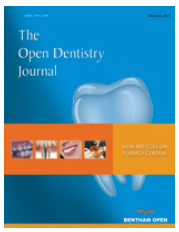

The Open Dentistry Journal

Content list available at: https://opendentistryjournal.com

REVIEW ARTICLE

Dental Implant Surgery for Patients Receiving Non-vitamin K Antagonist Oral Anticoagulants (NOACs); Clinical Considerations and Management: A Mini-review

Elias Lahham[1,*], Mahmoud Abu Ta'a[2], Anan Hayek[2] and Cezar Lahham[2]

[1]*Department of Medicine, Al-Quds University, Palestine*
[2]*Department of Dental Science, Faculty of Graduate Studies, Arab American University, Palestine*

Abstract:

Background:

Dental implants are one of the most prevalent operations in dental clinics, as they are the ideal solution to replace teeth. However, many patients who need this treatment are older and suffering from heart diseases, especially atrial fibrillation, which requires anticoagulants. Non-vitamin K antagonist oral anticoagulants (NOACs) are considered modern anticoagulants, and they include four common medications: dabigatran, rivaroxaban, apixaban, and edoxaban.

Materials and Methods:

In this study, we review the literature regarding the proper management of patients receiving NOACs in dental implant clinics based on papers published in the last decade (2010-2022). A comprehensive search on the PubMed, Scopus, and Web of Science databases was conducted to identify articles evaluating the relationship between Non-vitamin K dependent oral anticoagulants and dental implant surgery.

Results:

Despite the limitations of this study, it has been found that dental implants require discontinuation of NOACs for 24 hours or more prior to implant surgery. This depends on the type of anticoagulant and the creatinine clearance (CrCl).

Conclusion:

Implant surgery requires interruption of NOACs ≥24 hours preoperatively. However, there is a need for further clinical studies in order to establish more evidence-based guidelines.

Keywords: Dental implant, NOACs, Discontinuation, Anticoagulants, Creatinine clearance, Dabigatran.

Article History	Received: October 27, 2022	Revised: December 9, 2022	Accepted: January 11, 2023

1. INTRODUCTION

Nowadays, ischemic heart diseases and cerebral ischemia are common worldwide. They represent the leading cause of death [1, 2]. In Europe, they kill more than 1.7 million people annually, accounting for 20% of all deaths, and in the United States, they account for about 30% of all deaths over the age of 35 [3, 4]. These diseases are managed by the regular use of oral anticoagulants [5]. In the past, vitamin K antagonist oral anticoagulants (*e.g.*, warfarin) were commonly used. However, many foods that are rich in vitamin K, such as spinach, broccoli, and cashews, are known to be hazardous for patients anticoagulated with vitamin K antagonists [6, 7]. Fortunately, in the last decade, non-vitamin k antagonist oral anticoagulants (NOACs) were discovered. NOACs include the direct thrombin inhibitor (dabigatran) and factor Xa (FXa) inhibitors (rivaroxaban, apixaban, and edoxaban). These drugs have recently been approved for the prevention of stroke [8 - 11].

Bleeding is considered the main side effect of any anticoagulant. However, many clinical trials have shown that the bleeding risk for NOACs is relatively low, and it also depends on the procedure itself [12 - 15].

Dental implants are one of the most requested procedures in the dental clinic by patients. Many of these patients are

* Address correspondence to this author at the Department of Medicine, Al-Quds University, Palestine; E-mail: eliaslahham2011@hotmail.com

receiving NOACs. Dentists are familiarized with traditional anticoagulants (vitamin K inhibitors) and the methods of monitoring tests by using the international normalized ratio (INR), and thus determine the efficacy and safety of the drug and whether to perform or not an invasive dental procedure that involves bleeding [16, 17]. However, there are still not enough reliable clinical trials and consensus about the protocol to apply to patients on NOACs and undergoing dental procedures. Therefore, it is necessary to address all these issues and summarize them through a review of the literature available for the optimal management of these patients in the dental office [18].

The aim of this study is to review the literature regarding the proper management of patients receiving NOACs in dental implant clinics.

