



BRIEF REPORT

Dental extractions on direct oral anticoagulants vs. warfarin: The DENTST study

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Abstract

Background: Conflicting recommendations exist addressing the management of direct oral anticoagulants (DOACs) for invasive dental procedures.

Objectives: To determine the safety of DOAC continuation compared to warfarin continuation for dental extractions with regards to bleeding outcomes.

Methods: A single-center, prospective, cohort study was performed to compare 7-day bleeding outcomes between patients who continued their DOAC, and patients on warfarin with an International Normalized Ratio (INR) between 2.0 and 4.0. Blood tests including oral anticoagulant drug levels were measured immediately prior to extraction. The gauze used to apply pressure to the socket was weighed before and after extraction to estimate blood loss. Patients were contacted by phone 2 and 7 days after extraction.

Results: Eighty-six patients on a DOAC had a total of 145 teeth extracted, and 21 patients on warfarin had 50 teeth extracted. There were no major bleeding events. The rate of minor plus clinically relevant nonmajor bleeding was comparable between the DOAC and warfarin cohorts (36% and 43%, respectively; odds ratio, 0.75; 95% confidence interval, 0.29-1.98). Preextraction apixaban and dabigatran levels were comparable between bleeders and nonbleeders, while rivaroxaban levels were higher in those who bled. The weight change of gauze used to tamponade the socket was similar between the 2 cohorts.

Conclusion: Dental extractions on patients continuing DOACs led to bleeding rates similar to patients on warfarin with an INR between 2.0 and 4.0. There is no need to adjust DOAC dosing prior to dental extractions.

KEYWORDS

anticoagulants, antithrombins, factor Xa inhibitors, oral hemorrhage, tooth extraction, warfarin

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Essentials

- The management of direct oral anticoagulants (DOACs) for dental extractions is unclear.
- Bleeding rates after dental extractions were compared between patients on warfarin and DOACs.
- Bleeding rates were comparable between patients on warfarin and DOACs.
- Dental extractions can be performed without adjusting DOAC dosing or measuring drug levels.

1 | INTRODUCTION

Direct oral anticoagulants (DOACs) are now first-line treatment for the prevention of stroke/systemic embolism in patients with nonvalvular atrial fibrillation and treatment/prevention of venous thromboembolism.^{1,2} DOACs available in Australia are dabigatran, a direct thrombin inhibitor, and 2 factor Xa inhibitors, apixaban and rivaroxaban.

Periprocedural management of DOACs for procedures with minimal bleeding risk has been a challenge since DOACs entered clinical practice. Guidelines addressing dental procedures vary in their recommendations, ranging from DOAC continuation, avoiding times when DOAC drug levels are expected to be at their peak, to omitting 1 to 2 doses at the time of the procedure.³ Many of the earlier guidelines extrapolated from the warfarin data, in which drug continuation is well established in guidelines and in clinical practice.⁴⁻⁶ There is increasing evidence in support of DOAC continuation for dental procedures, albeit with methodological limitations in many of the published studies.^{3,7-10}

The aim of the Dental Extractions on NOAC Without Stopping Therapy (DENTST) study was to determine the safety of DOAC continuation compared to warfarin continuation for dental extractions with regard to bleeding outcomes. The secondary aim was to determine whether any of the predefined variables were associated with bleeding, including preextraction DOAC drug level and time from last DOAC ingestion.

2 | METHODS

2.1 | Patients

Consenting patients aged 18 years and above who presented to the Westmead Centre for Oral Health requiring dental extractions were included in the study if they were (a) on a DOAC with therapeutic intent, or (b) on warfarin with an International Normalized Ratio (INR) between 2.0 and 4.0 on the day of the procedure. Dental extractions of <4 contiguous teeth were allowed. Exclusion criteria included previous participation in the study, pregnancy, concomitant use of dual antiplatelet therapy, platelet count <50 ×10⁹/L, inadvertent omission of last DOAC dose prior to extraction, patient on warfarin with INR <2.0 or >4.0 on day of extraction, severe active oral infection associated with facial swelling, Cockcroft-Gault creatinine clearance <25 mL/min for patients on apixaban and <30 mL/min for patients on dabigatran or rivaroxaban, and surgical extraction of wisdom teeth.

