

## Dabigatran for Dental Procedures in Patients with High Risk Bleeding

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### ABSTRACT

**Background:** Management of patients with high risk of bleeding during oral and dental procedures faces many challenges. The aim of this study was review strategies for facing high risk of bleeding patients taking dabigatran under dental procedure.

**Methods:** Articles and scientific texts will be searched in the six main databases, such as PubMed, Scopus, Web of Science, Science Direct, Google Scholar and Cochrane Library from 2007 to 2022, with keywords “dabigatran” AND “bleeding” AND “dental procedures” OR “dental care”. The inclusion criteria for articles included in the study were papers published about treatment patients with dabigatran and undergoing a dental procedure, English language and design of case reports, case series, quasi-experimental studies and clinical trials. This study was performed using PRISMA.

**Results:** At first, 43 references included and finally 8 articles that met the inclusion criteria were select. CASP and STORBE checklists used for quality evaluation. Two reviewers checked eligibility of the selected articles, separately. Challenging Controversial results were found in selected studies. 4 studies demonstrated that Dabigatran should be interrupted at least 12 hours before invasive dental procedures. Some studies highlight that discontinuing Dabigatran depends on the patient's renal function. Also, it showed that deciding whether to stop Dabigatran or not by cardiologists determine based on elective or emergency high-risk patients.

**Conclusions:** Based on the results of the included studies, it is better to decide to stop or continue dabigatran before any dental treatment based on the type of intervention, the risk of bleeding and the patient's clinical situation. However, is preferred to discontinue taking this drug in high risk of bleeding dental procedures.

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## Introduction

Recently, Novel Oral Anticoagulants (NOACs) include dabigatran have been introduced clinic for patients with situation that need use of long term anticoagulant therapy included pulmonary embolism, venous thrombosis, atrial fibrillation, valves replacement [1-3]. The use of Due to changes in blood homeostasis and anticoagulant effects, these drugs may have a danger of thromboembolism or bleeding in patients [1].

The risk of post-operative bleeding in patients undergoing dental procedures is almost 1% [1-2]. In patients that continue using oral anticoagulants, there is the possibility of 9% of bleeding and 3.5% of serious bleeding that could not be controlled by local homeostatic agents [1]. Thus, the critical issue for a dentist is considering the risks of bleeding associated with varies types of dental procedures and the possibility of thromboembolic events for each patient [4-7].

According to the report published by the American Dental Association (ADA) 2018, there is not enough evidence regarding the pre-procedural strategies for management of patients using direct oral anticoagulants, who are undergoing dental procedures especially high risk of bleeding cases. Most patients on dabigatran is related to old age which result in rise incidence of dental disorders and surgical procedures. So, the assessed of the risks of bleeding (continue dabigatran) or thromboembolism (discontinue dabigatran) is an important issue. There has been a debate whether to stop dabigatran prior to a dental procedure and accepting the hazard of thromboembolic incidents or to continue taking them and accepting the risk of bleeding.

So, the aim of this systematic review was to analyze the best strategy for high risk of bleeding patients that use dabigatran undergoing a dental procedure.

## Methods

This systematic review was conducted based on reporting items for systematic reviews and meta-analysis protocol (PRISMA) ([www.prisma-statement.org](http://www.prisma-statement.org)) of 2022. A systematic review trend consists of background information, study question, inclusion and exclusion criteria, search strategy, study selection and evaluate items, retrieving the selected studies, extracting the relate data, appraising the retrieved studies, merging the data.

### Search strategy

To purpose of present study, an absolute search of main databases was done. Six electronic databases including Scopus, PubMed, Web of Science, Science Direct, Cochrane library and Google Scholar were searched. Including articles published in 2007-2022. The words

used were “dabigatran”, “bleeding” and “dental procedure” with the “and” or “OR” Boolean operator. Example of search strategy in Pub Med showed in Box 1. Also, asked to experts about verifiable grey literatures. Then, selected databases and grey literatures will be searched. After search for articles, we searched the reference lists of the included articles. Eventually, managed search library with use EndNote software version X8. Also, find duplications, and extract irrelevant articles done with this software.

### Inclusion & exclusion criteria

The inclusion criteria: 1. the papers published as a full text. 2. Papers with English language. 3. Papers published as case reports, case series or quasi-experimental studies and clinical trials.

