# Direct Oral Anticoagulants and Medical Comorbidities in Patients Needing Dental Extractions: Management of the Risk of Bleeding

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**Purpose:** The purpose of this study was to measure the frequency of bleeding during and after tooth extraction in patients exposed to direct oral anticoagulants (DOACs) and identify risk factors for prolonged or excessive bleeding.

**Materials and Methods:** This retrospective cohort study involved 100 patients who underwent tooth extractions according to the European Heart Rhythm Association protocol: continuation of DOAC therapy for extractions of up to 3 teeth in the same session performed at the (presumed) time of DOAC trough concentration. We respected an interval of at least 4 hours between extraction and last DOAC intake. The outcome of interest was incidence of mild, moderate, and severe bleeding during the intervention and in the 7-day follow-up period. Data analysis considered the presence of comorbidities as the primary predictor for bleeding; additional predictors were age, gender, type of comorbidity, indication for DOAC therapy, DOAC agent, and extraction of contiguous teeth.

**Results:** Of the patients, 64 had comorbidities (diabetes in 50%). The distributions of demographic, clinical, and dental variables were similar for patients with and without comorbidities. We observed 4 bleeding episodes (1 moderate episode 1 hour after the extraction and 3 mild episodes the day after the extraction) in the comorbidity group and none in the non-comorbidity group (4 of 64 vs 0 of 36, P = .29; overall bleeding rate, 4 of 100). The factor significantly triggering bleeding in patients with comorbidity was extractions of couples and triplets of multirooted teeth (P = .004).

**Conclusions:** Tooth extractions in patients with comorbidities taking DOACs may be safely managed as long as they are performed at least 4 hours after the last DOAC intake and do not involve 2 or 3 contiguous premolars and molars.

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The number of patients requiring dental procedures while taking direct oral anticoagulants (DOACs) has markedly increased in recent years.<sup>1</sup> The appropriate dental management of such patients is controversial, including a paucity of data on bleeding during and after these procedures.<sup>2-6</sup> The multidisciplinary preoperative approach used for major procedures is not always viable in dentistry, particularly in private practice.<sup>7,8</sup> Thus, how to prevent, at the same time, excessive bleeding and thromboembolic episodes is still unclear.<sup>9</sup>

In the absence of randomized clinical trials to formulate evidence-based guidelines,<sup>7</sup> a few organizations have issued guidance documents.<sup>10-13</sup> Most are in favor of not interrupting therapy for minor invasive procedures, including dental extractions. The European Heart Rhythm Association (EHRA) guidelines on the management of DOACs in patients with nonvalvular atrial fibrillation recommend continuation of therapy for extraction of up to 3 teeth in the same session performed at the time of DOAC trough concentration.<sup>14</sup> The determination of this timing is unfortunately not straightforward, depending on many parameters. The most commonly used DOACs are dabigatran, a direct thrombin inhibitor that has an 80 to 85% renal excretion rate and a half-life of 12 to 17 hours,<sup>15,16</sup> and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, which have renal excretion rates of 25 to 35% and half-lives of 5 to 9, 8 to 15, and 10 to 14 hours, respectively.<sup>17-24</sup> The suggestions for the timing of extraction range from a minimum of 4 hours to a maximum of 10 hours after DOAC intake,<sup>25</sup> depending on the DOAC agent and intake schedule. The situation is further clouded by the absence of reliable laboratory tests for clotting ability and of effective antidotes except for direct thrombin inhibitors.<sup>26,27</sup>

Assessment of the patient's medical background is generally recommended.<sup>28,29</sup> Poor coagulation is in fact not the only bleeding risk for DOAC patients. The cardiovascular pathologies that require DOACs are often associated, especially in elderly patients, with diabetes,<sup>30,31</sup> hepatic diseases,<sup>32-34</sup> and renal insufficiency.<sup>35-37</sup> These comorbidities hinder wound healing, foster perioperative bleeding, and may alter the DOAC elimination rate.