2. MATERIALS AND METHODS

A comprehensive literature search covering the period 2010-2022 was conducted using PubMed, Scopus, and Web of Science databases to locate clinical trials and guidelines that were appropriate and relevant for this review. The following keywords were used in the literature search: Eliquis, Savaysa, Pradaxa, Xarelto, dabigatran, rivaroxaban, apixaban, edoxaban, atrial fibrillation (A-Fib), venous thromboembolism (VTE), FXa inhibitors, direct thrombin inhibitor, novel oral anticoagulants, direct oral anticoagulant (DOAC), new oral anticoagulants, dental implant surgery, oral procedure, and dentistry.

3. CLASSES OF NOACS AND THEIR CONSIDERATIONS FOR PATIENTS UNDERGOING IMPLANT SURGERY

3.1. Direct Thrombin Inhibitor: Dabigatran

Dabigatran is a direct thrombin inhibitor that prevents fibrin formation, thereby hampering clot formation. Therefore, it is used to prevent thrombus and embolus formation [19, 20]. Dabigatran is characterized by a rapid onset that reaches peak concentration in the plasma within 2-4 hours after administration and has a terminal half-life of 12-17 hours [19, 21].

Many sensitive tests could be used to assess dabigatran effects, such as diluted thrombin time, ecarin clotting time, and partial thromboplastin time using HemoClot Thrombin Inhibitor assays [22, 23]. However, using prothrombin time and partial thromboplastin time tests is not reliable [24 - 26].

Dabigatran is eliminated mainly by the kidneys [27]. Therefore, CrCl should be evaluated prior to implant surgery [28, 29]. If CrCl is less than 50 mL/min, dabigatran should be discontinued 3-5 days prior to implant surgery. While if CrCl is 50 mL/min or more, it should be discontinued 1-2 days preoperatively [30, 31]. The randomized clinical trial published in 2012 by Healey et al. recommended that dabigatran should be stopped 2–3 half-lives before the procedure, and for high bleeding risk procedures, dabigatran should be stopped 4–5 half-lives prior to the procedure [32]. Normal dosage can be resumed 8 hours after implant surgery [33].

The most common side effects experienced by more than 15% of patients are epigastric pain, dyspepsia, and bloating [34, 35]. Events of minor bleeding have been reported in 8-33% of patients and events of major bleeding in ≤6% of patients [32, 36, 37]. In this situation, these can be managed by local measures, such as local pressure, sutures, and tranexamic acid [38]. In severe cases, these can be reversed within minutes by idarucizumab or hemodialysis [31, 39].

3.2. Factor Xa Inhibitors

3.2.1. Rivaroxaban

Rivaroxaban is a direct FXa inhibitor (xabans), preventing thrombin formation [40, 41]. It is rapidly absorbable and reaches peak plasma concentration approximately 2.5-4 hours after administration and exhibits a terminal half-life of 5-9 hours. The effect of rivaroxaban is evaluated using an anti-FXa test [36, 42, 43].

Literature regarding the interruption of rivaroxaban therapy is limited. However, several studies recommend discontinuing rivaroxaban one day prior to implant surgery [44 - 48]. In another study, Moreno *et al.* concluded that dental implant surgery in patients taking rivaroxaban is safe, with no need to discontinue the medication and emphasize the importance of performing postoperative local hemostatic measures [49 - 52]. While Hanken *et al.* concluded that rivaroxaban has a higher risk of bleeding than other oral anticoagulants [20]. A retrospective single-center observational study in 2015 showed postoperative bleeding complications to occur after oral surgery significantly more often in patients under continued rivaroxaban therapy (11.5%) than in the control cases without anticoagulation/antiplatelet medication (0.7%). All of the bleeding events were manageable, and all of them occurred during the first postoperative week [20].

Adverse effects are experienced by 1-10% of the patients. 1-2% of the patients have been reported to have major bleeding, and minor bleeding has been reported in 4-7% [41, 53, 54]. In cases where major bleeding has occurred, “Andexanet alfa” can be used as a reversal agent for rivaroxaban (Xarelto) and apixaban (Eliquis) [55 - 57].