2.2 | Extraction procedure

Use of an antibacterial mouthwash twice daily for 7 days prior to dental extraction was recommended but not mandated. Patients requiring infective endocarditis prophylaxis received a single dose of oral amoxicillin 2 g or clindamycin 600 mg 1 hour before extraction.⁵ Local anesthesia was achieved by local infiltration and/or regional anesthetic blocks using 2% lidocaine with 1:80 000 epinephrine. Extractions were either simple (elevation and forceps removal of the tooth) or surgical (requiring raising of a mucoperiosteal flap, bone removal, elevation, and forceps removal). Local hemostatic measures were performed for all extractions, namely, the placement of oxidized cellulose (Surgicel[®], Johnson & Johnson, North Ryde, NSW, Australia) in the saline-irrigated socket, which was then sutured with 3-0 chromic gut. Patients were instructed to bite on gauze for at least 30 minutes or until complete hemostasis was achieved. In the event of continued bleeding at 60 minutes after extraction, patients continued to bite on gauze soaked in 5% tranexamic acid solution.

2.3 | Bleeding outcomes

The weight difference in gauze before and after biting was measured to estimate immediate blood loss. Phone calls were made to patients 2 and 7 days after extraction to ascertain bleeding complications. Patients were also requested to contact the study dentist if they developed any bleeding.

Bleeding episodes were categorized as major according to the International Society on Thrombosis and Haemostasis definition,¹¹ with the additional definition of bleeding that threatened the airway. Clinically relevant nonmajor bleeding (CRNMB) was defined as bleeding that required medical intervention by a health care provider including oral anticoagulant discontinuation, bleeding that led to hospitalization or increased level of care without requiring surgical intervention, and bleeding that led to face-to-face evaluation. All other bleeds were categorized as minor.

2.4 | Laboratory assays

Blood samples were taken 30 to 60 minutes before extraction. All hemostasis testing was performed on STAR instrumentation (Diagnostica Stago, Parsippany, NJ, USA). INR was measured using Stago reagent. Dabigatran level was measured by dilute thrombin time using commercial reagents (Hemoclot; Hyphen BioMed,

TABLE 1 Patient and procedural characteristics

	Type of anticoagulant	
	Warfarin n = 21	DOAC n = 86
Patient characteristics		
Age, median (LQ; UQ)	71 (62; 79)	73 (67; 78)
BMI (kg/m ²), median (LQ; UQ)	28.8 (25.7; 31.6)	30.0 (26.2; 34.1)
Systolic blood pressure (mm Hg), median (LQ; UQ)	123 (118; 148)	133 (121; 146)
Cockcroft-Gault CrCl (mL/min), median (LQ; UQ)	78 (47; 121)	76 (54; 102)
Female gender, n (%)	3 (14)	32 (37)
Smoker, n (%)	1 (5)	7 (8)
Concurrent antiplatelet therapy, n (%)	0	9 (11)
Periodontitis as extraction indication, ^a n (%)	17 (81)	61 (71)
Oral anticoagulant indication, n (%)		
AF	13 (62)	69 (80)
VTE	5 (24)	13 (15)
AF + VTE	2 (10)	2 (2)
Other	1 (5)	2 (2)
DOAC dosing regimen, ^b n (%)		
		Apixaban
Higher dose		22 (54)
Lower dose		16 (39)
Other		3 (7)
		Dabigatran
		6 (40)
		8 (53)
		1 (7)
		Rivaroxaban
		25 (83)
		4 (13)
		1 (3)
Procedural characteristics		
Number of teeth extracted, median (LQ; UQ)	2 (1; 3)	1 (1; 2)
Extraction duration (mins), median (LQ; UQ)	22 (11; 37)	17 (11; 27)
Mouthwash use prior to dental extraction, n (%)	6 (29)	29/85 (34)
Preextraction antibiotic use, n (%)	3 (14)	10 (12)
Extraction of posterior teeth compared to anterior teeth only, n (%)	16 (76)	60 (70)
Gingival bleeding on probing, ^c n (%)	11/18 (61)	33/66 (50)
Surgical extraction compared to simple extraction, n (%)	2 (10)	15 (17)
Achievement of primary closure, n (%)	11 (52)	20 (23)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CrCl, creatinine clearance; LQ, lower quartile; NA, not applicable; UQ, upper quartile; VTE, venous thromboembolism.

^aNonperiodontitis indications include deep caries and cracked tooth.

^bHigher dose = apixaban 5 mg twice a day, dabigatran 150 mg twice a day, rivaroxaban 20 mg daily. Lower dose = apixaban 2.5 mg twice a day, dabigatran 110 mg twice a day, rivaroxaban 15 mg daily. Other (dosing outside the approved dosing regimen) = daily dosing of apixaban/dabigatran, alternate-day rivaroxaban.

