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Postextraction bleeding in patients taking warfarin: Focus on the utility of the HAS-BLED score : a retrospective cohort study

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3 Postextraction bleeding in patients taking warfarin: Focus on the utility of the HAS-BLED score :
4 a retrospective cohort study
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14

15 16 **ABSTRACT**

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18 Objective: Post-extraction bleeding is often experienced in our clinical unexpectedly. Therefore,
19 this study aimed to clarify the risk factors for bleeding after tooth extraction in patients taking
20 warfarin and to verify whether the HAS-BLED score is useful in predicting post-extraction
21 bleeding.
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24 Design: Retrospective cohort study.
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26 Setting: Department of Oral and Maxillofacial Surgery, Tokyo Women's Medical University.
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28 Participants: Subjects comprised 258 sequential cases (462 teeth) of inpatients who had
29 undergone tooth extraction between January 1, 2010 and December 31, 2012 while continuing
30 anticoagulant therapy.
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33 Main outcome measure: Post-extraction risk factors of bleeding. As predicting variables of
34 multivariate logistic analysis, extraction site, teeth type, stability of teeth, and extraction
35 procedure, PT-INR value, platelet count, HAS-BLED score, concomitant antiplatelet agents use
36 were collected.
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39 Results: Post-extraction bleeding was noted in 21 (8.1%) of the 258 cases. The risk of post-
40 extraction bleeding for wisdom teeth extraction was approximately seven times more than that
41 for incisor teeth (RR = 6.894; P = 0.027, univariate analysis). The HAS-BLED score was
42 insufficient for predicting post-extraction bleeding (AUC = 0.548, P = 0.867, multivariate
43 analysis). The risk of post-extraction bleeding was approximately three times more for patients
44 taking oral antiplatelet agents (RR = 2.881, P = 0.035, multivariate analysis).
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47 Conclusions: The HAS-BLED score alone was insufficient to predict post-extraction bleeding.
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50 The concomitant use of oral antiplatelet agents is a risk factor for post-extraction bleeding.
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53 However, because this was a retrospective study conducted at a single institution, we believe that
54 a large-scale prospective cohort study, including outpatient tooth extraction cases, will be
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necessary in the future.

Strengths and limitations of this study

- We investigated all cases of tooth extraction, including wisdom tooth and impacted tooth extractions.
- No previous reports have investigated the effects of each individual tooth extracted, extraction procedure, and effects of concomitant antiplatelet agents on post-extraction bleeding using statistical analyses and demonstrated a high level of evidence for correlations.
- This is the first study to verify the usefulness of the HAS-BLED score for predicting post-extraction bleeding risk.
- Because this is a retrospective cohort study conducted at a single institution, a large-scale, prospective cohort study including outpatients is required in the future.

INTRODUCTION

In western countries, patients undergoing anticoagulant therapy and who are scheduled to undergo tooth extraction are typically advised to undergo extraction while continuing anticoagulant therapy^{1,2}. In Japan, guidelines, such as the “Guidelines for management of anticoagulant and antiplatelet therapy in cardio-vascular disease³” as well as the JCS Joint Working Group’s “Guidelines for Pharmacotherapy of Atrial Fibrillation⁴” recommend that tooth extraction be performed while continuing anticoagulant therapy. Performing tooth extraction without temporarily discontinuing or reducing the dosage of anticoagulants offers a significant advantage of preventing the onset of potentially fatal thromboembolism⁵. However, there is an additional risk of bleeding due to the invasive treatment, and thus, sufficient measures must be taken to stop excessive post-extraction bleeding; furthermore, care must be taken to limit post-extraction bleeding. In the past, a number of studies have investigated tooth extraction while continuing anticoagulant therapy, with the frequency of post-extraction bleeding reported to range from 0% to 26%⁶⁻¹⁷. As each study involved significant differences in patient backgrounds (e.g., subjects including simple extraction cases only or differing prothrombin time-international normalized ratio (PT-INR) ranges), simple comparisons of post-extraction bleeding rates across different studies have limited value. Furthermore, anticoagulant therapy is known to be effective in Japanese people because they are highly sensitive to warfarin potassium

(hereinafter: “warfarin”) ¹⁸⁾. For example, although the recommended range for PT-INR in cases of valvular heart disease is 2.0–3.0, a slightly less intense treatment range is set for Japanese patients (1.6–2.8) ^{3,4)}. Accordingly, it appears inappropriate to compare the results of reports of patients in western countries, which are likely to include more cases of PT-INR treatment levels of 3.0 or above, with those of patients in Japan. Moreover, as is the case with warfarin, it is recommended to perform tooth extraction on patients taking antiplatelet agents at the maintenance antiplatelet therapy dose ^{19,20)}. However, the effects of taking warfarin and antiplatelet agents on post-extraction bleeding are unclear.

Recently, the HAS-BLED score ²¹⁻²³⁾ has been used as an index for evaluating the risk of bleeding complications in patients undergoing anticoagulant therapy. The HAS-BLED score evaluates nine risk factors for bleeding. The European Society of Cardiology guidelines ²⁴⁾ has stated that patients who score three points or higher are at a high risk of bleeding complications. No reports to date have investigated whether the HAS-BLED score is useful in predicting the risk of post-extraction bleeding.

The preoperative identification of patients with a high risk of post-extraction bleeding could facilitate appropriate preparations prior to performing tooth extraction. Therefore, we examined post-extraction bleeding risk factors in patients undergoing anticoagulant therapy with PT-INR treatment at levels of ≤ 3.0 and who underwent tooth extraction, including extraction of wisdom or impacted teeth, and additionally investigated whether the HAS-BLED score is useful in predicting post-extraction bleeding.

MATERIAL AND METHODS

Study design

This was a retrospective cohort study.

Study population and eligibility criteria

This study included patients who were hospitalized at the Department of Oral and Maxillofacial Surgery, Tokyo Women’s Medical University and who had undergone tooth extraction between January 1, 2010 and December 31, 2012 while receiving a maintenance dose of anticoagulant therapy. As a rule, tooth extraction for patients undergoing anticoagulant therapy shall be performed after the patient is admitted to the hospital. Antiplatelet agents, which were being

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3 concomitantly taken, were continued to be administered at the maintenance dose. Exclusion
4 criteria were as follows: 1) patients younger than 20 years at the time of hospital admission; 2)
5 presence of comorbid blood disease; and 3) a PT-INR level of ≥ 3.1 as indicated by the results of
6 the blood tests performed on the day of tooth extraction. Patients underwent follow-up
7 examinations for 1 month after discharge. The physician and nurse records obtained from
8 medical examination records were registered in a database along with the results of the clinical
9 tests. When the same patient was hospitalized and underwent tooth extraction more than once
10 during the study period, all instances were registered.
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18 19 20 Tooth extraction procedure

21 The primary physician for the underlying disease of each patient was preoperatively consulted
22 regarding the general medical status of the patient, including their use of anticoagulants. When
23 acute symptoms, such as periodontal abscesses, apical periodontitis, or pericoronitis were present
24 around the tooth that was determined to be eligible for tooth extraction, antibacterial drugs were
25 administered prior to tooth extraction and anti-inflammation procedures, such as incision and
26 drainage, were performed as necessary. During tooth extraction, electrocardiograms, blood
27 pressure, pulse rate, and percutaneous oxygen saturation levels were monitored. For local
28 anesthesia, 1.8–3.6 ml of 2% lidocaine containing 1/80000 epinephrine was administered. Tooth
29 extraction was performed with minimal invasion. When multiple teeth were indicated for
30 extraction and comprised within 1/3 of the jaw area, all the teeth were extracted in one procedure.
31 When the teeth comprised over 1/3 of the total jaw area, multiple teeth were extracted in one
32 procedure if the procedure was expected to take <30 min while considering the age and any
33 comorbid diseases of the patient. After extraction, a curettage of the inflammatory granulation
34 tissue around the wound border was performed, hemostatic gelatin sponge was inserted into the
35 socket (product name: Spongel, Astellas Pharma Inc.), and suturing was performed to reduce the
36 size of the wound border. The patient was requested to bite down on the absorbent cotton for
37 20 min after completing tooth extraction to achieve pressure hemostasis. At 30 min after tooth
38 extraction, the patient was examined to confirm that the bleeding had stopped. After extraction,
39 patients were instructed to avoid strong or frequent gargling and to rest as much as possible.
40 Post-extraction meals comprised rice gruel. In the patient group with a high risk of adverse
41 effects due to effective endocarditis onset ²⁵⁾, 2 g ampicillin was administered 30 min prior to
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3 tooth extraction, and 1 g ampicillin was intravenously administered 6 h after the initial dose.
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5 Patients who were allergic to penicillin were intravenously administered 600 and 300 mg
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7 clindamycin 30 min before tooth extraction and 6 h after the initial dose, respectively. For
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9 patients with a heart disease that did not necessarily require IE prophylaxis for dental procedures
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11 or patients receiving anticoagulant therapy, oral antibacterial drugs (750–1000 mg/day
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13 amoxicillin, 300 mg/day cefditoren pivoxil, 300 mg/day cefcapene pivoxil, and 500 mg/day
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15 levofloxacin) were administered for 3 days following tooth extraction. Five doses of analgesics
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17 comprising loxoprofen sodium or acetaminophen were prescribed as a potion when pain was
18
19 experienced.