As an oral surgery unit (OSU) of the dental school of a large teaching hospital, we are routinely involved in the management of dental extractions in DOAC patients with at least 1 comorbidity. A large number of these patients need extractions of contiguous teeth, as a preliminary to implant placement, to eliminate infectious foci before major surgery, or to prevent endocarditis and heart valve infections. Extraction of 2 or 3 contiguous teeth is within the EHRA guidelines; however, when it involves premolars and molars, it leaves a wide surgical wound in which healing is difficult.

On the basis of our experience, we hypothesized that the greatest risk of bleeding might arise from an unfortunate association of patient-related factors with modalities of the dental extraction. Our plan was to estimate and compare the bleeding risk in patients with and without comorbidities and to investigate its relationship with a number of demographic, clinical, and dental risk factors. Specifically, our goal was to find an answer to the following clinical questions: 1) Does the presence of diabetes, liver diseases, and renal insufficiency increase the frequency of excessive bleeding during and after teeth extractions? 2) Which other patient characteristics (comorbidities, old age, DOAC therapy) may foster bleeding? 3) Does the extraction of contiguous teeth represent an increased risk? 4) Which factors should be considered when drafting an extraction plan?

## **Materials and Methods**

#### STUDY DESIGN AND SAMPLE

To address the research purpose, we designed and implemented a retrospective cohort study on 100 patients taking DOACs. The study sample was obtained with a backward search from November 1, 2017, to November 2015 over all eligible patients referred to the OSU of our joint university-hospital dental school by in-hospital departments, private cardiologists, and general practitioners.

Patients had to meet several inclusion criteria. The principal criterion was an extraction session in compliance with the EHRA guidelines,<sup>14</sup> that is, therapy continuation and a maximum of 3 extractions per session, carried out at a low DOAC concentration. Our institution policy was to perform extractions only after making sure that at least 4 hours had elapsed from the last DOAC intake.

Other inclusion criteria were as follows: 1) extraction by the same 2 dentists (N.C. and M.B. with 15 years and 25 years of expertise in oral surgery, respectively); 2) extraction because of root or crown fractures, nonrestorable caries, residual roots, or periodontal and/or endodontic abnormalities; 3) records with full information on the DOAC therapy, including daily dosage and intake schedule; 4) information on the presence and type of comorbidities (diabetes, hepatic disease, and renal insufficiency); 5) information on the medications taken to control the disease and, for patients with renal insufficiency, creatine clearance rate greater than 50 mL/min; and 6) completion of 7 days' follow-up. We placed no exclusion criteria related to age, gender, comorbidity, degree of severity of comorbidities (except for the creatine clearance limit) or of cardiovascular pathology (including hospitalization), indication for DOAC, or type of DOAC.

This was a retrospective analysis of surgical procedures performed without any study-related clinical intervention. The analysis was performed in accordance with the guidelines of the local institutional review board and conformed to the tenets of the Declaration of Helsinki of 1975 and its subsequent modifications. Before the extraction session, all patients were informed about the surgical procedures and the possible use of their data for study purposes, and they signed an informed consent form. Patient information was anonymized before analysis.

#### STUDY VARIABLES

The primary outcome variable of interest was the incidence of excessive bleeding from a few hours up to 7 days after the extraction. The principal predictor was the presence of comorbidities; secondary predictors were age, gender, type of comorbidity, pathology for DOAC, DOAC agent, and extraction of contiguous teeth.

## SURGICAL PROTOCOL

All extractions were routine. After induction of local anesthesia (3% mepivacaine without epinephrine), the teeth were extracted in an atraumatic manner, with rotation and traction movements using dental forceps and elevators, with no mucoperiosteal flap raised and without the use of rotary instruments.

The extractions were carried out following our institution's guidelines for patients with increased bleeding risk.<sup>29-31</sup> All patients underwent local hemostatic measures including digital mechanical pressure and topical agents (eg, resorbable gelatin sponges [Spongostan; Ethicon, Cincinnati, OH]). The margins of wide alveolar sockets were drawn together by sutures using No. 3-0 silk, to be removed after 1 week.