Exclusion criteria: 1. assessing dental procedures with risk of bleeding as low and moderate. 2. Guidelines, letters, and news studies.

### Data extraction and analysis

The initial literature search gather nearly 43 references. At first, 4 duplications were set aside by the one author via EndNote software version X22. Then, after elapsing the titles of the articles, 38 articles with inclusion criteria (at least one) were selected and articles with exclusion criteria (at least one) were omitted. After reviewing abstracts of remain articles, 20 articles were maintained. At the next step, search the full texts of the maintain articles and inclusion and exclusion criteria assessed. At the end, the quality evaluation of the selected articles was done with CASP and STORBE checklist.

Two reviewers assessed the eligibility of the selected articles, separately. If both referees agree that the article meets the inclusion criteria, it was remain in our systematic review. Finally, 8 studies were included in our systematic review. (Figure 1) demonstrates a flowchart for the process of study selection.

### Data extraction and analysis

Due to the heterogeneity of the results of selected articles and the number of repeated or non-independent samples, meta-analysis was not possible to analyze data. Therefore, data analyzed with descriptive analysis. Summary of selected articles described in (Table 1).

### Novel Oral Anticoagulants

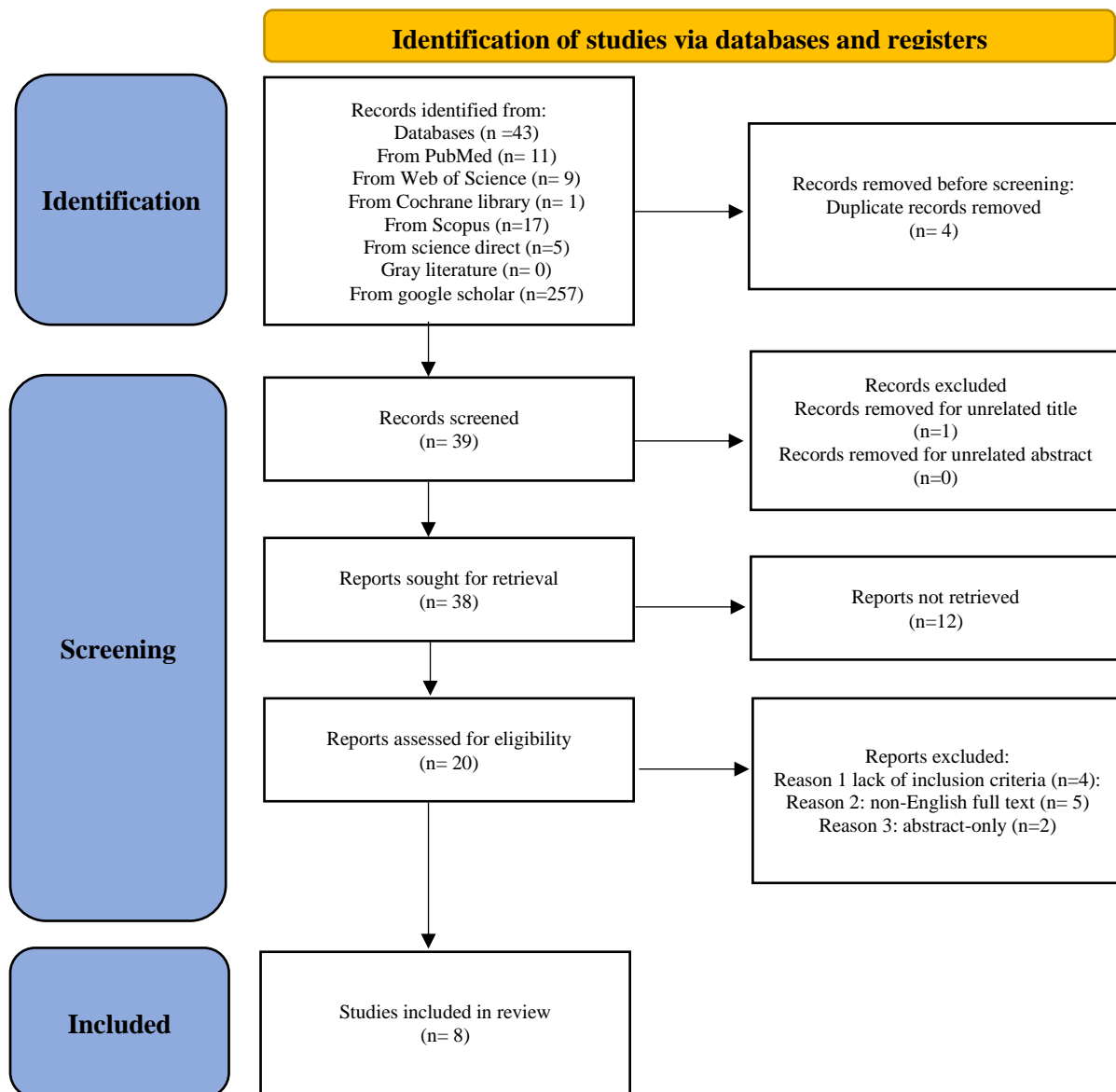
Recently, Novel Oral Anticoagulants (NOACs) have been raised to clinical practice in many countries. These drugs were made to confront the disadvantages of the Vitamin K antagonists. Relatively, NOACs have a rapid onset of action and short peak concentration. Currently, four types of NOACs are accepted by the U.S. Food and Drug Administration (FDA); Dabigatran, Apixaban, Rivaroxaban and Edoxaban [6].