20 21 Post-extraction Bleeding

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23 Patients who complained of bleeding during the examination 30 min after tooth extraction and
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25 who underwent some sort of hemostatic procedure were categorized in the post-extraction
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27 bleeding group. Hemostatic procedures performed in accordance with the decisions by the
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29 examining physician are described below. For mild bleeding, the patient was requested to bite
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31 down on a gauze or absorbent cotton placed on the tooth extraction wound to achieve pressure
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33 hemostasis. For cases of moderate or higher bleeding in which there was a large amount of
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35 bleeding that was determined to be difficult to resolve using primary hemostasis, we aimed to
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37 utilize the local vasoconstrictive effects of the local dental anesthetic epinephrine and
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39 administered a dose of 1.0–1.8 ml to achieve infiltration anesthesia around the tooth extraction
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41 wound. Pressure was then applied to the wound by requesting the patient to bite down on gauze
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43 or absorbent cotton. When it was determined that the bleeding could not sufficiently be halted by
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45 pressure hemostasis alone, the area was additionally filled with local hemostatic agents or
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47 additional or repeat suturing of the wound was performed as necessary. For cases of repeated
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49 bleeding or prolonged exudative bleeding after hemostatic procedures, a hemostatic splint was
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51 fabricated to apply continuous pressure on the wound and to allow the patient to rest. This was
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53 fitted after applying a cavity lining with a periodontal pack or denture base tissue conditioner.
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55 For cases in which the patient complained of bleeding and was examined but hemostatic
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57 procedures were not deemed necessary, patients were instructed to adequately rest and refrain
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59 from excessive gargling; regular follow-up examinations were performed. These patients were
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not included in the post-extraction hemorrhage group. Patients who did not require treatments,

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3 such as those outlined above for after bleeding, were placed into the non-post-extraction
4 hemorrhage group.
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8 9 Bleeding risk factors for tooth extraction

10 Details of extracted teeth, surgical procedure, bleeding tendency, and concomitant antiplatelet
11 agents were investigated as possible factors affecting post-extraction bleeding. With respect to
12 details noted regarding extracted teeth, the extraction site (maxilla/mandible), type of teeth
13 (incisor/premolar/molar/wisdom), and stability of teeth were examined. Regarding the stability
14 of teeth, teeth exhibiting alveolar bone resorption of at least 2/3 of the tooth root length as
15 determined by preoperative X-rays or teeth found to have clinical grade III instability were
16 defined to have poor stability. Other teeth were considered to have good tooth stability. The
17 surgical procedure was classified into simple and surgical extractions. For surgical extraction, the
18 strategy followed was to make an incision in the gingiva, detach and turn the mucoperiosteal flap
19 over, and extract the tooth after cutting off the alveolar bone or root separation. All extractions
20 other than that defined above were simple extractions. With regard to bleeding tendency, PT-
21 INR value and platelet count were investigated.
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34 HAS-BLED score

35 The HAS-BLED score was evaluated according to the European Society of Cardiology
36 guidelines²⁴⁾ (Table 1) and is described below. Patients with systolic blood pressure of
37 ≥ 160 mmHg, which was measured on arrival at the hospital, were categorized as having
38 “hypertension.” Patients receiving hemodialysis or those who had a kidney transplant; patients
39 with a serum creatinine level of ≥ 2.26 mg/dl in the most recent blood test; patients exhibiting
40 chronic liver disease, such as liver cirrhosis, and bilirubin levels of at least two times the normal
41 upper limit; and patients having at least three times the normal upper limit of either alanine
42 transaminase, aspartate aminotransferase, or alkaline phosphatase levels were categorized as
43 having “abnormal renal and liver function.” “Stroke” or “bleeding” was determined according to
44 the information of patients obtained from medical interviews on admission to the hospital.
45 “Labile INRs” were described as being in a poorly controlled anticoagulation state in cases, such
46 as directly after initiating anticoagulant therapy or during poor compliance, and additionally
47 during detection of a level of PT-INR ≥ 3.1 on the morning of tooth extraction. The “elderly”
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3 categorization was defined as a patient age ≥ 65 years at the time of tooth extraction. Patients
4 with long-term administration of antiplatelet agents or non-steroidal anti-inflammatory drug
5 (NSAIDs) or patients with alcohol dependence were categorized as “drug and alcohol.” One
6 point was allocated for each of these categories if a patient was applicable. Thus, patients were
7 scored according to a possible full score of nine points.
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10 11 12 13 14 Selection of representative teeth

15 One representative tooth was selected when the same patient underwent extraction of multiple
16 teeth. However, when the same patient underwent multiple tooth extraction operations during
17 different hospitalization periods, representative extracted teeth were selected for each instance.
18 The most posterior tooth was selected as the representative tooth, and in cases of multiple
19 posterior teeth, the upper tooth or the tooth showing good stability was selected.
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25 26 27 Statistical analyses

28 Univariate and multivariate logistic analysis were applied to analyze the bleeding risk factor for
29 tooth extraction data with the presence/absence of post-extraction bleeding as the response
30 variable and bleeding risk factor as the explanatory variable. The two variable values were used
31 to describe tooth extraction site (maxilla/mandible), four variable values were used to describe
32 the type of teeth (incisor/premolar/molar/wisdom), two variable values were used to describe
33 stability of teeth (good/poor), and two variable values were used to describe the surgical
34 procedure (simple /surgical extraction). For the PT-INR value and platelet count, the actual
35 measured values were analyzed as continuous variables, and the HAS-BLED score was used in
36 analysis with both a continuous and nominal variable. Concomitant antiplatelet agents were
37 evaluated as two variable values (yes/no). During logistic analysis, we calculated the risk ratio,
38 95% confidence interval (CI), and p value. The risk ratio was calculated as the ratio of maxilla to
39 mandible for a site, the tooth type within anterior teeth for type of teeth, good to poor for the
40 condition of the periodontium, and from surgical to simple for the surgical procedure. The risk
41 ratio for the HAS-BLED score was calculated for each level. For concomitant antiplatelet agents,
42 the risk ratio of “yes” to “no” was calculated. In multivariate analysis, risk factors were
43 combined to create post-extraction bleeding analysis models. For each model, we plotted the
44 receiver operating characteristic (ROC) curve and calculated the area under the curve (AUC) in
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addition to the p value and 95% CI for the C-statistic model overall. Many screening tools used a C-statistic value of ≥ 0.70 . We used C-statistic to compare between each model. Model 1 was constructed from extracted tooth state, surgical procedure, and bleeding tendency. Model 2 was constructed from the HAS-BLED score only. Model 3 was constructed by adding the HAS-BLED score to Model 1. Model 4 was constructed by adding concomitant antiplatelet agents as an explanatory variable to Model 1. Data were analyzed with the use of JMP Pro 11 software (2014 SAS Institute Inc., US) with a two-tailed alpha level of 0.05.

Ethics

This study was approved by the ethical review board of the Tokyo Women's Medical University (approval number: 3079). The first and second authors take complete responsibility for the integrity of the data and the accuracy of the data analysis.

RESULTS

A total of 462 extracted teeth in 258 patients (males: 157, females: 101, mean age: 66.4 years) were analyzed. Post-extraction bleeding was observed in 21 patients (8.1%).

Patient characteristics

Post-extraction bleeding was noted in 21 patients (males: 14, females: seven, mean age: 63.4 ± 13.2 years). Table 2 shows the underlying diseases for anticoagulant therapy. Mean warfarin dosage was 3.9 ± 1.4 mg, and median PT-INR was 2.1 (1.8–2.5). Mean platelet count was $16.8 \pm 5.3 \times 10^4/\mu\text{l}$. Eleven patients were taking only warfarin, whereas 10 were taking an antiplatelet agent in addition to warfarin. Aspirin was administered as the antiplatelet agent to all cases.

The non-post-extraction hemorrhaging group included 237 patients (males: 143, females: 94, mean age: 66.6 ± 13.7 years). Underlying diseases for anticoagulant therapy are shown in Table 2. Mean warfarin dosage was 3.2 ± 1.3 mg. The mean (25 percentile, 75 percentile) of PT-INR was 2.0 (1.8, 2.3). Mean platelet count was $18.2 \pm 5.8 \times 10^4/\mu\text{l}$. A total of 174 patients were taking warfarin only, whereas 63 patients were taking warfarin and an antiplatelet agent. Table 2 shows a breakdown of the antiplatelet agents. Seven patients who were taking two types of antiplatelet agents were all included in the non-post-extraction hemorrhaging group. A statistically significant difference was noted for warfarin dosage; however, no difference was

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3 noted for PT-INR. No differences were noted for age, sex, platelet count, or concomitant use of
4 antiplatelet agents.
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7 8 9 Details of extracted tooth

10 In the post-extraction hemorrhaging group, the tooth extraction site in 14 and seven cases was
11 the maxilla and mandible, respectively. For the non-post-extraction hemorrhaging group, it was
12 the maxilla and mandible in 122 and 115 cases, respectively. Thus, no differences were noted
13 between the two groups ($P = 0.254$, Fisher's exact test).
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16 17 18 Results for teeth type

19 Numbers of incisor:premolar:molar:wisdom teeth were 1:2:9:9, respectively, in the post-
20 extraction hemorrhaging group and 36:65:89:47, respectively, in the non-post-extraction
21 hemorrhaging group. Thus, a statistically significant difference was noted between the two
22 groups ($P = 0.039$, Fisher's exact test).
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25 In the post-extraction hemorrhaging group, the stability of teeth was good in 17 cases and poor in
26 four. In the non-post-extraction hemorrhaging group, stability was good in 158 cases and poor in
27 79. No statistically significant difference was noted between the two groups ($P = 0.227$, Fisher's
28 exact test).
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31 32 33 Extraction procedure

34 In the post-extraction hemorrhaging group, the extraction procedure selected was simple
35 extraction in 17 cases and surgical extraction in four cases. In the non-post-extraction
36 hemorrhaging group, the procedure selected was simple extraction in 165 cases and surgical
37 extraction in 72 cases. No differences were noted between the two groups ($P = 0.328$, Fisher's
38 exact test).
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41 42 43 Number of teeth extracted per operation

44 The number of teeth extracted per operation was 1.7 ± 0.6 in the post-extraction hemorrhaging
45 group and 1.8 ± 1.1 in the non-post-extraction hemorrhaging group. There were no cases of
46 multiple extractions of four or more teeth in the post-extraction hemorrhaging group. No
47 differences were noted between the two groups with regards to the number of teeth extracted per
48 operation ($P = 0.576$, Student's t-test).
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51 52 53 HAS-BLED score

54 The highest HAS-BLED score obtained was three points. The mean score was 1.3 ± 0.9 in the
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post-extraction hemorrhaging group and 1.2 ± 0.8 in the non-post-extraction hemorrhaging group. No statistically significant differences were noted between the two groups ($P = 0.467$, Student's t-test). In both the post-extraction and non-post-extraction hemorrhaging groups, scores were highest for the "elderly" group, followed by the "drug and alcohol" group, and then the "stroke" group.

Statistical examination

Univariate analysis demonstrated statistically significant differences between the wisdom teeth and incisor (RR = 8.894, $P = 0.027$) and for between concomitant antiplatelet agents (yes/no) (RR = 2.511, $P = 0.500$). RR was ≤ 1 for surgical procedure and platelet count. No statistically significant difference was noted for a HAS-BLED score of ≥ 3 compared with a HAS-BLED score of ≤ 2 (RR = 1.362, $P = 0.7033$).

No statistically significant differences were noted within multivariate analysis for any of the parameters in the models 1, 2, or 3. In Model 4, a statistically significant difference was noted for antiplatelet agents (yes) in the non-post-extraction hemorrhaging group (RR = 2.881, $P = 0.035$). AUCs for models 1, 3, and 4 were 0.7, with a statistically significant difference noted in Model 4 only. AUC for Model 2 was the lowest at 0.5, and a statistically significant difference was noted between models 2 and 3 ($P = 0.004$).