3.2.2. Apixaban

Apixaban has a similar mechanism of action to rivaroxaban. It acts as a direct inhibitor of Fxa [58]. It is characterized by a rapid onset of action, which reaches the peak concentration in the plasma within 3-4 hours after oral administration. 25-30% is excreted by renal metabolism. Apixaban’s half-life is 8-13 hours [59], which represents the longest half-life of current FXa inhibitors [60, 61]. In contrast to rivaroxaban, apixaban works in a reversible manner to selectively inhibit free and bound FXa as well as inhibit prothrombinase [60]. The effect of apixaban can be measured using the anti-FXa test [36, 62, 63].

Regarding implant surgery, some studies recommend apixaban interruption 24 hours prior to the procedure with low bleeding risks and 48 hours prior to procedures with high bleeding risks [59]. While other studies show no need to interrupt apixaban [64]. In general, it is recommended to let

patients ignore or postpone their morning dose on the day of the dental treatment. The patients can restart their medication only when haemostasis has been achieved [65 - 67].

3.2.3. Edoxaban

Edoxaban is a direct, reversible, and selective inhibitor of Fxa [68 - 70]. It is able to achieve peak plasma concentration more rapidly than all previously mentioned NOACs at 1-2 hours after administration [71]. Additionally, edoxaban has an approximate terminal half-life of approximately 10 hours [72]. Edoxaban's excretion is 35% renal. Therefore, renal function assessment could be helpful preoperatively [73]. If CrCl is less than 50 mL/min, dabigatran should be discontinued 2-4 days prior to implant surgery. While if CrCl is 50 mL/min or more, it should be discontinued 1-2 days preoperatively [74 - 76].

Table 1. Summary of NOACs with its considerations in the implant surgery clinic.

Classes of NOACs	Subclasses	Antidote	Considerations for Implant Surgery
Direct thrombin inhibitor	Dabigatran	Idarucizumab	CrCl should be evaluated prior to implant surgery [28, 29]. If CrCl is less than 50 mL/min, dabigatran should be discontinued 3-5 days prior to implant surgery. While if CrCl is 50 mL/min or more, it should be discontinued 1-2 days preoperatively [30, 31]
Factor Xa inhibitors	Rivaroxaban	Andexanet alfa	CrCl should be evaluated prior to implant surgery. If CrCl is less than 50 mL/min, it should be discontinued 2-4 days prior to implant surgery. While if CrCl is 50 mL/min or more, it should be discontinued 1-2 days preoperatively [74 - 76].
	Apixaban		
	Edoxaban		

CONCLUSION

Implant surgery requires interruption of NOACs ≥24 hours prior to the operation. The recommended duration of interruption depends on the NOAC subclass and the patient's renal function. The effects of direct thrombin inhibitor "dabigatran" can be measured using HemoClot Thrombin Inhibitor assays, while the anti-FXa test is used for FXa inhibitors "rivaroxaban, apixaban and edoxaban". In case of severe bleeding, dabigatran can be reversed by idarucizumab, while other NOACs can be reversed by andexanet alfa.

Despite an increase in the number of patients receiving NOACs, as listed in Table **1**, the available evidence-based guidelines are still weak. Therefore, additional studies and the collaboration of dental and medical professionals are needed.

LIST OF ABBREVIATIONS

INR	=	International Normalized Ratio
A-Fib	=	Atrial Fibrillation
VTE	=	Venous Thromboembolism
DOAC	=	Direct oral Anticoagulant

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data supporting this study's findings are available from the corresponding author, [E.L], on special request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Palomeras Soler E, Casado Ruiz V. Epidemiology and risk factors of cerebral ischemia and ischemic heart diseases: similarities and differences. Curr Cardiol Rev 2010; 6(3): 138-49. [http://dx.doi.org/10.2174/157340310791658785] [PMID: 21804773]

[2] Lozano R, Naghavi M, Foreman K, *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380(9859): 2095-128. [http://dx.doi.org/10.1016/S0140-6736(12)61728-0] [PMID: 23245604]

[3] Townsend N, Nichols M, Scarborough P, Rayner M. Cardiovascular disease in Europe — epidemiological update 2015. Eur Heart J 2015; 36(40): 2696-705. [http://dx.doi.org/10.1093/eurheartj/ehv428] [PMID: 26306399]