^cBleeding on probing is an indication of active gingival inflammation.

Neuville-sur-Oise, France). Apixaban and rivaroxaban levels were measured by chromogenic anti-Xa assays using STA drug-specific calibrators and STA reagents. DOAC predicted on-therapy ranges

used at Westmead Hospital are based on published literature and are adopted from the University of Washington Anticoagulation Services website.¹²

2.5 | Statistical analysis

Statistical analysis was performed using the computer package IBM SPSS Statistics V25 (IBM Corporation, Armonk, NY, USA). Categorical variables were summarized using frequencies and percentages with 95% confidence intervals (CIs).^{13,14} Due to the skewed distribution of several continuous variables, medians and the lower to upper quartile (LQ, UQ) were used as summary statistics. Multiple logistic regression analysis was used to compare bleeding rates in DOAC vs. warfarin users adjusted for sex, number of teeth extracted, and primary closure rates. Odds ratio (OR) with 95% CI were used to quantify the strength of association.

2.6 | Ethics

This study was approved by the local ethics committee (HREC/15/WMEAD/425) and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615001009505).

3 | RESULTS AND DISCUSSION

A total of 195 teeth were extracted from 107 patients: 50 teeth from 21 patients on warfarin and 145 teeth from 86 patients on a DOAC (41 apixaban, 30 rivaroxaban, 15 dabigatran). Patient characteristics are summarized in Table 1. In comparison to DOAC users, patients on warfarin were more often male, had more teeth extracted, and had higher rates of primary closure (ie, wound edges able to be brought together). Almost all warfarin users in the study (20/21; 95%) had an INR between 2 and 3, while one patient (5%) had an INR between 3 and 4. Nine patients on warfarin had unexpected subtherapeutic INRs on the day of procedure and therefore were excluded from the study. Two patients on a DOAC were excluded due to inadvertent omission of their last dose.

In the majority of patients (82%), hemostasis was achieved within the 30-minute observation period immediately after extraction. The weight change in gauze used to apply pressure to the socket was comparable between the 2 groups (weight change of gauze per tooth,

TABLE 2 7-day bleeding outcomes

Bleeding event	Warfarin n = 21	DOAC n = 86
Minor only, n (%) (95% CI)	7 (33) (17.2-54.6)	26 (30) (21.5-40.6)
CRNMB, n (%) (95% CI)	2 (10) (2.7-28.9)	5 (6) (2.5-12.9)
Any, n (%) (95% CI)	9 (43) (24.5-63.5)	31 (36) (26.7-46.6)

Note: There were no major bleeding events. Any bleeding is the sum of minor and CRNMB events.

Abbreviations: CI, confidence interval; CRNMB, clinically relevant nonmajor bleeding; DOAC, direct oral anticoagulant.

median [LQ; UQ]: warfarin 1.5 g [1.0; 2.4], DOAC 2.3 g [1.3; 3.8]). This weight was a combination of blood and saliva, but accepting, in theory, that all the weight gain was due to blood, this represented only a few milliliters of blood loss that is unlikely to have any clinical consequences.

Postextraction bleeding outcomes are summarized in Table 2. No patient experienced a major bleeding event. Bleeding rates were comparable between DOAC and warfarin users (36% and 43%, respectively). The unadjusted OR for any bleeding on DOAC vs. warfarin was 0.75 (95% CI, 0.29-1.98), and the OR adjusted for sex, number of teeth extracted, and primary closure rates was 0.88 (95% CI, 0.31-2.53). Furthermore, CRNMB rates were similar between DOAC and warfarin users (6% and 10%, respectively). The unadjusted OR for CRNMB on DOAC vs. warfarin was 0.59 (95% CI, 0.11-3.26), and the OR adjusted for sex, number of teeth extracted, and primary closure rates was 0.90 (95% CI, 0.14-5.80). Five (6%) patients on a DOAC experienced CRNMB at median 3 days after extraction (range, 0-7), namely, bleeding that required resuturing (n = 2), temporary DOAC cessation (n = 2), and dental clinic review (n = 2). All CRNMB were successfully managed with local hemostatic measures and temporary DOAC cessation in 2 patients.