Discussion

Many cases of tooth extraction performed while continuing anticoagulant therapy have been reported; tooth extraction may be performed while the patient continues the maintenance dose of anticoagulants if PT-INR is within the treatment range (PT-INR < 3.5–4.0) and local hemostasis is properly performed²⁶⁻²⁸). The optimal treatment range for warfarin in Japanese patients is considered to be PT-INR in a range of 1.6–3.0⁴), and it is recommended that tooth extraction be performed while continuing the maintenance dose of anticoagulants. However, in clinical settings, it is not uncommon to encounter post-extraction hemorrhaging during tooth extraction in cases of PT-INR ≤ 3 . Iwabuchi et al.²⁹) reported through a multicenter, large-scale study that risk factors for post-extraction bleeding in patients taking warfarin were age, PT-INR, and inflammation at the extraction site. Although many reports to date have not included cases of surgical extraction, such as the extraction of wisdom teeth and impacted teeth, these types of surgical extraction are often performed within clinical settings. Therefore, this study targeted

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3 cases that were managed according to the optimal treatment range for Japanese patients (PT-
4 INR \leq 3.0) and investigated all cases of tooth extraction, including the extraction of wisdom
5 teeth, impacted teeth, and multiple teeth concurrently. Our investigation of risk factors for
6 bleeding included extracted tooth state and surgical procedure. The HAS-BLED score is used in
7 the field of cardiology to evaluate the risk of hemorrhagic complications. We verified whether
8 the score is additionally useful for the evaluation of post-extraction hemorrhaging risk.

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10 We have many patients receiving anticoagulant therapy because of circulatory diseases at our
11 facility. As a rule, tooth extraction is performed on an inpatient basis because preoperative
12 antibacterial agent administration and monitoring of post-invasive procedures are necessary.
13 Approximately 50% of patients in this study had undergone heart valve replacement surgery
14 prior to tooth extraction.

15
16 Our investigation of 258 tooth extraction patients indicated that post-extraction bleeding
17 occurred in 21 patients (8%) or in 39 of the total 462 extracted teeth (8.4%). Various methods of
18 hemostasis have been reported for cases of tooth extraction performed while continuing
19 anticoagulant therapy. These include pressure hemostasis only, wound suturing, and the
20 application of local hemostatic agents³⁰⁻³³. To implement hemostasis, we placed a hemostatic
21 gelatin sponge in the extraction socket and routinely conducted pressure hemostasis using
22 absorbent cotton with suturing of the wound. Patients were examined 30 min after tooth
23 extraction to confirm whether the bleeding had stopped. Hemostasis was determined to have
24 been sufficient for all cases. As all patients underwent tooth extraction on an inpatient basis, the
25 patient could rapidly be examined by a physician or nurse and could receive early diagnosis and
26 appropriate treatment if post-extraction bleeding was suspected. However, although patients
27 were examined, many did not require hemostatic treatment. Of the patients who exhibited post-
28 extraction bleeding, no systemic hemostatic treatment, such as blood transfusion, was required in
29 any case.

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31 Investigation of conditions of the individual teeth extracted indicated that post-extraction
32 bleeding risk was five to six times higher for wisdom teeth compared with that for anterior teeth.
33 Extraction site and stability had little effect. Although no differences were observed for the
34 number of teeth extracted in one treatment, there were no cases of multiple extractions of four
35 teeth or more in the post-extraction hemorrhaging group. Results indicated that surgical
36 extraction hardly had any effect on post-extraction bleeding (RR = 0.539, P = 0.256). However,
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3 because cases that we defined as invasive tooth extraction also included many cases showing a
4 short tooth root remaining , we believe that this may have greatly affected the results.

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7 The effects of warfarin are easily influenced by factors, such as interaction with meals and/or
8 drugs, and additionally by the general state of the patient. In this study, to accurately determine
9 the anticoagulation state directly before tooth extraction, all blood tests were performed before
10 breakfast on the tooth extraction day or the first tooth extraction day if tooth extraction was
11 planned on consecutive days. Although post-extraction bleeding cases were being administered
12 high doses of warfarin, no difference was observed for PT-INR. There were no cases showing an
13 unstable anticoagulation state directly after warfarin introduction or with poor compliance.
14 Because cases of PT-INR > 3.1 were excluded on the basis of the eligibility criteria, no cases
15 were classified as labile INRs according to the HAS-BLED score. Accordingly, the PT-INR
16 value was investigated using actual measured values as the continuous variable. There were no
17 statistically significant differences noted for PT-INR values by either univariate or multivariate
18 analysis ($P \geq 0.1$), suggesting that the PT-INR value had little effect on post-extraction bleeding
19 in patients undergoing anticoagulant therapy while being managed within the optimal treatment
20 range (PT-INR ≤ 3.0).

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23 The HAS-BLED score is used in the field of cardiology to evaluate the risk of hemorrhaging in
24 patients showing good anticoagulation. As it would be highly significant if the HAS-BLED score
25 could be additionally used for predicting the risk of post-extraction hemorrhaging, we evaluated
26 its use in this study. In our study, the highest HAS-BLED score was three points. A score of one
27 point was the most commonly achieved among the 137 patients (53%). The most common risk
28 factor was found to be age (174 patients; 67%). No difference was noted for the mean HAS-
29 BLED score between the post-extraction hemorrhaging and non-post-extraction hemorrhaging
30 groups. The European Society of Cardiology has proposed that a score of HAS-BLED ≥ 3
31 indicates a high risk of hemorrhagic complications. In cases of post-extraction hemorrhaging, we
32 compared patients with a HAS-BLED score of three or higher and those with a score of two or
33 lower but did not detect any statistically significant difference (univariate analysis; RR = 1.362,
34 $P = 0.703$). Multivariate analysis indicated that there was little risk associated with the score
35 increasing by one (Table 6). AUC for HAS-BLED score alone (Model 2) was 0.55, which was
36 the lowest for all of the models we constructed. In Model 3, to which the details of extracted
37 teeth were added to the HAS-BLED score, AUC was 0.745, suggesting that this model is useful

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3 for predicting post-extraction bleeding. However, a statistically significant difference was noted
4 for Model 2 versus Model 3 ($P = 0.004$), indicating that the HAS-BLED score alone was
5 insufficient for predicting post-extraction bleeding.
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9 No fixed consensus has been reached regarding the concomitant use of warfarin and antiplatelet
10 agents because some reports have indicated that this increases the risk of post-extraction
11 bleeding^{1,34)}, whereas other reports have suggested that antiplatelet agents have little effect³⁵⁾.
12 Both of our univariate and multivariate analyses results indicated that the use of concomitant
13 antiplatelet agents was a significant factor affecting post-extraction bleeding. Of the models that
14 we created in this study, Model 4 exhibited the highest predictive ability for post-extraction
15 bleeding (AUC = 0.76, $P = 0.0309$). It has been reported that the concomitant use of two
16 antiplatelet agents significantly increases the frequency of intracranial hemorrhaging³⁶⁾.
17 Furthermore, a prospective observational study of hemorrhagic complications in Japanese
18 cerebral infarction patients³⁷⁾ found that compared with patients taking one antiplatelet agent
19 only; those taking two or three antiplatelet agents along with warfarin clearly exhibited higher
20 annual onset rates of intracranial hemorrhaging. We believe that these results suggest that
21 concomitant antiplatelet agents are a risk factor for post-extraction bleeding.
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25 The limitations of this study included the fact that data were obtained only at a single facility and
26 that outpatients were not included in the subjects investigated. Many patients treated at our
27 facility suffer from circulatory diseases (post-operative valve replacement patients are
28 particularly common). Furthermore, because our study excluded patients who exhibited PT-
29 INR of ≥ 3.1 during the blood testing performed on the day of tooth extraction, the current study
30 included patients whose anticoagulant therapy was being well managed. Thus, our subjects did
31 not exactly constitute generalized cases of tooth extraction patients taking warfarin. Moreover,
32 because this was a retrospective study, we believe that a large-scale, prospective, cohort study
33 including outpatient tooth extraction cases required to be conducted in the future.
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37 Moreover, we could not examine the drug interaction effects because our subjects included both
38 patients who intravenously received antibacterial agents and those who received oral
39 administration. Warfarin use results in a number of drug interactions, and many antibacterial
40 agents and NSAIDs have been reported to increase anticoagulant effects³⁸⁾. However, some
41 reports have stated that in most stable anticoagulant therapy patients, exposure to antibacterial
42 agents causes no clinical problems³⁹⁾; furthermore, other reports have found that NSAIDs and
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antibacterial agents often increased warfarin effects in cases of long-term administration¹⁷). We also believe that the short-term or low-dose administration of NSAIDs or antibacterial agents does not cause any prolongation of clinically problematic PT-INR.

Of the models used for our multivariate analysis, Model 4 exhibited the highest AUC, demonstrating that it could predict post-extraction bleeding. However, because there were no significant differences observed between Model 1 or 3 versus Model 4, we were unable to construct an optimal model for predicting post-extraction bleeding. To increase model precision, it may be optimal to add factors demonstrating surgeon skill (e.g. years of surgeon experience or time required for one tooth extraction), which were not included in our current investigation. Furthermore, it will be necessary to put all extraction data from outpatients into analysis set to conduct a multilevel analysis.

CONCLUSIONS

1. We investigated post-extraction bleeding risk factors for all types of tooth extraction, including wisdom teeth and impacted teeth in patients taking warfarin (PT-INR \leq 3.0). Post-extraction bleeding requiring hemostatic treatment was observed in 8% patients.
2. The risk of post-extraction bleeding was five to six times more for the wisdom teeth than that for the incisor teeth.
3. Post-extraction bleeding could not be predicted using the HAS-BLED score alone.
4. Concomitant use of antiplatelet agents is a risk factor for post-extraction bleeding. More care must be taken regarding post-extraction bleeding within these cases than in cases with the administration of warfarin alone.

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Contributors

TA and TK were involved in the planning of the study concept and design. TK wrote the drafting of the manuscript. KH and TK were involved in the statistical analysis. TA and TK reviewed and revised the manuscript. All authors read and approved the final manuscript.

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The authors have no conflicts of interest to declare regarding this study.

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No additional data are available.