[4] Benjamin EJ, Virani SS, Callaway CW, *et al.* Heart disease and stroke statistics - 2018 update: A report from the American Heart Association. Circulation 2018; 137(12): e67-e492. [http://dx.doi.org/10.1161/CIR.0000000000000558] [PMID: 29386200]

[5] Katholing A, Wallenhorst C, Freedman SB, Martinez C. Therapy persistence in newly diagnosed non-valvular atrial fibrillation treated with warfarin or NOAC. Thromb Haemost 2016; 115(1): 31-9. [http://dx.doi.org/10.1160/TH15-04-0350] [PMID: 26246112]

[6] Jensen MB, Rød KE, Švarc PL, Oveland E, Jakobsen J. Vitamin K (phylloquinone and menaquinones) in foods – Cost-effective quantification by LC-ESI-MS/MS. Food Chem 2022; 385: 132672. [http://dx.doi.org/10.1016/j.foodchem.2022.132672] [PMID: 35287105]

[7] Pettit SJ, Japp AG, Gardner RS. The hazards of brussels sprouts consumption at Christmas. Med J Aust 2012; 197(11-12): 661-2. [http://dx.doi.org/10.5694/mja12.11304] [PMID: 23230944]

[8] Kitazono T. Evidence of novel oral anticoagulants (NOAC). Rinsho Shinkeigaku 2013; 53(11): 992-3. [http://dx.doi.org/10.5692/clinicalneurol.53.992] [PMID: 24291856]

[9] Yang H, Bouma BJ, Dimopoulos K, *et al.* Non-vitamin K antagonist oral anticoagulants (NOACs) for thromboembolic prevention, are they safe in congenital heart disease? Results of a worldwide study. Int J Cardiol 2020; 299: 123-30. [http://dx.doi.org/10.1016/j.ijcard.2019.06.014] [PMID: 31307847]

[10] Haas S, Camm AJ, Bassand JP, *et al.* Predictors of NOAC versus VKA use for stroke prevention in patients with newly diagnosed atrial fibrillation: Results from GARFIELD-AF. Am Heart J 2019; 213: 35-46. [http://dx.doi.org/10.1016/j.ahj.2019.03.013] [PMID: 31128503]

[11] Táborský M, Tomek A, Čihák R, Škoda O, Daněk J, Kolek M. Cost-effectiveness analysis of first-line NOAC prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation Cor Vasa 2019; 61(4): e354-69. [http://dx.doi.org/10.33678/cor.2019.058]

[12] Garcia D, Alexander JH, Wallentin L, *et al.* Management and clinical outcomes in patients treated with apixaban vs warfarin undergoing