Bleeding rates between the DOAC types were comparable, as summarized in Table 3 (apixaban, 39%; rivaroxaban, 37%; dabigatran 27%). Preextraction apixaban and dabigatran levels were similar between the bleeders and nonbleeders, while rivaroxaban levels were approximately 2-fold higher in those who bled (Table 3). Most of the rivaroxaban patients who bled had ingested rivaroxaban the morning of the extraction (82%; 95% CI, 52.3-94.9), compared to 18% (95% CI,

TABLE 3 7-day bleeding outcomes stratified by DOAC type and preextraction DOAC level

	Apixaban n = 41	Rivaroxaban n = 30	Dabigatran n = 15
Bleeding event			
Minor only, n (%) (95% CI)	14 (34) (21.6-49.5)	9 (30) (16.7-47.9)	3 (20) (7.1-45.2)
CRNMB, n (%) (95% CI)	2 (5) (1.4-16.1)	2 (7) (1.9-21.3)	1 (7) (1.2-29.8)
Any, n (%) (95% CI)	16 (39) (25.7-54.3)	11 (37) (21.9-54.5)	4 (27) (10.9-52.0)
DOAC drug level			
Bleeders			
DOAC level (ng/mL), median (LQ; UQ)	112 (75; 170)	173 (55; 295)	96 (48; 147)
Nonbleeders			
DOAC level (ng/mL), median (LQ; UQ)	135 (97; 181)	79 (33; 191)	81 (38; 97)

Note: There were no major bleeding events. Any bleeding is the sum of minor and CRNMB events.

Abbreviations: CI, confidence interval; CRNMB, clinically relevant nonmajor bleeding; DOAC, direct oral anticoagulant; LQ, lower quartile; UQ, upper quartile.

5.1-47.7) who had ingested the last dose of rivaroxaban in the evening prior to the extraction. It is therefore conceivable that the daily dosing of rivaroxaban resulted in the higher peak levels (vs. twice daily dosing for the other DOACs). Although it is possible that taking rivaroxaban in the evening prior to teeth extractions may reduce bleeding, it remains that the overall bleeding rates on rivaroxaban were comparable to the other DOACs and to warfarin. For warfarin users, preextraction INRs were similar between bleeders and nonbleeders (INR, median [LQ; UQ]: bleeders, 2.3 [2.0; 2.4], nonbleeders, 2.3 [2.1; 2.5]). The patient with an INR between 3 and 4 had a minor bleed after extraction.

Preextraction DOAC levels varied greatly. Six patients had a DOAC level outside the predicted on-therapy range: 2 (2%) lower, and 4 (5%) higher than predicted levels. The patient with a low apixaban level (23 ng/mL) did not experience any bleeding, while the patient with a low dabigatran level (17 ng/mL) developed a CRNMB

on day 0 despite initially achieving complete hemostasis within the 30-minute observation period. The 4 patients with higher-than-predicted levels were all on rivaroxaban 20 mg daily (436, 470, 487, 581 ng/mL), only 1 of whom had a minor bleed.

Although conclusive associations cannot be made given the small sample size, bleeding in the DOAC users tended to occur after extraction of posterior teeth (81% vs. 64%) and surgical extraction (26% vs. 13%) (Table 4). Extraction of posterior teeth is predicted to result in larger extraction socket surface, while surgical extraction may reflect technically more difficult procedures, potentially resulting in greater tissue damage. Variables predicted to reflect gingival inflammation were similar between bleeders and nonbleeders, including gingival bleeding on probing, periodontitis as extraction indication, and lack of mouthwash use. Variables that may potentially influence DOAC levels were also similar, including