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Table 1 HAS-BLED bleeding risk score		clinical characteristics
risk factor		
H	Hypertension	uncontrolled, >160mmHg systolic
A	Abnormal renal and liver function (1 point each)	presence of chonic dialysis, renal pramsplantation or serum creatinine ≥ 200 $\mu\text{mol/L}$ chornic hepatic disease(eg, cirrhosis), bilirubin >2X upper limit of normal, AST/ALT/ALP >3X upper limit of normal
S	Stroke	previous history
B	Bleeding	bleeding history or predisposition
L	Labile INRs	unstable/high INRs (PT-INR>3.1)
E	Elderly	>65 years
D	Drugs or alcohol (1 point each)	concomitantly antiplatelet agents and NSAIDs, alcohol excess
Criteria from the European Society of Cardiology ²⁴ were used.		
AST=aspartate aminotransferase, ALT=alanine aminotransferase, ALP=alkaline phosphatase, NSAIDs=nonsteroidal antiinflammatory drugs		

Table 2 Clinical profile				
	post-extraction bleeding group N=21	non post-extraction bleeding group N=237	p value	χ^2 value
	number of patients	number of patients		
Age (mean \pm SD)	63.4 \pm 13.2	66.6 \pm 13.7	0.2944 ^a	
Gender(Male/Female)	14/7	143/94	0.6463 ^c	0.32
Primary disease				
post Heart Valve Prosthesis Implantation	17	120		
atrial fibrillation	2	76		
cerebral infarction	2	13		
dilated cardiomyopathy	1	9		
myocardial infarction	0	23		
deep vein thrombosis	0	11		
arteriosclerosis obliterans	0	3		
intracardiac thrombus	0	2		
Anticoagulation				
warfarin dose(mg) (mean \pm SD)	3.9 \pm 1.4	3.2 \pm 1.3	0.0241 ^a *	
PT-INR value (mean [25%tile, 75%tile])	2.1[1.8, 2.5]	2.0[1.8, 2.3]	0.3296 ^b	
Platelet count($\times 10^4/\mu\text{l}$)	16.8 \pm 5.3	18.2 \pm 5.8	0.2978 ^a	
Concomitant antiplatelet agents				
yes	10	63	0.0732 ^c	4.21
aspirin	10	52		
ticlopidine	0	8		
ethyl icosapentate	0	6		
cilostazol	0	2		
limaprost	0	1		
dipyridamole	0	1		
SD:standard deviation, Multiple factors possible for underlying disease, All seven patients using two types of antiplatelet agents were included in the non-post-extraction hemorrhaging group. a: Student's t-test, b:Mann-Whitney U test, c:Fisher's exact test *:p < 0.05 was considered significant.				

Table 3 Situation of extracted teeth				
	post-extraction bleeding group N=21	non post-extraction bleeding group N=237	p value	χ^2 value
	number of patients or mean \pm SD	number of patients or mean \pm SD		
Extraction site				
maxilla	14	122	0.254 ^c	1.79
mandibula	7	115		
Teeth type				
incisor	1	36	0.039 ^c *	8.70
premolar	2	65		
molar	9	89		
wisdom	9	47		
Stability of teeth				
good	17	158	0.227 ^c	1.80
poor	4	79		
Extraction procedure				
simple	17	165	0.328 ^c	1.19
surgical	4	72		
Number of teeth extracted in one procedure	1.7 \pm 0.6	1.8 \pm 1.1	0.576 ^a	
One tooth	8	125	0.188 ^c	9.12
Two tooth	12	65		
Three tooth	1	24		
Four tooth	0	18		
Five tooth	0	3		
Six tooth	0	1		
Seven tooth	0	1		
SD:standard deviation, a; Student's t-test, c:fisher's exact test *:p (0.05 was considered significant.				

Table 4 HAS-BLED score				
	post-extraction bleeding group	non post-extraction bleeding group	p value	χ^2 value
	N=21	N=237		
	mean \pm SD	mean \pm SD		
	or number of patients	or number of patients		
HAS-BLED score	1.3 \pm 0.9	1.2 \pm 0.8	0.467 ^a	
0	3	41	0.804 ^c	0.75
1	10	127		
2	6	52		
3	2	17		
4	0	0		
5	0	0		
6	0	0		
7	0	0		
8	0	0		
9	0	0		
risk factor				
H	1	3		
A	1	11		
S	2	38		
B	0	5		
L	0	0		
E	13	161		
D	11	63		
SD:standard deviation,				
a; Student's t-test, c:Fisher's exact test				

Table 5 Univariate analysis of bleeding risk factor in teeth extraction					
	RR	95%CI		p value	
		lower	upper		
Extraction site					
maxilla/mandibula	1.885	0.756	5.128	0.177	
Teeth type					
premolar/incisor	1.108	0.103	24.300	0.934	
molar/incisor	3.640	0.649	68.346	0.160	
wisdom/incisor	6.894	1.213	130.039	0.027	*
Stability of teeth					
good/poor	2.125	0.756	7.572	0.161	
Extraction procedure					
surgical/simple	0.539	0.151	1.518	0.256	
PT-INR value	1.782	0.597	5.387	0.300	
Platelet count($\times 10^4/\mu\text{l}$)	0.959	0.887	1.037	0.296	
HAS-BLED score					
1/0	1.076	0.312	4.968	0.914	
2/0	1.577	0.391	7.825	0.529	
3/0	1.608	0.199	10.551	0.626	
2/1	1.465	0.477	4.157	0.487	
3/1	1.494	0.218	6.305	0.636	
3/2	1.020	0.140	4.922	0.982	
3/ less than 2	1.362	0.206	5.255	0.703	
Concomitant antiplatelet agents use					
yes/no	2.511	1.001	6.238	0.050	*
• Criteria from the European Society of Cardiology ²⁴⁾ were used.					
RR:risk ratio					
*:p<0.05 was considered significant.					

Table 6 Multi-variate analysis of postextraction hemorrhage

	model 1			model 2			model 3			model 4				
	risk ratio	95%CI	p value	risk ratio	95%CI	p value	risk ratio	95%CI	p value	risk ratio	95%CI	p value		
Extraction site														
maxilla/mandibula	1.855	0.7	5.286	0.216	—	—	1.914	0.716	5.494	0.198	1.936	0.722	5.585	0.192
Teeth type														
premolar/incisor	1.118	0.102	24.727	0.928	—	—	1.045	0.095	23.222	0.972	1.159	0.104	25.901	0.906
molar/incisor	3.468	0.594	65.974	0.188	—	—	3.388	0.579	64.544	0.199	3.730	0.630	71.468	0.164
wisdom/incisor	5.228	0.85	101.628	0.078	—	—	5.380	0.860	105.301	0.075	5.113	0.804	100.719	0.804
Stability of teeth														
good/poor	1.790	0.551	6.994	0.344	—	—	1.961	0.588	7.893	0.283	1.916	0.568	7.780	0.304
Extraction procedure														
surgical/simple	0.624	0.166	1.915	0.425	—	—	0.674	0.177	2.125	0.515	0.670	0.175	2.117	0.509
PT-INR value	2.078	0.681	6.606	0.204	—	—	2.288	0.727	7.543	0.162	2.687	0.831	9.349	0.107
Platelet count(x10 ⁴ /ul)	0.970	0.892	1.053	0.461	—	—	0.968	0.889	1.053	0.443	0.970	0.894	1.052	0.465
HAS-BLED score														
1/0	—	—	—	—	1.076	0.312	4.968	0.914	—	—	1.197	0.325	5.777	0.798
2/0	—	—	—	—	1.577	0.391	7.825	0.529	—	—	2.271	0.515	12.242	0.284
3/0	—	—	—	—	1.608	0.199	10.551	0.626	—	—	2.338	0.269	16.989	0.410
2/1	—	—	—	—	1.465	0.477	4.157	0.487	—	—	1.897	0.580	5.871	0.279
3/1	—	—	—	—	1.494	0.218	6.305	0.636	—	—	1.954	0.266	9.403	0.463
3/2	—	—	—	—	1.020	0.14	4.922	0.982	—	—	1.030	0.130	5.605	0.975
Concomitant antiplatelet agents use														
yes/no	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Criteria from the European Society of Cardiology ^{2,3)} were used.	—	—	—	—	—	—	—	—	—	—	2.881	1.079	7.740	0.035

*. *: p<0.05

Table 7 Comparison of the model					
		95%CI			
	AUC	lower	upper	p value	
model 1	0.738	0.630	0.824	0.083	
model 2	0.548	0.425	0.666	0.867	
model 3	0.745	0.632	0.832	0.148	
model 4	0.763	0.650	0.847	0.031	*
model 1vs3				0.727	
model 1vs4				0.441	
model 2vs3				0.004	*
model 3vs4				0.398	
* *: p<0.05					
AUC;area under the curve					

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HAS-BLED score alone could not be predict post-extraction bleeding: a retrospective cohort study.

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1 HAS-BLED score alone could not be predict post-extraction bleeding: a retrospective cohort
2 study.

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8 **ABSTRACT**

9 Objective: Post-extraction bleeding is often experienced in our clinical unexpectedly. It is very
10 beneficial if the determination is post-extraction bleeding risk prior to surgery in the
11 anticoagulant therapy patient. Therefore, this study aimed to verify whether the HAS-BLED
12 score is useful in predicting post-extraction bleeding in patients taking warfarin.

13 Design: Retrospective cohort study.

14 Setting: Department of Oral and Maxillofacial Surgery, Tokyo Women's Medical University.

15 Participants: Subjects comprised 258 sequential cases (462 teeth) of inpatients who had
16 undergone tooth extraction between January 1, 2010 and December 31, 2012 while continuing
17 warfarin therapy.

18 Main outcome measure: Post-extraction risk factors of bleeding. As predicting variables of
19 multivariate logistic analysis, HAS-BLED score, extraction site, teeth type, stability of teeth, and
20 extraction procedure, PT-INR value, platelet count, concomitant antiplatelet agents use were
21 collected.

22 Results: Post-extraction bleeding was noted in 21 (8.1%) of the 258 cases. Whole post-extraction
23 bleeding was hemostasis in localized hemostatic procedure. The HAS-BLED score was
24 insufficient for predicting post-extraction bleeding (AUC = 0.548, P = 0.867, multivariate
25 analysis). The risk of post-extraction bleeding was approximately three times more for patients
26 taking oral antiplatelet agents (RR = 2.881, P = 0.035, multivariate analysis).

27 Conclusions: The HAS-BLED score alone could not be predict post-extraction bleeding. The
28 concomitant use of oral antiplatelet agents is a risk factor for post-extraction bleeding. This study
29 was no post-extraction bleeding that required more than localized hemostatic procedure.
30 However, because this was a retrospective study conducted at a single institution, we believe that
31 a large-scale prospective cohort study, including outpatient tooth extraction cases, will be

1 necessary in the future.

2 3 **Strengths and limitations of this study**

- 4 • This is the first study to verify the usefulness of the HAS-BLED score for predicting post-
5 extraction bleeding risk.
- 6 • We investigated all cases of tooth extraction, including wisdom tooth and impacted tooth
7 extractions.
- 8 • No previous reports have investigated the effects of each individual tooth extracted,
9 extraction procedure, and effects of concomitant antiplatelet agents on post-extraction
10 bleeding using statistical analyses and demonstrated a high level of evidence for correlations.
- 11 • In this study, we think need to prospective cohort studies, including a large-scale outpatient
12 in the future. Because it is a retrospective cohort study conducted at a single institution.

13 14 **INTRODUCTION**

15 Patients undergoing anticoagulant therapy and who are scheduled to undergo tooth extraction are
16 typically advised to undergo extraction while continuing anticoagulant therapy¹⁻⁴). Although
17 post-extraction bleeding is often experienced in our clinical unexpectedly. In the past, a number
18 of studies have investigated tooth extraction while continuing anticoagulant therapy, with the
19 frequency of post-extraction bleeding reported to range from 0% to 26%⁵⁻¹⁶).