procedures. Blood 2014; 124(25): 3692-8.
[http://dx.doi.org/10.1182/blood-2014-08-595496] [PMID: 25320240]
[13] Beyer-Westendorf J, Gelbricht V, Förster K, *et al.* Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J 2014; 35(28): 1888-96.
[http://dx.doi.org/10.1093/eurheartj/eht557] [PMID: 24394381]
[14] Eyileten C, Postula M, Jakubik D, *et al.* Non-vitamin k oral anticoagulants (Noac) versus vitamin k antagonists (vka) for atrial fibrillation with elective or urgent percutaneous coronary intervention: A meta-analysis with a particular focus on combination type. J Clin Med 2020; 9(4): 1120.
[http://dx.doi.org/10.3390/jcm9041120] [PMID: 32295160]
[15] Pirlog CD, Pirlog AM, Maghiar T. A systematic review of hemorrhage risk in patients on the new oral anticoagulant therapy postdental implant placement. World J Dent 2019; 10(2): 154-7.
[http://dx.doi.org/10.5005/jp-journals-10015-1623]
[16] Prevalence of and risk factors for postoperative hemorrhage after lower third molar extraction on warfarin therapy: a multicenter retrospective study in Japan. Odontology 2020; 108(3): 462-69.
[http://dx.doi.org/10.1007/s10266-019-00474-y]
[17] Brennan Y, Gu Y, Schifter M, Crowther H, Favaloro EJ, Curnow J. Dental extractions on direct oral anticoagulants vs. warfarin: The DENTST study. Res Pract Thromb Haemost 2020; 4(2): 278-84.
[http://dx.doi.org/10.1002/rth2.12307] [PMID: 32110759]
[18] Lanau N, Mareque J, Giner L, Zabalza M. Direct oral anticoagulants and its implications in dentistry. A review of literature. J Clin Exp Dent 2017; 9(11): 0.
[http://dx.doi.org/10.4317/jced.54004] [PMID: 29302288]
[19] Comin J, Kallmes DF. Dabigatran (Pradaxa). AJNR Am J Neuroradiol 2012; 33(3): 426-8.
[http://dx.doi.org/10.3174/ajnr.A3000] [PMID: 22345499]
[20] Hanken H, Gröbe A, Heiland M, *et al.* Postoperative bleeding risk for oral surgery under continued rivaroxaban anticoagulant therapy. Clin Oral Investig 2016; 20(6): 1279-82.
[http://dx.doi.org/10.1007/s00784-015-1627-9] [PMID: 26498769]
[21] Dubois EA, Cohen AF. Dabigatran etexilate. Br J Clin Pharmacol 2010; 70(1): 14-5.
[http://dx.doi.org/10.1111/j.1365-2125.2010.03644.x] [PMID: 20642542]
[22] Stancheva A G. Thrombelastometry monitoring of the anticoagulant effect of dabigatran etexilate. J Thromb Haemost 2013; 11
[23] Halton JML, Picard A-C, Harper R, *et al.* Pharmacokinetics (PK) and Pharmacodynamics (PD), safety and tolerability of a single-dose oral solution of dabigatran etexilate given after standard anticoagulant therapy in children from birth to less than one year old, with venous thromboembolism. Blood 2016; 128(22): 1441.
[http://dx.doi.org/10.1182/blood.V128.22.1441.1441]
[24] Sivolella S, De Biagi M, Brunello G, Berengo M, Pengo V. Managing dentoalveolar surgical procedures in patients taking new oral anticoagulants. Odontology 2015; 103(3): 258-63.
[http://dx.doi.org/10.1007/s10266-015-0195-4] [PMID: 25656043]
[25] Kitchen D, Chow AW-C, Peart S Munroe, *et al.* 109Accuracy of test results for Direct Oral Anticoagulants (DOACs) and Warfarin-importance of External Quality Assessment (EQA). EP Eur 2017; 19(suppl_1): 146.
[http://dx.doi.org/10.1093/europace/eux283.103]
[26] Levy JH, Szlam F, Wolberg AS, Winkler A. Clinical use of the activated partial thromboplastin time and prothrombin time for screening: a review of the literature and current guidelines for testing. Clin Lab Med 2014; 34(3): 453-77.
[http://dx.doi.org/10.1016/j.cll.2014.06.005] [PMID: 25168937]
[27] Alquwaizani M, Buckley L, Adams C, Fanikos J. Anticoagulants: A review of the pharmacology, dosing, and complications. Curr Emerg Hosp Med Rep 2013; 1(2): 83-97.
[http://dx.doi.org/10.1007/s40138-013-0014-6] [PMID: 23687625]
[28] Chan KE, Giugliano RP, Patel MR, *et al.* Nonvitamin K anticoagulant agents in patients with advanced chronic kidney disease or on dialysis with AF. J Am Coll Cardiol 2016; 67(24): 2888-99.
[http://dx.doi.org/10.1016/j.jacc.2016.02.082] [PMID: 27311528]
[29] Švarcová T, Veselý J. Anticoagulation therapy in patients with chronic kidney disease Cor Vasa 2019; 61(6): 599-605.
[http://dx.doi.org/10.33678/cor.2019.049]