All patients were given the same post-extraction treatment. They were permitted to leave the OSU on the day of surgery, after at least 1 hour of monitoring and a final satisfactory examination for hemostasis. Before dismissal, they were cautioned against mouth rinsing and hot beverages. All of them were given dressings impregnated with 5% tranexamic acid (TA), which has been shown to be effective in reducing minor bleeding complications.<sup>38</sup> TA prevents proteolytic degradation of fibrin, which impairs the fixation of plasminogen and plasmin. The advantage of local inhibition of fibrinolysis in anticoagulated patients is the simplicity and efficacy of the treatment in addition to the lack of serious side effects.

Patients were instructed on the normal postprocedural course and the measures to be taken in case of mild, moderate, or severe bleeding. Mild bleeding or oozing was defined as blood loss manageable by the patient by applying a dressing saturated with TA on the post-alveolar socket for 20 minutes. Moderate bleeding was defined as protracted blood loss not manageable by the patient. In cases of moderate bleeding, the patient was instructed to immediately contact the OSU to undergo a reintervention to remove the necrotic clot and place a new suture. Severe bleeding was defined as blood loss not manageable using topical hemostatic measures, thus requiring systemic therapy and/or specific hospitalization.

The analgesic therapy prescribed was paracetamol (acetaminophen), 1,000 mg as 1 tablet, twice daily, for 2 days. Antibiotic prophylaxis was given when necessary. The surgeon who performed the extraction checked on each patient on days 1, 3, and 7 after extraction to assess wound healing and the presence of bleeding or hematoma.

#### STATISTICAL METHODS

Age was expressed as mean and standard deviation and compared with the Mann-Whitney test. Categorical variables, expressed as counts and percentages, were compared by the  $\chi^2$  test (with Yates correction for 2 × 2 tables) or, when more appropriate, by the Fisher exact test. The 95% confidence interval (CI) of a percentage was computed with the Wilson score when the number of observed events was greater than 0. When the number of events was 0, we used the simple "clinical rule of the three" to obtain the upper limit as 3/N, in which *N* is the total number of observations.<sup>39</sup>

Significance was defined as a *P* value ( $\alpha$  error) of less than .05. Calculations were performed using Statplus for Macintosh (version 6; AnalystSoft, Walnut, CA).

## Results

#### DESCRIPTIVE STATISTICS

The number of patients with known comorbidities amounted to 64. All of them were under medical control for their comorbidity: 32 (50%) had diabetes, 20 (31%) had liver diseases, and 12 (19%) had various degrees of renal insufficiency. Eight (12%) were hospitalized for their comorbidity or cardiovascular pathology. None of the 36 patients without comorbidities were hospitalized.

The demographic, clinical, and dental study variables of the 2 groups are summarized and compared in Table 1. All variables are equally distributed between the 2 groups.

The extractions performed in both groups of patients are detailed in Figure 1 for the comorbidity group and Figure 2 for the non-comorbidity group. Each group is subdivided according to the predictor

Study Variables	Comorbidities	No Comorbidities	<i>P</i> Value
Patients n	64	36	
Demographic	01	50	
Age vr	$69 \pm 10$	$685 \pm 10$	> 99
$\geq 80 \text{ yr n}$	8 (12.5%)	6(17%)	//
Female n	39 (61%)	15 (42%)	10
Pathology for	57 (01/0)	1)(12/0)	25
DOAC n			
NVAF	39 (61%)	21 (58%)	
VT	10 (16%)	10 (28%)	
Others	15 (23%)	5 (14%)	
DOAC agent, n	-> (-5)	> ()	.20
Dabigatran	21 (33%)	18 (50%)	
Apixaban	25 (39%)	12 (33%)	
Rivaroxaban	18 (28%)	6 (17%)	
Extractions, n			
Single or not	41 (64%)	19 (53%)	.57
Couples of multirooted teeth*	17 (26.5%)	8 (22%)	.80
	13 (20%)	6 (17%)	.86
Triplets of multirooted teeth*	6 (9%)	9 (25%)	.07
	5 (8%)	6 (17%)	.31

Table 1. DEMOGRAPHIC, CLINICAL, AND DENTAL STUDY VARIABLES VERSUS PRINCIPAL PREDICTOR (PRESENCE OF COMORBIDITIES)

Abbreviations: DOAC, direct oral anticoagulant; NVAF, non-valvular atrial fibrillation; VT, deep venous thrombosis and thrombosis prevention.