20 Recently, the HAS-BLED score¹⁷⁻¹⁹) has been used as an index for evaluating the risk of bleeding
21 complications in patients undergoing anticoagulant therapy. The HAS-BLED score evaluates
22 nine risk factors for bleeding. The European Society of Cardiology guidelines²⁰) has stated that
23 patients who score three points or higher are at a high risk of bleeding complications. No reports
24 to date have investigated whether the HAS-BLED score is useful in predicting the risk of post-
25 extraction bleeding. The preoperative identification of patients with a high risk of post-extraction
26 bleeding could facilitate appropriate preparations prior to performing tooth extraction.

27 Therefore, we examined whether the HAS-BLED score is useful in predicting post-extraction
28 bleeding in patients undergoing warfarin therapy.

29 **MATERIAL AND METHODS**

30 **Study design**

31 This was a retrospective cohort study.

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5 2 Study population and eligibility criteria
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7 3 This study subject included 258 sequential cases that were hospitalized at the Department of
8
9 4 Oral and Maxillofacial Surgery, Tokyo Women's Medical University and who had undergone
10
11 5 tooth extraction between January 1, 2010 and December 31, 2012 while receiving a maintenance
12
13 6 dose of warfarin therapy. As a rule, tooth extraction for patients undergoing warfarin therapy
14
15 7 shall be performed after the patient is admitted to the hospital. Antiplatelet agents, which were
16
17 8 being concomitantly taken, were continued to be administered at the maintenance dose.
18
19 9 Exclusion criteria were as follows: 1) patients younger than 20 years at the time of hospital
20
21 10 admission; 2) presence of comorbid blood disease; and 3) a PT-INR level of ≥ 3.1 as indicated by
22
23 11 the results of the blood tests performed on the day of tooth extraction. Patients underwent follow-
24
25 12 up examinations for 1 month after discharge. The doctors and nurse records obtained from
26
27 13 medical examination records were registered in a database along with the results of the clinical
28
29 14 tests. When the same patient was hospitalized and underwent tooth extraction more than once
30
31 15 during the study period, all instances were registered.

16 17 17 Tooth extraction procedure

18
19 18 The primary physician for the underlying disease of each patient was preoperatively consulted
20
21 19 regarding the general medical status of the patient, including their use of anticoagulants. When
22
23 20 acute symptoms, such as periodontal abscesses, apical periodontitis, or pericoronitis were present
24
25 21 around the tooth that was determined to be eligible for tooth extraction, antibiotics were
26
27 22 administered at least three days and anti-inflammation procedures, such as incision and drainage,
28
29 23 were performed as necessary. During tooth extraction, electrocardiograms, blood pressure, pulse
30
31 24 rate, and percutaneous oxygen saturation levels were monitored. For local anesthesia, 1.8–3.6 ml
32
33 25 of 2% lidocaine containing 1/80000 epinephrine was administered. Tooth extraction was
34
35 26 performed with minimal invasion. When multiple teeth were indicated for extraction and
36
37 27 comprised within 1/3 of the jaw area, all the teeth were extracted in one procedure. When the
38
39 28 teeth comprised over 1/3 of the total jaw area, multiple teeth were extracted in one procedure if
40
41 29 the procedure was expected to take <30 min while considering the age and any comorbid
42
43 30 diseases of the patient. After extraction, a curettage of the inflammatory granulation tissue
44
45 31 around the wound border was performed, hemostatic gelatin sponge was inserted into the socket

1 (product name: Spongel, Astellas Pharma Inc.), and suturing was performed to reduce the size of
2 the wound border. The patient was requested to bite down on the absorbent cotton for 20 min
3 after completing tooth extraction to achieve pressure hemostasis. At 30 min after tooth extraction,
4 the patient was examined to confirm that the bleeding had stopped. After extraction, patients
5 were instructed to avoid strong or frequent gargling and to rest as much as possible. Post-
6 extraction meals comprised rice gruel. In the patient group with a high risk of adverse effects due
7 to infective endocarditis onset²¹⁾, antibiotics were administered before surgery intravenously,
8 after tooth extraction was prescribed to oral antibiotics for three days. For patients with a heart
9 disease that did not necessarily require IE prophylaxis for dental procedures or patients receiving
10 anticoagulant therapy, oral antibacterial drugs were administered for 3 days following tooth
11 extraction. Five doses of analgesics comprising loxoprofen sodium or acetaminophen were
12 prescribed as a potion when pain was experienced.

13 14 Post-extraction Bleeding

15 For cases in which the patient complained of bleeding and was examined but hemostatic
16 procedures were not deemed necessary, patients were instructed to adequately rest and refrain
17 from excessive gargling; regular follow-up examinations were performed. In mild bleeding as
18 oozing, the patient was requested to bite down on a gauze or absorbent cotton for twenty minutes
19 placed on the tooth extraction wound to achieve pressure hemostasis. Patients who did not
20 require treatments, such as those outlined above for post-extractive bleeding, were placed into
21 the non post-extraction bleeding group.

22 Patients who complained of bleeding since the examination after tooth extraction and who
23 underwent some medical hemostatic procedures were categorized in the post-extraction bleeding
24 group. Hemostatic procedures performed in accordance with the decisions by the examining
25 oral surgeon are described below. For cases of moderate or higher bleeding in which there was a
26 large amount of bleeding that was determined to be difficult to resolve using primary hemostasis,
27 we aimed to utilize the local vasoconstrictive effects of the local dental anesthetic epinephrine
28 and administered a dose of 1.0–1.8 ml to achieve infiltration anesthesia around the tooth
29 extraction wound. Pressure was then applied to the wound by requesting the patient to bite down
30 on gauze or absorbent cotton. When it was determined that the bleeding could not sufficiently be
31 halted by pressure hemostasis alone, the area was additionally filled with local hemostatic agents

1 or additional or repeat suturing of the wound was performed as necessary. For cases of repeated
2 bleeding or prolonged exudative bleeding after hemostatic procedures, a hemostatic splint was
3 fabricated to cover of wound. This was fitted after applying a cavity lining with a periodontal
4 pack or denture base tissue conditioner.

5 6 Bleeding risk factors for tooth extraction

7 Details of extracted teeth, surgical procedure, bleeding tendency, and concomitant antiplatelet
8 agents were investigated as possible factors affecting post-extraction bleeding. With respect to
9 details noted regarding extracted teeth, the extraction site (maxilla/mandible), type of teeth
10 (incisor/premolar/molar/wisdom), and stability of teeth were examined. Regarding the stability
11 of teeth, teeth exhibiting alveolar bone resorption of at least 2/3 of the tooth root length as
12 determined by preoperative X-rays or teeth found to have clinical grade III instability were
13 defined to have poor stability. Other teeth were considered to have good tooth stability. The
14 surgical procedure was classified into simple and surgical extractions. For surgical extraction, the
15 strategy followed was to make an incision in the gingiva, detach and turn the mucoperiosteal flap
16 over, and extract the tooth after cutting off the alveolar bone or root separation. All extractions
17 other than that defined above were simple extractions. With regard to bleeding tendency, PT-
18 INR value and platelet count were investigated.

19 20 HAS-BLED score

21 The HAS-BLED score was evaluated according to the European Society of Cardiology
22 guidelines²⁰⁾ (Table 1) and is described below. Patients with systolic blood pressure of
23 ≥ 160 mmHg, which was measured on arrival at the hospital, were categorized as having
24 “hypertension.” Patients receiving hemodialysis or those who had a kidney transplant; patients
25 with a serum creatinine level of ≥ 2.26 mg/dl in the most recent blood test; patients exhibiting
26 chronic liver disease, such as liver cirrhosis, and bilirubin levels of at least two times the normal
27 upper limit; and patients having at least three times the normal upper limit of either alanine
28 transaminase, aspartate aminotransferase, or alkaline phosphatase levels were categorized as
29 having “abnormal renal and liver function.” “Stroke” or “bleeding” was determined according to
30 the information of patients obtained from medical interviews on admission to the hospital.
31 “Labile INRs” were described to unstable/high INRs or poor time in therapeutic range (e.g.

1 <60%). The “elderly” categorization was defined as a patient age ≥ 65 years at the time of tooth
2 extraction. Patients with long-term administration of antiplatelet agents or non-steroidal anti-
3 inflammatory drug (NSAIDs) or patients with alcohol dependence were categorized as “drug and
4 alcohol.” One point was allocated for each of these categories if a patient was applicable. Thus,
5 patients were scored according to a possible full score of nine points.

6 7 Selection of representative teeth

8 Since the subject is sequential cases in this study, the same patient will duplicate where the tooth
9 extraction was done in other period, but age and PT-INR value and tooth extraction site is
10 different. There is a case that extraction of multiple teeth in the same patient. Therefore, it was an
11 independent data for each period by selected representative teeth following procedure. The most
12 posterior tooth was selected as the representative tooth, and in cases of multiple posterior teeth,
13 the upper tooth or the tooth showing good stability was selected.

14 15 Statistical analyses

16 Statistical analysis was processing the data of the patient with a representative tooth. Univariate
17 and multivariate logistic analysis were applied to analyze the bleeding risk factor for tooth
18 extraction data with the presence/absence of post-extraction bleeding as the response variable
19 and bleeding risk factor as the explanatory variable. The variable values were used to
20 describe tooth extraction site (maxilla/mandible), four variable values were used to describe the
21 type of teeth (incisor/premolar/molar/wisdom), two variable values were used to describe
22 stability of teeth (good/poor), and two variable values were used to describe the surgical
23 procedure (simple /surgical extraction). For the PT-INR value and platelet count, the actual
24 measured values were analyzed as continuous variables, and the HAS-BLED score was used in
25 analysis with both a continuous and nominal variable. Concomitant antiplatelet agents were
26 evaluated as two variable values (yes/no). During logistic analysis, we calculated the risk ratio,
27 95% confidence interval (CI), and p value. The risk ratio was calculated as the ratio of maxilla to
28 mandible for a site, the tooth type within anterior teeth for type of teeth, good to poor for the
29 condition of the periodontium, and from surgical to simple for the surgical procedure. The risk
30 ratio for the HAS-BLED score was calculated for each level. For concomitant antiplatelet agents,
31 the risk ratio of “yes” to “no” was calculated. In multivariate analysis, risk factors were

1 combined to create post-extraction bleeding analysis models. For each model, we plotted the
2 receiver operating characteristic (ROC) curve and calculated the area under the curve (AUC) in
3 addition to the p value and 95% CI for the C-statistic model overall. Many screening tools used a
4 C-statistic value of ≥ 0.70 . We used C-statistic to compare between each model. Model 1 was
5 constructed from extracted tooth state, surgical procedure, and bleeding tendency. Model 2 was
6 constructed from the HAS-BLED score only. Model 3 was constructed by adding the HAS-
7 BLED score to Model 1. Model 4 was constructed by adding concomitant antiplatelet agents as
8 an explanatory variable to Model 1. Data were analyzed with the use of JMP Pro 11 software
9 (2014 SAS Institute Inc., US) with a two-tailed alpha level of 0.05.

