, dabigatran etexilate, which has a rapid absorption via gastrointestinal tract, and quickly becomes dabigatran; 20% of the drug is metabolized in the liver, and 80% is excreted primarily by the kidneys; thus having a half-life of about 12 to 17 hours. Patients with a creatinine clearance <50 ml/min may have a longer elimination and higher drug levels in plasma. In patients with severe renal failure (creatinine clearance <30 ml/min), dabigatran should be used with caution or contraindicated (3,4,9,11,15).

Dabigatran’s peak effect occurs two hours after administration of the first dose, reaching a state of stability 3 days after starting treatment with a regular dosage (e.g., 150 mg twice daily). The effect duration is approximately 22 hours.

The advantage of this drug is that it does not need motorization of the patient by means of coagulation tests (INR), thus far, introducing stable and predictable pharmacodynamics 5,9. However, there is no coagulation measurement that could accurately predict the degree of anticoagulation in a patient medicated with dabigatran, and there are no guidelines for routine monitoring of coagulation in these patients (3,5,13).

Moreover, there is no consensus on what lab test is more effective to assess the clotting level in a patient, since measuring INR, a test familiar to physicians, does not display correctly the degree of coagulation of the patient (17,19). The most accessible laboratory tests to determine the presence or absence of anticoagulant effect in patients taking dabigatran in case of emergencies are the aPTT and TT (15,19); however, the most appropriate and sensitive test to quantify the anticoagulant effect of this drug are ECT, dTT (diluted thrombin time) and the trial thrombin inhibitor Hemoclot ® (Hyphen BioMed, Neuville-sur-Oise, France) (10,18,19).

In Europe, dabigatran has been approved for the prevention of venous thromboembolism after orthopedic surgery, such as total hip or knee replacement, and the prevention of stroke and systemic arterial embolism in high-risk patients with non-valvular atrial fibrillation (1,2,11,12,18).

A meta-analysis conducted in 2012 by Miller et al. (20) on the efficacy and safety of new anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation, found that new anticoagulants are more effective than warfarin for the prevention of stroke and systemic arterial embolism in patients with atrial fibrillation. Also they noted that intracranial hemorrhage risk is less, and therefore, have a higher safety than warfarin. Nevertheless, Healy et al. (7) have determined that dabigatran has an increased risk of bleeding when the patient is subjected to an urgent surgical procedure; in non-urgent cases, the risk of bleeding is similar in both dabigatran and warfarin.

Dabigatran is well tolerated in single and multiple doses.
Table 3. Summary of papers regarding patients taking dabigatran who are undergoing dental procedures that cause bleeding.

| Author and year | Withdrawal of dabigatran or not | Prior measures | Subsequent measures |
|-----------------|---------------------------------|----------------|---------------------|
| Little et al. (9) 2012 | No withdrawal | Consult with patient’s healthcare physician. | Local measures |
| Firriolo and Hupp (10) 2012 | No discontinue if low risk of bleeding and normal renal function. Discontinue use 24 hours prior if there is high risk of bleeding Discontinue use 1-5 days prior depending on renal function Resume use 24-48h after | Tests: TT and aPTT Consult with patient’s physician. | Cautious prescription of NSAIDs, opioid analgesics and macrolides. Sutures, gelatin or cellulose sponges tranexamic acid. |
| Weitz et al. (12) 2012 | No withdrawal. Perform cleanings or extractions 10 hours after last dose | | |
| Van Diermen et al. (13) 2013 | No withdrawal for simple procedures (up to 3 extractions, 3 implants, scaling and root planning, flap surgeries, apicectomies and alveoplasties) | Consult with patient’s healthcare physician. | Local measures: minimize trauma, suture wounds, local pressure, local hemostatics. |
| Coehn et al. (5) 2013 | Minor periodontal surgery or less than 3 extractions: do not withdraw. Mayor surgery or more than 3 extractions: remove 48 hours prior to and resume 24 hours after procedure (normal renal function). | Detailed medical history. Consult with patient’s physician. | Sutures, gelatin hemostatic sponges. |
| Davis et al. (11) 2013 | Do not discontinue if low risk of bleeding and normal renal function. Discontinue use 24 hours before if high risk of bleeding. Discontinue 1-5 days before according to renal function Resume 24-48h after | Tests: TT and aPTT Consult with patient’s healthcare physician | Sutures, gelatin or cellulose hemostatic sponges, Sutures, gelatin or cellulose hemostatic sponges, mouthrinse with 5% tranexamic acid. |
| Kerr et al. (14) 2013 | No | Consult with patient’s physician. | Suture, local compression and hemostats. |
| Romond et al. (15) 2013 | Discontinue 24 hours before if there is high risk of bleeding | | Sutures, local hemostatics and compression, local anesthesia with vasoconstriction |
| Breik et al. (16) 2014 | Do not discontinue in cleanings, root canals, fillings with matrices or extractions of one tooth. Multiple extractions: assess withdrawal 24 hours before. Resume 24-48h after | Tests: TT and aPTT Consult with patient’s physician | Mechanical pressure, sutures and local hemostatic |
| Curtin et al. (17) 2014 | Surgeries with low risk of bleeding: do not withdraw. If withdrawal, monitor renal function and consult with patient’s physician. | Consult with patient’s physician | Mouthrinses with tranexamic acid |
| Sivolella et al. (18) 2015 | Do not withdraw if low risk of bleeding and normal renal function. Discontinue use 24 hours before if high risk of bleeding. Discontinue use 1-5 days before according to renal function. Resume 24-48h after | Consult with patient’s physician | Local measures |
| Gómez-Moreno et al. (8) 2015 | There are no recommendations | Consult with patient’s physician | Local measures |
without occurrence of serious adverse effects. Minor adverse reactions include headache, gastrointestinal disturbances, peripheral edema, back pain, arthralgia, nasopharyngitis and insomnia (3,11). There is a high incidence of dyspepsia, gastritis-like symptoms, and hypersensitivity reactions (4,9).