[30] Fda, 'PRADAXA (dabigatran etexilate mesylate) capsules for oral use Label. Fda 2011.
[31] Breik O, Cheng A, Sambrook PJ, Goss AN. Protocol in managing oral surgical patients taking dabigatran. Aust Dent J 2014; 59(3): 296-301.
[http://dx.doi.org/10.1111/adj.12199] [PMID: 24889878]
[32] Healey JS, Eikelboom J, Douketis J, *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(3): 343-8.
[http://dx.doi.org/10.1161/CIRCULATIONAHA.111.090464] [PMID: 22700854]
[33] Abayon M, Kolokythas A, Harrison S, Elad S. Dental management of patients on direct oral anticoagulants: Case series and literature review. Quintessence Int (Berl) 2016; 47(8): 687-96.
[http://dx.doi.org/10.3290/j.qi.a36325] [PMID: 27574712]
[34] Rajdev A, Bradley J, Petrini J, Alexander J. A community experience of the novel anticoagulant pradaxa. J Am Coll Cardiol 2012; 59(13): E601.
[http://dx.doi.org/10.1016/S0735-1097(12)60602-0]
[35] Diener HC, *et al.* Dabigatran for stroke prevention in patients with TIA or ischaemic stroke and atrial fibrillation: Practical apects. Aktuelle Neurol 2011; 38(5): 261-66.
[http://dx.doi.org/10.1055/s-0031-1283146]
[36] Firriolo 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(4): 431-41.
[http://dx.doi.org/10.1016/j.oooo.2011.10.005] [PMID: 22668425]
[37] Staerk L, Gislason GH, Lip GYH, *et al.* Risk of gastrointestinal adverse effects of dabigatran compared with warfarin among patients with atrial fibrillation: a nationwide cohort study. Europace 2015; 17(8): 1215-22.
[http://dx.doi.org/10.1093/europace/euv119] [PMID: 25995392]
[38] Ockerman A, Miclotte I, Vanhaverbeke M, *et al.* Tranexamic acid and bleeding in patients treated with non-vitamin K oral anticoagulants undergoing dental extraction: The EXTRACT-NOAC randomized clinical trial. PLoS Med 2021; 18(5): e1003601.
[http://dx.doi.org/10.1371/journal.pmed.1003601] [PMID: 33939696]
[39] Chang DN, Dager WE, Chin AI. Removal of dabigatran by hemodialysis. Am J Kidney Dis 2013; 61(3): 487-9.
[http://dx.doi.org/10.1053/j.ajkd.2012.08.047] [PMID: 23219111]
[40] Misselwitz F, Berkowitz SD, Perzborn E. The discovery and development of rivaroxaban. Ann N Y Acad Sci 2011; 1222(1): 64-75.
[http://dx.doi.org/10.1111/j.1749-6632.2011.05971.x] [PMID: 21434944]
[41] Scheen AJ. [Rivaroxaban (Xarelto): new anticoagulant inhibitor of factor Xa]. Rev Med Liege 2009; 64(10): 538-43.
[PMID: 19911670]
[42] Mueck W, Schwers S, Stampfuss J. Rivaroxaban and other novel oral anticoagulants: pharmacokinetics in healthy subjects, specific patient populations and relevance of coagulation monitoring. Thromb J 2013; 11(1): 10.
[http://dx.doi.org/10.1186/1477-9560-11-10] [PMID: 23809871]
[43] Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet 2014; 53(1): 1-16.
[http://dx.doi.org/10.1007/s40262-013-0100-7] [PMID: 23999929]
[44] XARELTO (Rivaroxaban) Prescribing Information. FDA 2017.
[45] ElMaghawry M. ROCKET AF adds more concerns about Digoxin safety in patients with atrial fibrillation. Glob Cardiol Sci Pract 2015; 2015(3): 35.
[http://dx.doi.org/10.5339/gcsp.2015.35] [PMID: 26779514]
[46] Curto A. Management of patients taking rivaroxaban for dental treatments. Eur J Gen Dent 2017; 6(1): 1-4.
[http://dx.doi.org/10.4103/2278-9626.198585]
[47] Galletti G, Alfonsi F, Raffaele A, *et al.* Implant placement in patients under treatment with rivaroxaban: A retrospective clinical study. Int J Environ Res Public Health 2020; 17(12): 4607.
[http://dx.doi.org/10.3390/ijerph17124607] [PMID: 32604907]
[48] Kim C, Dam C, Jeong J, Kwak EJ, Park W. Delayed bleeding after implant surgery in patients taking novel oral anticoagulants: a case report. J Dent Anesth Pain Med 2017; 17(2): 143-7.
[http://dx.doi.org/10.17245/jdapm.2017.17.2.143] [PMID: 28879343]
[49] Costa FWG, Rodrigues RR, Sousa LHT, *et al.* Local hemostatic measures in anticoagulated patients undergoing oral surgery: a systematized literature review. Acta Cir Bras 2013; 28(1): 78-83. [http://dx.doi.org/10.1590/S0102-86502013000100013] [PMID: 23338118]
[50] Schmitt CM, Rusche B, Clemm R, Neukam FW, Buchbender M. Management of anticoagulated patients in dentoalveolar surgery: a clinical comparative study. Clin Oral Investig 2020; 24(8): 2653-62.