### Definition of Dabigatran

Dabigatran (Praxada®) as an anticoagulant medication, can be taken orally and it was used first in RE-LY study in 2008 [7]. It was administrated as a drug in knee or hip replacement surgeries and non-valvular atrial fibrillation [8-9]. Unlike Other NOACs, there is an antidote for Dabigatran called Idarucizumab which can be used in case of emergency (FDA approved in 2015) [10]. The half-life of this drug is 12 to 17 hours, which is a short half-life (but this time could be expanded into 27 hours for elderlies). Dabigatran is capable to reach its peak in 2-3 hours, considering as a rapid onset of action [11]. It is usually prescribed twice a day.

The NOACs are superior as they omit the routine monitoring need for anticoagulant. In case of emergency

surgeries, ECT and TT are the most sensitive tests, and test of the activated Partial Thromboplastin Time (aPTT) is the second choice because it is less sensitive but widely available. Prothrombin Test (PT) is not used for this drug [11-12]. Dabigatran is a direct thrombin inhibitor and, it works through inhibiting the thrombus formation in coagulation cascade; so that consequently, fibrinogen would not transform into fibrin [13]. Almost 80% of Dabigatran is eliminate and cleared by the renal function and, its residual would be cleared by the hepatic metabolism [14]. Thus, adjust dose is recommended in patients with creatinine clearance of  $\leq 50\text{mL/min}$  [15].



**Figure 1- Flow diagram PRISMA 2022**

**Table 1- Summary of selected articles**

Ref	Authors	Journal	Year	Type of study	Sample size	Dental procedure	Recommendations
21	Healey JS. et al	Circulation Journal	2012	Clinical trial	20*	Invasive dental procedures	Discontinue taking Dabigatran 4 to 5 half-lives before surgery
22	Hong et al	Clinical Oral Investigation	2017	Retrospective	138*	Implant - Multiple tooth extraction - Deep scaling with local inflammation	Discontinue taking NOACs (such as dabigatran) at least 1 day before procedure
27	Schulman S, et al	Circulation Journal	2015	Retrospective	217	Elective/emergency surgeries, invasive diagnostic procedures	6 days interruption of Dabigatran without Heparin bridging
29	Jan Beyer-Westendorf1 et al	European Heart Journal	2013	Prospective	595	Tooth extraction	Avoid Heparin bridging if thromboembolic risk is not high
14	O. Breik et al	Australian Dental journal	2014	Case report	1*	Tooth extraction	Stop taking Dabigatran 24-48 hours before procedure
30	Romond et al.	Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology	2013	Case report	1	Dental extractions, alveoloplasty and tuberosity reduction	discontinued 24 h prior to elective oral surgery
18	R. Clemm et al. (28)	Clinical Oral Implants Research	2016	Prospective comparative	12*	Multiple implant insertion, sinus augmentation, alveolar bone augmentation	Do not interrupt taking NOACs (such as dabigatran).
20	Gomez Moreno et al.	Clinical Oral Implants Research	2018	Clinical trial	71	Implant	The last dose of dabigatran should be taken 12 hours prior to implant and start retaking the drug 8 hours after procedure