\* Premolars and molars.

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of dental interest, that is, extractions of 2 or 3 contiguous teeth (hereon referred to as "couples" or "triplets") versus extractions of noncontiguous teeth.

Among the 64 patients with comorbidities, 23 (36%) had sessions with extractions of either 2 or 3 contiguous teeth: 17 couples, 13 of 17 of which (76%) involved multirooted teeth, and 6 triplets, 5 of 6 of which (83%) involved multirooted teeth. The remaining 41 patients (64%) had sessions with extraction of a single tooth or of noncontiguous teeth. Overall, the number of teeth extracted in patients with comorbidities was 72: 13 incisors or canines (18%), 51 premolars (71%), and 8 molars (11%).

Among the 36 patients without comorbidities, 8 (22%) had sessions with extraction of couples, 6 of 8 of which (75%) involved multirooted teeth, and 9 (47%) had sessions with extraction of triplets, 6 of 9 of which (67%) involved multirooted teeth. Nineteen patients had extractions of a single tooth or of noncontiguous teeth. The total number of teeth extracted was 66: 30 incisors or canines (45%), 20 premolars (30%), and 16 molars (24%).

#### **BLEEDING RATE**

We labeled bleeding that occurred during the extraction as perioperative bleeding, bleeding in the hours after the extraction as postoperative bleeding, and bleeding in the 7-day follow-up period as delayed bleeding.

The 36 patients without comorbidities had no bleeding. Conversely, among the 64 patients with comorbidities, 1 case of moderate postoperative bleeding and 3 cases of mild delayed bleeding occurred. The total bleeding rates were 0 of 36 (0%; 95% CI, 0 to 8%) for patients without comorbidities and 4 of 64 (6.25%; 95% CI, 2.5 to 15%) for patients with comorbidities (P = .29).

The characteristics of the 4 patients affected by bleeding are presented in Table 2. The moderate bleeding episode occurred approximately 1 hour after extraction of a premolar-premolar-molar triplet in a middle-aged patient with diabetes. The extraction was carried out about 6 hours after her morning intake of rivaroxaban, whose short halflife was presumed to warrant its low concentration already after 4 to 5 hours. Despite this, the bleeding could not be stopped by compression with gauze pads, so we performed a surgical revision applying additional sutures and TA wraps in the alveolar sockets. The patient's cardiologist allowed suspension of the NOAC therapy for the evening and following morning, by which time the bleeding had stopped.

The 3 mild delayed bleeding episodes occurred on the first day after the extraction, after the patients had taken 1 or 2 DOAC doses. No patient required follow-up sessions beyond day 7 or hospitalization for protracted bleeding.

Table 3 reports the study variables of the 64 patients with comorbidities versus the primary outcome variable (ie, occurrence of bleeding). No statistical differences were found in the distribution of any of the demographic and clinical variables (age, gender, pathology for DOAC, DOAC agent). However, extractions of couples and triplets of multirooted teeth were identified as a significant bleeding risk: 100% in the bleeding group versus 23% in the nonbleeding group (P = .004).

Table 4 focuses on the 23 patients with both comorbidities and extractions of contiguous teeth: No study variable constituted a significant additional bleeding risk.



FIGURE 1. Details of extractions in comorbidity group of patients (pts).

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# Discussion

The absence of evidence-based guidelines for patients taking DOACs leaves many doubts in the dentist community about the safest procedures to follow when performing extractions (even routine ones) in these patients. This is all the more true when the patient, in addition to the therapyinduced poor coagulation ability, has diabetes, liver diseases, or renal insufficiency. Despite these comorbidities being present in a large portion of patients taking DOACs, they are in fact not mentioned in most of the practical guidelines issued by different



FIGURE 2. Details of extractions in non-comorbidity group of patients (pts).