11 Ethics

12 This study was approved by the ethical review board of the Tokyo Women's Medical University
13 (approval number: 3079). The first and second authors take complete responsibility for the
14 integrity of the data and the accuracy of the data analysis.

16 RESULTS

17 A total of 462 extracted teeth in 258 patients (males: 157, females: 101, mean age: 66.4 years)
18 were analyzed. Post-extraction bleeding was observed in 21 patients (8.1%). Whole post-
19 extraction bleeding was hemostasis in localized hemostatic procedure, and none died patients
20 due to hemorrhage.

22 Patient characteristics

23 Post-extraction bleeding was noted in 21 patients (males: 14, females: 7, mean age: $63.4 \pm$
24 13.2 years). Table 2 shows the underlying diseases for anticoagulant therapy. Mean warfarin
25 dosage was 3.9 ± 1.4 mg, and median (25 percentile, 75 percentile) of PT-INR was 2.1 (1.8,2.5).
26 Mean platelet count was $16.8 \pm 5.3 \times 10^4/\mu\text{l}$. Eleven patients were taking only warfarin, whereas
27 10 were taking an antiplatelet agent in addition to warfarin. Aspirin was administered as the
28 antiplatelet agent to all cases.

29 The non post-extraction bleeding group included 237 patients (males: 143, females: 94, mean
30 age: 66.6 ± 13.7 years). Underlying diseases for anticoagulant therapy are shown in Table 2.

31 Mean warfarin dosage was 3.2 ± 1.3 mg. The mean (25 percentile, 75 percentile) of PT-INR was

1 2.0 (1.8, 2.3). Mean platelet count was $18.2 \pm 5.8 \times 10^4/\mu\text{l}$. A total of 174 patients were taking
2 warfarin only, whereas 63 patients were taking warfarin and an antiplatelet agent. Table 2 shows
3 a breakdown of the antiplatelet agents. Seven patients who were taking two types of antiplatelet
4 agents were all included in the non post-extraction bleeding group. A statistically significant
5 difference was noted for warfarin dosage; however, no difference was noted for PT-INR. No
6 differences were noted for age, sex, platelet count, or concomitant antiplatelet agents use.

7 8 Details of extracted tooth

9 In the post-extraction bleeding group, the tooth extraction site in 14 and seven cases was the
10 maxilla and mandible, respectively. For the non post-extraction bleeding group, it was the
11 maxilla and mandible in 122 and 115 cases, respectively. Thus, no differences were noted
12 between the two groups ($P = 0.254$, Fisher's exact test; table 3).

13 Results for teeth type

14 Numbers of incisor:premolar:molar:wisdom teeth were 1:2:9:9, respectively, in the post-
15 extraction bleeding group and 36:65:89:47, respectively, in the non post-extraction bleeding
16 group. Thus, a statistically significant difference was noted between the two groups ($P = 0.039$,
17 Fisher's exact test; table 3).

18 In the post-extraction bleeding group, the stability of teeth was good in 17 cases and poor in four.
19 In the non post-extraction bleeding group, stability was good in 158 cases and poor in 79. No
20 statistically significant difference was noted between the two groups ($P = 0.227$, Fisher's exact
21 test; table 3).

22 Extraction procedure

23 In the post-extraction bleeding group, the extraction procedure selected was simple extraction in
24 17 cases and surgical extraction in four cases. In the non post-extraction bleeding group, the
25 procedure selected was simple extraction in 165 cases and surgical extraction in 72 cases. No
26 differences were noted between the two groups ($P = 0.328$, Fisher's exact test; table 3).

27 Number of teeth extracted per operation

28 The number of teeth extracted per operation was 1.7 ± 0.6 in the post-extraction bleeding group
29 and 1.8 ± 1.1 in the non post-extraction bleeding group. There were no cases of multiple
30 extractions of four or more teeth in the post-extraction bleeding group. No differences were
31 noted between the two groups with regards to the number of teeth extracted per operation

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3 1 ($P = 0.576$, Student's t-test; table 3).
4
5 2
6

7 3 HAS-BLED score

8
9 4 The highest HAS-BLED score obtained was three points. The mean score was 1.3 ± 0.9 in the
10
11 5 post-extraction bleeding group and 1.2 ± 0.8 in the non post-extraction bleeding group. No
12
13 6 statistically significant differences were noted between the two groups ($P = 0.467$, Student's t-
14
15 7 test; table 4). In both the post-extraction and non post-extraction bleeding groups, scores were
16
17 8 highest for the "elderly" group, followed by the "drug and alcohol" group, and then the "stroke"
18
19 9 group.
20

21 10
22 11 Statistical examination

23 12 Univariate analysis demonstrated statistically significant differences between the wisdom teeth
24
25 13 and incisor ($RR = 8.894$, $P = 0.027$) and for between concomitant antiplatelet agents (yes/no)
26
27 14 ($RR = 2.511$, $P = 0.500$). RR was ≤ 1 for surgical procedure and platelet count. No statistically
28
29 15 significant difference was noted for a HAS-BLED score of ≥ 3 compared with a HAS-BLED
30
31 16 score of ≤ 2 ($RR = 1.362$, $P = 0.7033$) (table 5).

32 17 No statistically significant differences were noted within multivariate analysis for any of the
33
34 18 parameters in the models 1, 2, or 3. In Model 4, a statistically significant difference was noted for
35
36 19 antiplatelet agents (yes) in the non post-extraction bleeding group ($RR = 2.881$, $P = 0.035$) (table
37
38 20 6). AUCs for models 1, 3, and 4 were 0.7, with a statistically significant difference noted in
39
40 21 Model 4 only. AUC for Model 2 was the lowest at 0.5, and a statistically significant difference
41
42 22 was noted between models 2 and 3 ($P = 0.004$) (table 7).
43

44 23
45 24 **Discussion**

46 25 Our investigation of 258 tooth extraction patients indicated that post-extraction bleeding
47
48 26 occurred in 21 patients (8%) or in 39 of the total 462 extracted teeth (8%). Whole post-extraction
49
50 27 bleeding was possible hemostasis in localized hemostatic procedure. The HAS-BLED score
51
52 28 alone it was not possible to predict post-extraction bleeding. As a result of considering the risk
53
54 29 factors for post-extraction bleeding statistically, the concomitant antiplatelet agents use were risk
55
56 30 factors. It has reported that the incidence of bleeding in the anticoagulation group is the same
57
58 31 (about 6-7%) as in the anticoagulation withdrawal group²²). The post-extraction bleeding in this

1 study was in accordance with their report.

2 Many cases of tooth extraction performed while continuing anticoagulant therapy have been
3 reported²³⁻²⁵). However, in clinical settings, it is not uncommon to encounter post-extraction
4 bleeding during tooth extraction in cases of optimal INR value range. Iwabuchi et al.²⁶) reported
5 through a multicenter, large-scale study that risk factors for post-extraction bleeding in patients
6 taking warfarin were age, PT-INR, and inflammation at the extraction site. Although many
7 reports to date have not included cases of surgical extraction, such as the extraction of wisdom
8 teeth and impacted teeth, these types of surgical extraction are often performed within clinical
9 settings. Therefore, this study targeted cases that were managed according to the optimal
10 treatment range and investigated all cases of tooth extraction, including the extraction of wisdom
11 teeth, impacted teeth, and multiple teeth concurrently.

12 Various methods of hemostasis have been reported for cases of tooth extraction performed
13 while continuing warfarin therapy. These include pressure hemostasis only, wound suturing, and
14 the application of local hemostatic agents²⁷⁻³⁰). To implement hemostasis, we placed a hemostatic
15 gelatin sponge in the extraction socket and routinely conducted pressure hemostasis using
16 absorbent cotton with suturing of the wound. Patients were examined 30 min after tooth
17 extraction to confirm whether the bleeding had stopped. Hemostasis was determined to have
18 been sufficient for all cases. As all patients underwent tooth extraction on an inpatient basis, the
19 patient could rapidly be examined by a physician or nurse and could receive early diagnosis and
20 appropriate treatment if post-extraction bleeding was suspected. However, although patients
21 were examined, many did not require hemostatic treatment. Of the patients who exhibited post-
22 extraction bleeding, no systemic hemostatic treatment, such as blood transfusion, was required in
23 any case.

24 The HAS-BLED score is used in the field of cardiology to evaluate the risk of hemorrhaging in
25 patients showing good anticoagulation. As it would be highly significant if the HAS-BLED score
26 could be additionally used for predicting the risk of post-extraction hemorrhaging, we evaluated
27 its use in this study. In our study, the highest HAS-BLED score was three points. A score of one
28 point was the most commonly achieved among the 137 patients (53%). The most common risk
29 factor was found to be age (174 patients; 67%). No difference was noted for the mean HAS-
30 BLED score between the post-extraction hemorrhaging and non-post-extraction hemorrhaging
31 groups. The European Society of Cardiology has proposed that a score of HAS-BLED ≥ 3

1 indicates a high risk of hemorrhagic complications. In cases of post-extraction hemorrhaging, we compared patients with a HAS-BLED score of three or higher and those with a score of two or lower but did not detect any statistically significant difference (univariate analysis; RR = 1.362, $P = 0.703$). Multivariate analysis indicated that there was little risk associated with the score increasing by one (Table 6). AUC for HAS-BLED score alone (Model 2) was 0.55, which was the lowest for all of the models we constructed. In Model 3, to which the details of extracted teeth were added to the HAS-BLED score, AUC was 0.745, suggesting that this model is useful for predicting post-extraction bleeding. However, a statistically significant difference was noted for Model 2 versus Model 3 ($P = 0.004$), indicating that the HAS-BLED score alone was insufficient for predicting post-extraction bleeding.

As a bleeding risk factors for tooth extraction, investigation of conditions of the individual teeth extracted indicated that post-extraction bleeding risk was five to six times higher for wisdom teeth compared with that for anterior teeth. Extraction site and stability had little effect. Although no differences were observed for the number of teeth extracted in one treatment, there were no cases of multiple extractions of four teeth or more in the post-extraction hemorrhaging group. Although we had predicted Surgical extraction as a risk factor of post-extraction bleeding, results indicated that surgical extraction hardly had any effect on post-extraction bleeding (RR = 0.539, $P = 0.256$).

The effects of warfarin are easily influenced by factors, such as interaction with meals and/or drugs, and additionally by the general state of the patient. In this study, to accurately determine the anticoagulation state directly before tooth extraction, all blood tests were performed before breakfast on the tooth extraction day or the first tooth extraction day if tooth extraction was planned on consecutive days. Although post-extraction bleeding cases were being administered high doses of warfarin, no difference was observed for PT-INR. There were no cases classified as labile INRs. Accordingly, the PT-INR value was investigated using actual measured values as the continuous variable. There were no statistically significant differences noted for PT-INR values by either univariate or multivariate analysis ($P \geq 0.1$), suggesting that the PT-INR value had little effect on post-extraction bleeding in patients undergoing anticoagulant therapy while being managed within the optimal treatment range.