Abbreviation: NOAC: Novel Oral Anticoagulant; N: number of participants

## Results

As results of study, 2 of these papers were case reports on patients taking Dabigatran and, both authors suggested the discontinuation of this drug. There are controversies in the results of the studies. For example, in the studies of Morimoto et al, Henning Hanken et al, and R. Clemm et al. [16-18] it has been recommended to continue the Rivaroxaban for all types of dental procedures. However, Eun-Jung Kwak et al. performed a study with retrospective design in 2017 and, they recommended ceasing all NOACs at least 1 day prior to invasive dental

procedure [19]. Gomez in a clinical trial showed that, there is no need to discontinue the Rivaroxaban. But, Dabigatran ceasing is recommended 12 hours before the procedure and, its retake is recommended 8 hours post-procedure [20]. Davis et al, in a study reviewed the implications of Dabigatran in 2013. They suggested stopping the Dabigatran 2 to 4 days before invasive dental procedures [15].

Healey et al. (2012) compared Dabigatran with Warfarin in terms of pre-procedural bleeding and thromboembolism during a 2-year follow-up. They suggested that patient's renal function is essential criteria

to discontinuing Dabigatran. For example, for patients with creatinine clearance of <30 mL/min, Dabigatran is preferred to be stopped 5 days before operation [21].

In 2014, O'breik et al. in their study reported 5 cases, and only one of them was considered as a case with high risk procedure (extraction of multiple teeth). Dabigatran was not ceased pre-operatively in this case and, as a result significant post-operative bleeding occurred. O'breik divided dental procedures into two categories: elective and emergency procedures. In elective high risk treatments, patient's cardiologist or physician decides whether to stop Dabigatran or not. In cases such as atrial fibrillation without previous stroke, it is safe to stop Dabigatran for 24 hours before dental procedure. However, in patients with history of deep venous thrombosis, it is recommended to continue the anticoagulant or to bridge it with Heparin. Renal malfunction may cause to stop Dabigatran 2 to 5 days before surgery. In emergency surgeries, hemodialysis needs to be considered for clearing Dabigatran from the plasma. In the case of bleeding, it can be ceased by mechanical pressure [14].

Base on the results of some studies, patients with multiple extractions more than 3, surgery duration > 45 minutes and surgery of head cancer should be stop dabigatran. Subcutaneous heparin as an alternative treatment for these cases [22-25]. Also, in study of Curto and colleagues, emphasized that for discontinue dabigatran specialist physician should be share at. Based on the guide to stop dabigatran in dental surgical and procedures in patients with high risk bleeding include, CLCr more than 80, 2 days before, CLCr 50-80, 3 days before, CLCr 30-50, 4 days before, CLCr less than 30, 5 days before [26].

## Discussion

The management of high risk patients undergoing the novel oral anticoagulant therapy include dabigatran in dental procedures depends on many factors. Besides, thrombotic risk needs to be assessed by clinicians. If the risk bleeding a patient is high, we might have to consider the bridge therapy. While, for a patient undergoing the invasive high risk of bleeding dental procedures, it is better to stop the anticoagulant. Here, the challenge emerges when a high risk patient undergoes a high risk of bleeding dental procedure.

Each patient who is a candidate for dental surgery, it should be determined based on the characteristics of each patient and invasive procedures should be delayed until enough information is accessed about the patient's medical history. The preferable time for patients who are taking anticoagulant is earlier in the week and morning. Three important factors should be noted before beginning any invasive dental procedures for these patients: 1) risk of bleeding of the procedure, 2) Renal function, 3)

Availability of local haemostatic measures. Local haemostatic agents such as, tranexamic acid and gel foams are used to help the healing process and, to decrease the post-operative bleedings [27]. The prescribe anti-thrombin and FXa anticoagulants must be discontinued after oral surgeries in order to minimize the post-operative bleeding [28].

Besides evaluating the bleeding risk for patients taking Dabigatran, Creatinine Clearance (CrCl) should also be taken into consideration [27]. It is important to note that, the final decision regarding continuing or discontinuing dabigatran depends on the decision made by the patient's cardiologist or physician and, dentists should avoid making decisions on their own [29-30].

## Conclusions

Based on the results of this review, before any dental treatment in high risk bleeding patients such as major maxillofacial surgery, alveolar surgery (bone removal) and periodontal surgery. Multiple extractions, it is better to decide based on intervention, the predicted risk of bleeding and the clinical situation and medical history of each patient such as CLCr. However, in high risk of bleeding dental procedures, it is preferred to stop use this drug.

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