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	Mild Bleeding			Moderate Bleeding
Variable	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Male	Female	Female	Female
Age, yr	79	64	58	65
Pathology	NVAF	NVAF	VT	NVAF
Drug	Apixaban	Rivaroxaban	Apixaban	Rivaroxaban
Comorbidity	Controlled diabetes	Controlled liver disease	Controlled renal insufficiency	Controlled diabetes
Dental extraction	Couple of multirooted teeth	Couple of multirooted teeth	Triplet of multirooted teeth	Triplet of multirooted teeth
Time of bleeding	Day 1	Day 1	Day 1	Day 0, 1 hour after intervention

#### Table 2. CHARACTERISTICS OF PATIENTS WITH BLEEDING

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associations, including the EHRA guidelines followed by our OSU.

EHRA guidelines recommend to not interrupt oral anticoagulation for up to 3 extractions per session and to perform the sessions at the time of DOAC trough concentration. Ideally, to meet the latter requirement, the extraction should be carried out as far as possible from the last DOAC intake and as close as possible to the next DOAC intake. Several practical factors (unknown excretion rates for specific drugs by different patients, intake schedules, and compliance with the clinician's and patient's availability), however, make it difficult to respect this ideal timing. Our bottom-line policy was to wait for at least 4 hours after the last DOAC intake before performing the extraction. Whether this timing actually could guarantee an acceptably low concentration is not easy to determine, depending on many variables, most of them unknown to the dentist and to the patient. In any case, this choice led to a satisfying outcome, with postoperative bleeding in 1 of 100 patients and delayed bleeding in 3 of 100, for an overall bleeding rate of 4 of 100.

The postoperative case of moderate bleeding occurred approximately 1 hour after extraction of a premolar-premolar-molar triplet in a middle-aged woman with diabetes. The patient was taking rivaroxaban, a DOAC with a half-life inferior to the 6-hour interval between her morning dose and extraction session. Her cardiologist allowed skipping of the 2 successive DOAC doses (evening and following morning), so that bleeding could be arrested. Diabetes had already emerged as a powerful bleeding risk for patients receiving oral anticoagulant therapy with vitamin K antagonists, with a significantly higher degree of association with bleeding (31%), compared with liver diseases (15%) and kidney failure (11%).<sup>31</sup>

The 3 (of 100) cases of mild delayed bleeding occurred on the first day after the extraction. No

bleeding was observed after the second day. No severe bleeding requiring hospitalization was recorded in the 7 days of follow-up.

An important outcome of our study was that bleeding affected only patients with a comorbidity and extractions of contiguous multirooted teeth. The analysis was thus aimed at these 2 factors. Of 100 patients, 64 had comorbidities: 32 (50%) had diabetes, 20 (31%) had liver diseases, and 12 (19%) had various degrees of renal insufficiency. The study variables were age, gender, type of comorbidity, pathology for DOAC therapy (nonvalvular atrial fibrillation in 60%), DOAC agent (factor Xa inhibitors in 61%), and

#### Table 3. PATIENTS WITH COMORBIDITIES (N = 64): DEMOGRAPHIC, CLINICAL, AND DENTAL STUDY VARIABLES VERSUS PRINCIPAL OUTCOME (MILD AND MODERATE BLEEDING)

	Bleeding (n = 4)	No Bleeding (n = 60)	<i>P</i> Value
Age, yr	$66.5\pm8.9$	$68 \pm 11$	.76
$\geq$ 80 yr (n = 8), n	0 (0%)	8 (13%)	≥.99
Female ( $n = 39$ ), n	3 (75%)	36 (60%)	.65
NVAF (n = 39), n	3 (75%)	36 (60%)	.65
Factor Xa inhibitors	4 (100%)	39 (65%)	.29
(n = 43), n			
Diabetes ( $n = 32$ ), n	3 (75%)	29 (48%)	.61
Extraction of	4 (100%)	14 (23%)	.004*
contiguous			
inultirooted teeth			
(n = 18), n			

Abbreviation: NVAF, nonvalvular atrial fibrillation. \* Statistical significance.