No fixed consensus has been reached regarding the concomitant use of warfarin and antiplatelet agents because some reports have indicated that this increases the risk of post-extraction

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2
3 1 bleeding^{1,31)}, whereas other reports have suggested that antiplatelet agents have little effect^{14,32)}.
4
5 2 In this study, incidence of 13.7% of post-extraction bleeding in concomitant antiplatelet drugs, in
6
7 3 the warfarin alone was 5.9%. Both of our univariate and multivariate analyses results indicated
8
9 4 that the use of concomitant antiplatelet agents was a significant factor affecting post-extraction
10
11 5 bleeding. It has been reported that the concomitant use of two antiplatelet agents significantly
12
13 6 increases the frequency of intracranial hemorrhaging³³⁾. Furthermore, a prospective observational
14
15 7 study of hemorrhagic complications in Japanese cerebral infarction patients³⁴⁾ found that
16
17 8 compared with patients taking one antiplatelet agent only; those taking two or three antiplatelet
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19 9 agents along with warfarin clearly exhibited higher annual onset rates of intracranial
20
21 10 hemorrhaging. We believe that these results suggest that concomitant antiplatelet agents are a
22
23 11 risk factor for post-extraction bleeding.

24
25 12 The limitations of this study included the fact that data were obtained only at a single facility and
26
27 13 that outpatients were not included in the subjects investigated. In our facility were many
28
29 14 cardiovascular disease patients (especially post-operative valve replacement patients was about
30
31 15 50%). Furthermore, because our study excluded patients who exhibited PT-INR of ≥ 3.1 during
32
33 16 the blood testing performed on the day of tooth extraction, the current study included patients
34
35 17 whose anticoagulant therapy was being well managed. Thus, our subjects did not exactly
36
37 18 constitute generalized cases of tooth extraction patients taking warfarin. Moreover, because this
38
39 19 was a retrospective study, we believe that a large-scale, prospective, cohort study including
40
41 20 outpatient tooth extraction cases required to be conducted in the future.

42
43 21 Moreover, we could not examine the drug interaction effects because our subjects included both
44
45 22 patients who intravenously received antibacterial agents and those who received oral
46
47 23 administration. Warfarin use results in a number of drug interactions. Holbrook et al.³⁵⁾ has stated
48
49 24 to enhance anti-infective agents, lipid-lowering drugs, NSAIDs including COX-2 selective
50
51 25 NSAIDs, selective serotonin reuptake inhibitors, amiodarone, omeprazole, fluorouracil, a and
52
53 26 cimetidine of warfarin anticoagulant effects. In these drugs suggest to consider changes to the
54
55 27 small alternative agent of interaction with warfarin. However, some reports have stated that in
56
57 28 most stable anticoagulant therapy patients, exposure to antibacterial agents causes no clinical
58
59 29 problems³⁶⁾; furthermore, other reports have found that NSAIDs and antibacterial agents often
60
30 increased warfarin effects in cases of long-term administration¹⁶⁾. We also believe that the short-
31
term or low-dose administration of NSAIDs or antibacterial agents does not cause any

1 prolongation of clinically problematic PT-INR.

2 Of the models that we created in this study, Model 4 exhibited the highest predictive ability for
3 post-extraction bleeding (AUC = 0.76, $P = 0.0309$). However, because there were no significant
4 differences observed between Model 1 or 3 versus Model 4, we were unable to construct an
5 optimal model for predicting post-extraction bleeding. To increase model precision, it may be
6 optimal to add factors demonstrating surgeon skill (e.g. years of surgeon experience or time
7 required for one tooth extraction), which were not included in our current investigation.
8 Furthermore, it will be necessary to put all extraction data from outpatients into analysis set to
9 conduct a multilevel analysis.

10 Finally, all the patients had post-extraction bleeding be hemostasis in localized hemostatic
11 procedure, there was no systemic hemostatic treatment was required cases. There was no case
12 that was extended hospitalization period by post-extraction bleeding. Wahl et al.²²⁾ has stated that
13 bleeding complications requiring more than local hemostatic measures after dental surgery are
14 exceedingly rare. It was also our results. In order to not cause the onset of fatal severe
15 thromboembolism³⁷⁾, there is no need of warfarin interruption or pause for tooth extraction. The
16 special environment to the post-extraction bleeding procedure is not necessary. If condition are
17 prepared, we believe extraction of warfarin therapy patient is possible in a private office.

18 CONCLUSIONS

- 19 1. We investigated post-extraction bleeding risk factors for all types of tooth extraction, including
20 wisdom teeth and impacted teeth in patients taking warfarin. Post-extraction bleeding requiring
21 hemostatic treatment was observed in 8% patients.
- 22 2. Whole post-extraction bleeding was hemostasis in localized hemostatic procedure. There was
23 no systemic hemostatic treatment was required cases, and none died patients due to hemorrhage.
- 24 3. The HAS-BLED score alone could not be predict post-extraction bleeding in patients taking
25 warfarin.
- 26 4. Concomitant antiplatelet agents use is a risk factor for post-extraction bleeding. More care
27 must be taken regarding post-extraction bleeding within these cases than in cases with the
28 administration of warfarin alone.

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2 Maxillofacial Surgery at Tokyo Women's Medical University who offered their kind cooperation
3 in this study.

4 **Contributors**

5 TA and TK were involved in the planning of the study concept and design. TK wrote the drafting
6 of the manuscript. KH and TK were involved in the statistical analysis. TA and TK reviewed and
7 revised the manuscript. All authors read and approved the final manuscript.

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10 **Conflicts of interest**

11 The authors have no conflicts of interest to declare regarding this study.

12 **Data sharing statement**

13 No additional data are available.

14 **Provenance and peer review**

15 Not commissioned; externally peer reviewed.

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1 Table 1 HAS-BLED bleeding risk score

risk factor		clinical characteristics
H	Hypertension	uncontrolled, >160mmHg systolic
A	Abnormal renal and liver function (1point each)	presence of chonic dialysis, renal pramsplantation or serum creatinine $\geq 200\mu\text{mol/L}$
		chornic hepatic disease(eg, cirrhosis), bilirubin >2X upper limit of nomal,
		AST/ALT/ALP >3X upper limit of nomal
S	Stroke	previous history
B	Bleeding	bleeding history or predisposition
L	Labile INRs	unstable/high INRs or poor time in therapeutic range (e.g. 60%)
E	Elderly	>65 years
D	Drugs or alcohol (1point each)	concomitantly antiplatelet agents and NSAIDs,
		alcohol excess

- 2 Criteria from the European Society of Cardiology²⁰⁾ were used. AST=aspartate
 3 aminotransferase, ; table 3 ALT=alanine aminotransferase, ALP=alkaline phosphatase,
 4 NSAIDs=nonsteroidal antiinflammatory drugs

1 Table 2 Patient characteristics

	post-extraction bleeding group	non post extraction bleeding group	p value	significant difference	χ^2 value
	N=21	N=237			
	number of patients	number of patients			
Age (mean \pm SD)	63.4 \pm 13.2	66.6 \pm 13.7	0.2944 ^a		
Gender(Male/Female)	14/7	143/94	0.6463 ^c		0.32
Primary disease					
post Heart Valve Prosthesis Implantation	17	120			
atrial fibrillation	2	76			
cerebral infarction	2	13			
dilated cardiomyopathy	1	9			
myocardial infarction	0	23			
deep vein thrombosis	0	11			
arteriosclerosis obliterans	0	3			
intracardiac thrombus	0	2			
Anticoagulation					
warfarin dose(mg) (mean \pm SD)	3.9 \pm 1.4	3.2 \pm 1.3	0.0241 ^a	*	
PT-INR value (mean[25%tile, 75tile])	2.1[1.8, 2.5]	2.0[1.8, 2.3]	0.3296 ^b		
Platelet count($\times 10^4/\mu\text{l}$)	16.8 \pm 5.3	18.2 \pm 5.8	0.2978 ^a		
Concomitant antiplatelet agents					
yes	10	63	0.0732 ^c		4.21
aspirin	10	52			
ticlopidine	0	8			
ethyl icosapentate	0	6			
cilostazol	0	2			
limaprost	0	1			
dipyridamole	0	1			

2 SD:standard deviation, Multiple factors possible for underlying disease, All seven patients ;
3 table 3 using two types of antiplatelet agents were included in the non post-extraction bleeding
4 group. A;Student's t-test, b;Mann-Whitney U test, c;Fisher's exact test, *:p <0.05 was
5 considered significant.

6

1 Table 3 Details of extracted teeth

	post-extraction bleeding group	non post-extraction bleeding group	p value	significant difference	χ^2 value
	N=21	N=237			
	number of patients	number of patients			
	or mean \pm SD	or mean \pm SD			
Extraction site					
maxilla	14	122	0.254 ^c		1.79
mandibula	7	115			
Teeth type					
incisor	1	36	0.039 ^c	*	8.70
premolar	2	65			
molar	9	89			
wisdom	9	47			
Stability of teeth					
good	17	158	0.227 ^c		1.80
poor	4	79			
Extraction procedure					
simple	17	165	0.328 ^c		1.19
surgical	4	72			
Number of teeth extracted in operation	1.7 \pm 0.6	1.8 \pm 1.1	0.576 ^a		
One tooth	8	125	0.188 ^c		9.12
Two tooth	12	65			
Three tooth	1	24			
Four tooth	0	18			
Five tooth	0	3			
Six tooth	0	1			
Seven tooth	0	1			

2 SD:standard deviation, a; Student's t-test, c:fisher's exact test, ; table 3

3 *:p < 0.05 was considered significant.