Dabigatran has few interactions that are relevant from a clinical point of view. Rifampicin reduces the anticoagulant effect of dabigatran, and as can also do other inducers of P-glycoprotein such as dexamethasone and carbamazepine. Inhibitors of P-glycoprotein as ketoconazole, itraconazole, erythromycin, clarithromycin, verapamil and amiodarone tend to increase the anticoagulant effect. Its use with other anticoagulants, antiplatelet agents, NSAIDs, salicylates and certain herbs (alfalfa, anise...) do not pose an interaction, but they can increase the risk of bleeding, and therefore, should be avoided. Drugs that can be used to control pain in patients taking dabigatran are opioids or acetaminophen (9-11).

In conclusion, we can add that the advantages of dabigatran are speed of action, the wide therapeutic window, the low potential to cause interactions with other drugs or foods, and predictable anticoagulant effect, which eliminates the need for routine patient monitoring and management of the drug in fixed-doses (18).

On the other hand, its disadvantages include the patient in treatment with dabigatran should comply strictly with taking scheduled doses (4,9). In addition, there is a high incidence of dyspepsia, gastritis-like symptoms and hypersensitivity (urticaria, rush, pruritus and anaphylactic shock) (4,8). It has also been seen, when compared with warfarin, the bleeding risk is greater when the patient undergoes a surgical procedure (7). In cases of major bleeding, there is no antidote to reverse the anticoagulant effect (4,9); although some researchers have recently identified a possible antidote, an antibody fragment a Dabi-Fab, which directly neutralizes dabigatran (21).

- Management of patients anticoagulated with dabigatran prior to dental procedures that involve bleeding. There is no consensus regarding how to manage a patient medicated with dabigatran who needs to undergo a surgical procedure. However, all authors agree that we should individualize each case taking into consideration the risk of bleeding during surgery, along with the risk of embolism (if we discontinue the medication) and renal function of the patient.

Healey et al. (7) in 2012 conducted a randomized clinical trial which compared the risk of bleeding after surgical procedures (including oral surgery as well) in patients taking dabigatran and patients taking warfarin, and came to the conclusion that bleeding complications are similar in both cases. Authors like Golembiewski advise that dabigatran should be discontinued before any surgical procedure that could have a bleeding risk. Drug withdrawal time is dependent on such bleeding risk, (standard or high) and renal function of the patient (4).

Unlike what happens with antiplatelet and anticoagulants such as warfarin or acenocoumarol, for which there are clear guidelines for action on withdrawing or not the medication, as well as pre and postoperative measures taken with patients in the dental practice (5,13); nowadays there are recommendations for dabigatran based only on the pharmacological properties of the drug, and on experiences with isolated case reports or small groups of patients.

Almost all of the studies reviewed focus on patient management during extractions, with no papers and no specific recommendations for other oral treatments that produce bleeding, such as dental cleanings or scaling and root planning.

In cases in which minor bleeding occurs after surgery, it is recommended to postpone the next dose of the drug and adopt local measures. If bleeding is severe, treatments available at the hospital level include mechanical compression, surgical interventions, fluid replacement, hemodynamic support, intake of activated carbon and hemodialysis (2).

In view of this systematic review, in which we have found no reliable clinical data derived from clinical trials and general recommendations for the management of these patients in the dental office, we could include the following recommendations (Table 4):

- Always perform a thorough medical history, in which both the dose and the cause of drug intake are noted. It must include diseases related to coagulation disorders, such as liver disease. Before any procedure in which we anticipate bleeding, one should consult with the patient’s physician to develop a joint plan of action. This plan could include coagulation testing; it seems that the most appropriate and accessible tests in the case of dabigatran are TT and aPTT.