TABLE 4 Potential bleeding risk factors for patients taking a DOAC

Variable	Any bleed n = 31	No bleed n = 55
Age, median (LQ; UQ)	74 (71; 79)	73 (66; 78)
BMI (kg/m ²), median (LQ; UQ)	29.4 (23.4; 34.0)	30.1 (26.4; 34.6)
Systolic blood pressure (mm Hg), median (LQ; UQ)	135 (128; 146)	131 (120; 147)
Number of teeth extracted, median (LQ; UQ)	2 (1; 2)	1 (1; 2)
Extraction duration (min), median (LQ; UQ)	20 (15; 32)	15 (11; 24)
Cockcroft-Gault CrCl (mL/min), median (LQ; UQ)	71 (54; 101)	82 (59; 107)
Hours since DOAC ingestion, median (LQ; UQ)	5.0 (3.3; 7.0)	5.5 (3.3; 6.8)
Higher DOAC dose, ^a n (%) (95% CI)	19 (61) (43.8-76.3)	35 (64) (50.4-75.1)
Patient reported history of excessive bleeding, n (%), (95% CI)	7 (23) (11.4-39.8)	9 (16) (8.9-28.3)
Smoker, n (%) (95% CI)	2 (6) (1.8-20.7)	5/54 (9) (4.1-19.9)
Concurrent antiplatelet therapy, n (%) (95% CI)	3 (10) (3.4-24.9)	6 (11) (5.1-21.8)
Mouthwash use prior to dental extraction, n (%), (95% CI)	13 (42) (26.4-59.3)	16/54 (30) (19.1-42.8)
Preextraction antibiotic use, n (%) (95% CI)	2 (6) (1.8-20.7)	8 (15) (7.7-26.2)
Extraction of posterior teeth compared to anterior teeth only, n (%) (95% CI)	25 (81) (63.7-90.8)	33 (64) (46.8-71.9)
Gingival bleeding on probing, ^b n (%) (95% CI)	14/26 (54) (35.5-71.3)	19/41 (48) (32.1-61.3)
Periodontitis as extraction indication, ^c n (%) (95% CI)	21 (68) (50.1-81.4)	40 (73) (59.8-82.7)
Surgical extraction compared to simple extraction, n (%) (95% CI)	8 (26) (13.7-43.3)	7 (13) (6.3-24.1)
Achievement of primary closure, n (%) (95% CI)	8 (26) (13.7-43.3)	12 (22) (13.0-34.4)

Abbreviations: BMI, body mass index; CI, confidence interval; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; LQ, lower quartile; UQ, upper quartile.

^aHigher dose = apixaban 5 mg twice a day, dabigatran 150 mg twice a day, rivaroxaban 20 mg daily.

^bBleeding on probing is an indication of active gingival inflammation.

^cNonperiodontitis indications include deep caries and cracked tooth.

body mass index, renal function, time from last DOAC ingestion, and DOAC dose.

In this study, continuing DOACs at the time of teeth extractions led to bleeding rates similar to patients on warfarin who had an INR between 2.0 and 4.0, adding further evidence to the growing literature recommending DOAC continuation for dental extractions.^{7,9,10,15} The majority of the bleeding episodes were minor “nuisance” bleeds, with only 6% of DOAC patients developing a CRNMB in the 7 days following dental extractions. Therefore, timing dental extractions to avoid peak concentrations^{7,16} or targeting trough concentrations¹⁷ is unlikely to provide any additional clinical benefit. Omitting DOAC doses¹⁸ places the patient at undue risk for thromboembolism, yet upon DOAC commencement, the patient will again be at risk of bleeding.

In this study, there was no “safe lower limit” of DOAC drug level below which dental extractions may be performed without postextraction bleeding. Therefore, we do not recommend measuring DOAC drug levels prior to dental extractions to predict bleeding outcomes. Our findings support the current practice of standardized perioperative DOAC management based on the drug’s pharmacokinetic properties and type of surgical procedure, rather than drug levels.^{19,20}

We recognize that this study has a number of limitations. First, as the sample size of each cohort was limited to the eligible patients who presented to our department and provided informed consent, sample size calculations were not performed. Second, the number of patients was relatively small, particularly for those on warfarin. Despite our best efforts, recruiting patients on warfarin was difficult due to few patients on warfarin presenting to our hospital with the need for dental extractions. In addition, several warfarin patients had to be excluded from the study due to unexpected subtherapeutic INRs on the day of the procedure. Third, patients were on various DOAC dosing regimens, which may have influenced outcomes. Fourth, given that this study was not randomized, results may have been affected by residual confounding.

In conclusion, dental extractions incorporating local hemostatic measures was just as safe for patients continuing their usual DOAC dosing regimen as it was for patients on warfarin with a therapeutic INR. Our results suggest that there is no need to adjust DOAC dosing prior to dental extractions, nor is there a need to time the dental extractions around DOAC doses. DOACs and warfarin can be safely continued for simple or surgical dental extractions, eliminating the thrombotic risk associated with anticoagulant interruption.

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RELATIONSHIP DISCLOSURE

JC has received personal fees from Pfizer/BMS, Bayer, Boehringer Ingelheim, Takeda, Alexion, and Mylan, and travel support from

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AUTHOR CONTRIBUTIONS

All authors contributed to study design. YG recruited the participants and performed the majority of dental extractions. YB and YG collected, analyzed, and interpreted the data. EF helped to arrange laboratory testing. YB drafted the manuscript. All authors revised the manuscript.

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