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#### Table 4. PATIENTS WITH COMORBIDITIES AND EXTRACTION OF CONTIGUOUS TEETH (N = 23): DEMOGRAPHIC, CLINICAL, AND DENTAL STUDY VARIABLES VERSUS PRINCIPAL OUTCOME (MILD AND MODERATE BLEEDING)

	Bleeding (n = 4)	No Bleeding (n = 19)	<i>P</i> Value
Age, yr	$66.5\pm8.9$	$68\pm10$	.76
Female ( $n = 13$ ), n	3 (75%)	10 (53%)	.60
NVAF ( $n = 16$ ), $n$	3 (75%)	13 (68%)	≥.99
Factor Xa inhibitors	4 (100%)	11 (58%)	.26
(n = 15), n			
Diabetes ( $n = 11$ ), n	3 (75%)	8 (42%)	.32

Abbreviation: NVAF, nonvalvular atrial fibrillation.

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extraction of 2 or 3 contiguous teeth (multirooted in 30%). All variables were equally distributed between the 2 groups of patients with and without comorbidities. The non-comorbidity sample (36 patients) had no bleeding, whereas the comorbidity sample (64 patients) had 4 cases of bleeding. Comparison of the 2 bleeding rates, 0% (95% CI, 0 to 8%) for the non-comorbidity group and 6.25% (95% CI, 2.5 to 15%) for the comorbidity group (P = .29), indicates that the bleeding risk for patients with a comorbidity is not significantly higher than that for other patients. This is an important result because the existence of a comorbidity is a patient's characteristic that cannot be controlled by the dentist.

Among the 64 patients with comorbidities, the factor triggering the bleeding was the extraction of contiguous multirooted teeth: incidence of 4 of 4 (100%) among bleeding patients versus 14 of 60 (23%) among nonbleeding patients (P = .0004). The bleeding risk associated with these extractions is not very worrisome because the scheduling of extractions is, in most cases, within the power of the dentist, who can spread the extractions over more than 1 session.

The results of our study show that the bleeding rate in dental extractions without interruption of the DOAC therapy depends on many factors. Great caution must thus be used when comparing studies of different authors; in the absence of information on comorbidities, DOAC therapy, and extraction timing, the risk of hazardous and even misleading conclusions must not be underestimated.

Mauprivez et al<sup>25</sup> reported postoperative bleeding in 5 of 31 patients (16.1%; 95% CI, 3.2 to 29.1%), mostly in those who underwent extraction less than 3 hours after taking the DOAC, which was thus still present at a high concentration in the bloodstream. As such, they concluded that patients taking DOACs should wait at least 4 to 6 hours after the last dose before dental extractions.

The absence of bleeding in our 36 patients without comorbidities is in agreement with the findings of Miranda et al,<sup>40</sup> who reported 0 cases of bleeding in 12 patients (0%) undergoing multiple dental extractions. Miranda et al followed the EHRA guidelines for DOAC patients but excluded patients affected by liver disease or severe renal failure. The absence of bleeding in our patients undergoing extraction of single teeth is in contrast to the high bleeding rate (7 of 38 cases, 18%) reported by Caliskan et al<sup>41</sup> for similar extractions; however, they did not provide information on the interval between drug intake and tooth extraction. Similarly, comparison of our overall bleeding rate of 4 of 100 patients (4%) with that reported by Yagyuu et al<sup>42</sup> (4 of 41 cases, 9.7%) is hampered by lack of information regarding their number of extractions per session, the proportion of patients with comorbidities, and the timing of extraction.

Our study has a few limitations, the first of which is its retrospective nature. The study involved a single center; if this warranted homogeneity, it also limited the sample size. Even if our sample size was larger than that in similar studies, the small number of bleeding events (good clinical outcome) damped the test power, preventing sound statistical conclusions on some issues.

Patients taking DOACs can be safely managed, even when affected by comorbidities. The 2 causes possibly favoring excessive bleeding can in fact be controlled by the dentist. The first is the timing of the extraction, which must respect an interval of at least 4 hours after the last DOAC intake. The second is the extraction of 2 or 3 contiguous premolars and molars, which should be avoided by scheduling more than 1 session. If 1 or both of these precautions cannot be satisfied, the collaboration of the patient's cardiologist needs to be sought.

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