To decide whether or not to withdraw the drug before surgery, one must assess the risk of bleeding from the dental treatment and the patient’s renal function. Depending on the type of treatment to be performed, the practitioner must consider certain variables to establish the risk of bleeding. When extracting teeth, one will have to assess the number of teeth, the difficulty of the extractions, and the need for flaps. In case of implants, the number of implants to be placed will be assessed, if they are going to be placed in the maxilla or mandible (as the risk of bleeding will be different), and the need for mucoperiosteal detachment. In periodontal therapy one should assess gingival inflammation, plaque index (PI) and pocket probing depth (PPD). If it is necessary to biopsy soft tissue, one should consider the anatomical area from which the sample is going to be taken, the size of the tissue to be removed, and whether or not suturing the area. As for restorative dentistry, if neces-
necessary to perform any subgingival restoration, it would be advisable to reduce gingival inflammation prior to restoration to lessen the risk of bleeding.

As discussed in other papers, it is necessary to perform a procedure as atraumatic as possible and after surgery, local measures such as the use of sutures, gelatin or cellulose sponges, tranexamic acid rinses and local pressure should be applied.

As for prescription medication, one should be cautious with opioid analgesics and macrolides; and azole antifungals are contraindicated. Overall, one should prescribe paracetamol as analgesic and should avoid aspirin and NSAIDs, and prescribe paracetamol. If great post-operative pain is expected, associate paracetamol and codeine (in moderation because it is an opioid). In case of great post-surgical inflammation expected, evaluate the use of locally injected corticoids.

It will be important to consider the risk of embolism and postoperative bleeding, and renal function of the patient. All procedures should be as minimally invasive as possible and appropriate local anti-hemolytic measures should be taken. However, more properly designed studies should be designed to determine a common protocol for treating these patients, just as we have for patients treated with warfarin or acenocoumarol.

**References**

1. Quintero Gonzalez JA. Fifty years of clinical use of warfarin. Invest Clin. 2010;51:269-87.
2. Zheng Y, Sorensen SV, Gonschior AK, Noack H, Heinrich-Nols J, Sunderland T, et al. Comparison of the cost-effectiveness of new oral anticoagulants for the prevention of stroke and systemic embolism in atrial fibrillation in a UK setting. Clin Ther. 2014;36:2015-28.
3. Nishio H, Ieko M, Nakabayashi T. New therapeutic option for thromboembolism—dabigatran etexilate. Expert Opin Pharmacother. 2008;9:2509-17.
4. Golembiewski JA. Dabigatran: a new oral anticoagulant. J Peri-anesth Nurs. 2011;26:420-3.
5. Cohen HV, Quek SY, Subramanian G, Abbas A. New antiplatelet and anticoagulant drugs. Considerations for dental patient management. JNJ Dent Assoc. 2013;84:30-3.
6. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al. American College of Chest Physicians. Prevention of VTE in non-surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e195S-226S.
7. Healey JS, Eikelboom J, Douketis J, Wallentijn L, Oldgren J, Yang S, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. Circulation. 2012;126:343-8.
8. Gómez-Moreno G, Aguilar-Salvatierra A, Martín-Piedra MA, Guardia J, Calvo-Guirado JL, Cabrera M, et al. Dabigatran and rivaroxaban, new oral anticoagulants, new approaches in dentistry. J Clin Exp Dent. 2010;2:e1-5.
9. Little JW. New oral anticoagulants: will they replace warfarin? Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113:575-80.
10. Firiolo FJ, Hupp WS. Beyond warfarin: the new generation of oral anticoagulants and their implications for the management of dental patients. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113:431-41.
11. Davis C, Robertson C, Shivakumar S, Lee M. Implications of Dabigatran, a direct thrombin inhibitor, for oral surgery practice. J Can Dent Assoc. 2013;79:74.
12. Weitz JI, Quinlan DJ, Eikelboom JW. Periprocedural management and approach to bleeding in patients taking dabigatran. Circulation. 2012;126:2428-32.
13. Van Diermen DE, van der Waal I, Hoogstraten J. Management recommendations for invasive dental treatment in patients using oral antithrombotic medication, including novel oral anticoagulants. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;116:709-16.
14. Kerr R, Ogden G, Sime G. Anticoagulant guidelines. Br Dent J. 2013;214:430.
15. Romond KK, Miller CS, Henry RG. Dental management considerations for a patient taking dabigatran etexilate: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;116:e191-5.
16. Breik O, Cheng A, Sambrook P, Goss A. Protocol in managing oral surgical patients taking dabigatran. Aust Dent J. 2014;59:296-301.
17. Curtin C, Hayes JM, Hayes J. Dental Implications of new oral anticoagulants for atrial fibrillation. Dent Update. 2014;41:526-31.
18. Sivolella S, De Biaggi M, Brunello G, Berengo M, Pengo V. Managing dentoalveolar surgical procedures in patients taking new oral anticoagulants. Odontology. 2015;103:258-63.
19. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, et al. Dabigatran etexilate--a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010;103:1116-27.
20. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. Am J Cardiol. 2012;110:453-60.
21. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, Park J, et al. A specific antidote for dabigatran: functional and structural characterization. Blood. 2013;121:3554-62.

Conflict of Interest
The authors have declared that no conflict of interest exist.