[http://dx.doi.org/10.1007/s00784-019-03124-3] [PMID: 31713746]

[51] Queiroz S, Alves H, Assis G, Conceicao T, Germano A, Silva J. An evaluation of the efficacy of local hemostatic measures in dental patients taking oral anticoagulants: A critical review of the literature over the past two decades. Curr Clin Pharmacol 2016; 11(4): 230-40. [http://dx.doi.org/10.2174/1574884711666161003163217] [PMID: 27697071]

[52] Gómez-Moreno G, Aguilar-Salvatierra A, Fernández-Cejas E, Delgado-Ruiz RA, Markovic A, Calvo-Guirado JL. Dental implant surgery in patients in treatment with the anticoagulant oral rivaroxaban. Clin Oral Implants Res 2016; 27(6): 730-3. [http://dx.doi.org/10.1111/clr.12653] [PMID: 26073481]

[53] Sherid M, Sulaiman S, Samo S, *et al.* Risk of Gastrointestinal Bleeding with Rivaroxaban: A Comparative Study with Warfarin. Gastroenterol Res Pract 2016; 2016: 1-9. [http://dx.doi.org/10.1155/2016/9589036] [PMID: 26880901]

[54] Weeda ER, White CM, Peacock WF, Coleman CI. Rates of major bleeding with rivaroxaban in real-world studies of nonvalvular atrial fibrillation patients: a meta-analysis. Curr Med Res Opin 2016; 32(6): 1117-20. [http://dx.doi.org/10.1185/03007995.2016.1161610] [PMID: 26934003]

[55] Brown CS, Scott RA, Sridharan M, Rabinstein AA. Real-world utilization of andexanet alfa. Am J Emerg Med 2020; 38(4): 810-4. [http://dx.doi.org/10.1016/j.ajem.2019.12.008] [PMID: 31870672]

[56] Carpenter E, Singh D, Dietrich E, Gums J. Andexanet alfa for reversal of factor Xa inhibitor-associated anticoagulation. Ther Adv Drug Saf 2019; 10 [http://dx.doi.org/10.1177/2042098619888133] [PMID: 31807265]

[57] Favresse J, Hardy M, van Dievoet MA, *et al.* Andexanet alfa for the reversal of factor Xa inhibitors. Expert Opin Biol Ther 2019; 19(5): 387-97. [http://dx.doi.org/10.1080/14712598.2019.1599355] [PMID: 30974977]

[58] Savinova AV, Petrova MM, Shnayder NA, Bochanova EN, Nasyrova RF. Pharmacokinetics and pharmacogenetics of apixaban. Ration Pharmacother Cardiol 2020; 16(5): 852-60. [http://dx.doi.org/10.20996/1819-6446-2020-10-17]

[59] BMS. ELIQUIS (Apixaban) Prescribing Information. Fda 2016.

[60] Food and Drug Administration. Eliquis. Pharmacology 2016.

[61] Vu A, Qu TT, Ryu R, Nandkeolyar S, Jacobson A, Hong LT. Critical analysis of apixaban dose adjustment criteria. Clin Appl Thromb Hemost 2021; 27: 1-6. [http://dx.doi.org/10.1177/10760296211021158] [PMID: 34075813]

[62] Hillarp A, Gustafsson KM, Faxälv L, *et al.* Effects of the oral, direct factor Xa inhibitor apixaban on routine coagulation assays and anti-FXa assays. J Thromb Haemost 2014; 12(9): 1545-53. [http://dx.doi.org/10.1111/jth.12649] [PMID: 24965851]

[63] Doğanay Ö, Yücesoy T, Alkan A. Management of patients using oral anticoagulant agent in dental practice. Bezmialem Sci 2019; 7(3): 240-4. [http://dx.doi.org/10.14235/bas.galenos.2018.2199]

[64] Mauprivez C, Khonsari RH, Razouk O, Goudot P, Lesclous P, Descroix V. Management of dental extraction in patients undergoing anticoagulant oral direct treatment: A pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol 2016; 122(5): e146-55. [http://dx.doi.org/10.1016/j.oooo.2016.06.003] [PMID: 27554378]

[65] Elad S, Marshall J, Meyerowitz C, Connolly G. Novel anticoagulants: General overview and practical considerations for dental practitioners. Oral Dis 2016; 22(1): 23-32. [http://dx.doi.org/10.1111/odi.12371] [PMID: 26386350]

[66] Curto A, Albaladejo A. Implications of apixaban for dental treatments. J Clin Exp Dent 2016; 8(5): e111-16. [http://dx.doi.org/10.4317/jced.53004] [PMID: 27957279]

[67] Escolar G, Fernandez-Gallego V, Arellano-Rodrigo E, *et al.* Reversal of apixaban induced alterations in hemostasis by different coagulation factor concentrates: Significance of studies *in vitro* with circulating human blood. PLoS One 2013; 8(11): e78696. [http://dx.doi.org/10.1371/journal.pone.0078696] [PMID: 24244342]

[68] Wang Z, Frost C, Shenker A, Barrett YC. Clinical laboratory measurement of direct factor Xa inhibitors: Anti-Xa assay is preferable to prothrombin time assay. Thromb Haemost 2010; 104(12): 1263-71. [http://dx.doi.org/10.1160/TH10-05-0328] [PMID: 20978714]

[69] Bode C, Ahrens I. Oral anticoagulation with edoxaban. Hamostaseologie 2012; 32(3): 212-5. [http://dx.doi.org/10.5482/HAMO-12-05-0004]

[70] Ikushima I, Akasaka T, Morishima Y, Takita A, Motohashi T, Kimura T. Effects of concomitant use of prasugrel with edoxaban on bleeding time, pharmacodynamics, and pharmacokinetics of edoxaban in healthy elderly Japanese male subjects: A clinical pharmacology study. Thromb J 2020; 18(1): 10. [http://dx.doi.org/10.1186/s12959-020-00223-0] [PMID: 32536828]

[71] Gómez-Outes A, Suárez-Gea ML, Lecumberri R, Terleira-Fernández AI, Vargas-Castrillón E. Direct-acting oral anticoagulants: pharmacology, indications, management, and future perspectives. Eur J Haematol 2015; 95(5): 389-404. [http://dx.doi.org/10.1111/ejh.12610] [PMID: 26095540]

[72] Cuker A, Husseinzadeh H. Laboratory measurement of the anticoagulant activity of edoxaban: A systematic review. J Thromb Thrombolysis 2015; 39(3): 288-94. [http://dx.doi.org/10.1007/s11239-015-1185-7] [PMID: 25669624]

[73] Padrini R. Clinical pharmacokinetics and pharmacodynamics of direct oral anticoagulants in patients with renal failure. Eur J Drug Metab Pharmacokinet 2019; 44(1): 1-12. [http://dx.doi.org/10.1007/s13318-018-0501-y] [PMID: 30167998]

[74] Curto A, Curto D, Sanchez J. Managing patients taking edoxaban in dentistry. J Clin Exp Dent 2017; 9(2): e308-11. [http://dx.doi.org/10.4317/jced.53431] [PMID: 28210454]

[75] Remková A, Deglovič J, Šupler M. Dental procedures during oral anticoagulant treatment / dental procedures in oral anticoagulation therapy. Cardiology letters 2020; 29(3): 154-9. [http://dx.doi.org/10.4149/Cardiol_2020_3_6]

[76] Ansell JE, Bakhru SH, Laulicht BE, *et al.* Single-dose ciraparantag safely and completely reverses anticoagulant effects of edoxaban. Thromb Haemost 2017; 117(2): 238-45. [http://dx.doi.org/10.1160/TH16-03-0224] [PMID: 27853809]

© 2023 Lahham *et al*.

This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International Public License (CC-BY 4.0), a copy of which is available at: https://creativecommons.org/licenses/by/4.0/legalcode. This license permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.