4

1 Table 4 HAS-BLED score

	post-extraction bleeding group	non post-extraction bleeding group	p value	significant difference	χ^2 value
	N=21	N=237			
	mean \pm SD or number of patients	mean \pm SD or number of patients			
HAS-BLED score	1.3 \pm 0.9	1.2 \pm 0.8	0.467 a		
0	3	41	0.804 c		0.75
1	10	127			
2	6	52			
3	2	17			
4	0	0			
5	0	0			
6	0	0			
7	0	0			
8	0	0			
9	0	0			
risk factor					
H	1	3			
A	1	11			
S	2	38			
B	0	5			
L	0	0			
E	13	161			
D	11	63			

2 SD:standard deviation, a;Student's t-test, c;Fisher's exact test; table 3

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1 Table 5 Univariate analysis of bleeding risk factor in teeth extraction

	RR	95%CI		p value	significant difference
		lower	upper		
Extraction site					
maxilla/mandibula	1.885	0.756	5.128	0.177	
Teeth type					
premolar/incisor	1.108	0.103	24.300	0.934	
molar/incisor	3.640	0.649	68.346	0.160	
wisdom/incisor	6.894	1.213	130.039	0.027	*
Stability of teeth					
good/poor	2.125	0.756	7.572	0.161	
Extraction procedure					
surgical/simple	0.539	0.151	1.518	0.256	
PT-INR value	1.782	0.597	5.387	0.300	
Platelet count($\times 10^4/\mu\text{l}$)	0.959	0.887	1.037	0.296	
HAS-BLED score					
1/0	1.076	0.312	4.968	0.914	
2/0	1.577	0.391	7.825	0.529	
3/0	1.608	0.199	10.551	0.626	
2/1	1.465	0.477	4.157	0.487	
3/1	1.494	0.218	6.305	0.636	
3/2	1.020	0.140	4.922	0.982	
3/ less than 2	1.362	0.206	5.255	0.703	
Concomitant antiplatelet agents use					
yes/no	2.511	1.001	6.238	0.050	*

2 Criteria from the European Society of Cardiology²⁰⁾ were used. ;

3 RR:risk ratio *: $p < 0.05$ was considered significant.

4

1 Table 6 Multivariate analysis of postextraction hemorrhage

	model 1				
	risk ratio	95%CI		p value	significant difference
		lower	upper		
Extraction site					
maxilla/mandibula	1.855	0.7	5.286	0.216	
Teeth type					
premolar/incisor	1.118	0.102	24.727	0.928	
molar/incisor	3.468	0.594	65.974	0.188	
wisdom/incisor	5.228	0.85	101.628	0.078	
Stability of teeth					
good/poor	1.790	0.551	6.994	0.344	
Extraction procedure					
surgical/simple	0.624	0.166	1.915	0.425	
PT-INR value	2.078	0.681	6.606	0.204	
Platelet count($\times 10^4$ /ul)	0.970	0.892	1.053	0.461	
HAS-BLED score					
1/0	—	—	—	—	
2/0	—	—	—	—	
3/0	—	—	—	—	
2/1	—	—	—	—	
3/1	—	—	—	—	
3/2	—	—	—	—	
Concomitant antiplatelet agents use					
yes/no	—	—	—	—	

2 Criteria from the European Society of Cardiology²⁰ were used. *: $p < 0.05$

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1 Table 6 continuation

	model 2				
	risk ratio	95%CI		p value	significant difference
		lower	upper		
Extraction site					
maxilla/mandibula	—	—	—	—	
Teeth type					
premolar/incisor	—	—	—	—	
molar/incisor	—	—	—	—	
wisdom/incisor	—	—	—	—	
Stability of teeth					
good/poor	—	—	—	—	
Extraction procedure					
surgical/simple	—	—	—	—	
PT-INR value	—	—	—	—	
Platelet count($\times 10^4$ /ul)	—	—	—	—	
HAS-BLED score					
1/0	1.076	0.312	4.968	0.914	
2/0	1.577	0.391	7.825	0.529	
3/0	1.608	0.199	10.551	0.626	
2/1	1.465	0.477	4.157	0.487	
3/1	1.494	0.218	6.305	0.636	
3/2	1.020	0.14	4.922	0.982	
Concomitant antiplatelet agents use					
yes/no	—	—	—	—	

2 Criteria from the European Society of Cardiology²⁰ were used. ** : $p < 0.05$

1 Table 6 continuation

	model 3				
	risk ratio	95%CI		p value	significant difference
		lower	upper		
Extraction site					
maxilla/mandibula	1.914	0.716	5.494	0.198	
Teeth type					
premolar/incisor	1.045	0.095	23.222	0.972	
molar/incisor	3.388	0.579	64.544	0.199	
wisdom/incisor	5.380	0.860	105.301	0.075	
Stability of teeth					
good/poor	1.961	0.588	7.893	0.283	
Extraction procedure					
surgical/simple	0.674	0.177	2.125	0.515	
PT-INR value	2.288	0.727	7.543	0.162	
Platelet count(x10 ⁴ /ul)	0.968	0.889	1.053	0.443	
HAS-BLED score					
1/0	1.197	0.325	5.777	0.798	
2/0	2.271	0.515	12.242	0.284	
3/0	2.338	0.269	16.989	0.410	
2/1	1.897	0.580	5.871	0.279	
3/1	1.954	0.266	9.403	0.463	
3/2	1.030	0.130	5.605	0.975	
Concomitant antiplatelet agents use					
yes/no	—	—	—	—	

2 Criteria from the European Society of Cardiology²⁰ were used. *: p<0.05

3

1 Table 6 continuation

	model 4				
	risk ratio	95%CI		p value	significant difference
		lower	upper		
Extraction site					
maxilla/mandibula	1.936	0.722	5.585	0.192	
Teeth type					
premolar/incisor	1.159	0.104	25.901	0.906	
molar/incisor	3.730	0.630	71.468	0.164	
wisdom/incisor	5.113	0.804	100.719	0.804	
Stability of teeth					
good/poor	1.916	0.568	7.780	0.304	
Extraction procedure					
surgical/simple	0.670	0.175	2.117	0.509	
PT-INR value	2.687	0.831	9.349	0.107	
Platelet count(x10 ⁴ /ul)	0.970	0.894	1.052	0.465	
HAS-BLED score					
1/0	—	—	—	—	
2/0	—	—	—	—	
3/0	—	—	—	—	
2/1	—	—	—	—	
3/1	—	—	—	—	
3/2	—	—	—	—	
Concomitant antiplatelet agents use					
yes/no	2.881	1.079	7.740	0.035	*

2 Criteria from the European Society of Cardiology²⁰⁾ were used. *: p<0.05

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1 Table 7 Comparison of the model

	AUC	95%CI		p value	significant difference
		lower	upper		
model 1	0.738	0.630	0.824	0.083	
model 2	0.548	0.425	0.666	0.867	
model 3	0.745	0.632	0.832	0.148	
model 4	0.763	0.650	0.847	0.031	*
model 1vs3				0.727	
model 1vs4				0.441	
model 2vs3				0.004	*
model 3vs4				0.398	

2 *: p<0.05, AUC:area under the curve

3

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Check
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	✓
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	✓
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✓
Objectives	3	State specific objectives, including any prespecified hypotheses	✓
Methods			
Study design	4	Present key elements of study design early in the paper	✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	✓
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓
Bias	9	Describe any efforts to address potential sources of bias	✓
Study size	10	Explain how the study size was arrived at	✓
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	✓
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) If applicable, explain how loss to follow-up was addressed	
		(e) Describe any sensitivity analyses	✓
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	✓
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓
		(b) Report category boundaries when continuous variables were categorized	✓

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		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	✓
Discussion			
Key results	18	Summarise key results with reference to study objectives	✓
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓

BMJ Open

Is the HAS-BLED score useful in predicting post-extraction bleeding in patients taking warfarin?: a retrospective cohort study.

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SCHOLARONE™
Manuscripts

1 Is the HAS-BLED score useful in predicting post-extraction bleeding in patients taking warfarin?
2 a retrospective cohort study

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8 **ABSTRACT**

9 Objective: Unexpected post-extraction bleeding is often experienced in clinical practice.

10 Therefore, determining the risk of post-extraction bleeding in patients receiving anticoagulant
11 therapy prior to surgery is beneficial. This study aimed to verify whether the HAS-BLED score
12 was useful in predicting post-extraction bleeding in patients taking warfarin.

13 Design: Retrospective cohort study.

14 Setting: Department of Oral and Maxillofacial Surgery, Tokyo Women's Medical University.

15 Participants: Subjects 258 sequential cases (462 teeth) who had undergone tooth extraction
16 between January 1, 2010 and December 31, 2012 while continuing warfarin therapy.

17 Main outcome measure: Post-extraction risk factors for bleeding. The following data were
18 collected as the predicting variables for multivariate logistic analysis: the HAS-BLED score,
19 extraction site, tooth type, stability of teeth, extraction procedure, prothrombin time-international
20 normalized ratio value, platelet count, and the use of concomitant antiplatelet agents.

21 Results: Post-extraction bleeding was noted in 21 (8.1%) of the 258 cases. Hemostasis was
22 achieved with localized hemostatic procedures in all the cases of post-extraction bleeding. The
23 HAS-BLED score was found to be insufficient in predicting post-extraction bleeding (area under
24 the curve = 0.548, P = 0.867, multivariate analysis). The risk of post-extraction bleeding was
25 approximately three time greater in patients taking concomitant oral antiplatelet agents (risk
26 ratio= 2.881, P = 0.035, multivariate analysis).

27 Conclusions: The HAS-BLED score alone could not predict post-extraction bleeding. The
28 concomitant use of oral antiplatelet agents was a risk factor for post-extraction bleeding. No
29 episodes of post-extraction bleeding required more than local measures for hemostasis. However,
30 because this was a retrospective study conducted at a single institution, large-scale prospective
31 cohort studies, which include cases of outpatient tooth extraction, will be necessary in the future.

Strengths and limitations of this study

- This is the first study to investigate the usefulness of the HAS-BLED score for predicting the risk of post-extraction bleeding. We investigated all cases of tooth extraction, including wisdom teeth and impacted tooth extractions.

- No previous reports have investigated the effects of each individual tooth extracted, the extraction procedure, and the effects of concomitant antiplatelet agents on post-extraction bleeding using statistical analyses or demonstrated a high level of evidence for these correlations.

- As this study was a retrospective cohort study conducted at a single institution, large-scale prospective cohort studies, including outpatients, are needed in the future.

INTRODUCTION

Patients on anticoagulant therapy who are scheduled to undergo tooth extraction are typically advised continue anticoagulant therapy¹⁻⁴. Unexpected post-extraction bleeding is often experienced in clinical practice; however, the Development of thromboembolism after tooth extraction because of the discontinuation or reduction of anticoagulant therapy has been reported^{5, 6}. Although fatal adverse events must be prevented, there is the additional risk of bleeding because of invasive treatment in these patients, and sufficient measures must be taken to prevent and limit excessive post-extraction bleeding. In the past, a number of studies have investigated tooth extraction with continued anticoagulant therapy and have reported that the frequency of post-extraction bleeding was in the range of 0%–26%⁷⁻¹⁸). Blinder et al.⁹) and Evans et al.¹⁰) reported that there were no differences in the incidences of post-extraction bleeding between a group of patients who had discontinued anticoagulant therapy and a group of those who had continued anticoagulant therapy. Even if the uniform consensus was to perform tooth extraction with continued anticoagulant therapy, the risk of post-extraction bleeding remains. Morimoto et al.¹⁹) suggested that post-extraction bleeding was strongly affected by local inflammatory conditions. However, there are few reports on the systemic factors contributing to post-extraction bleeding. Recently, the HAS-BLED score²⁰⁻²²) has been used as an index for evaluating the risk of bleeding complications in patients taking anticoagulant therapy. The HAS-BLED score evaluates nine risk factors for bleeding. The European Society of Cardiology guidelines²³) has stated that patients who score three points or higher are at a high risk of

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3 1 bleeding complications. However, to date, no reports have examined the relationship between
4 post-extraction bleeding and the HAS-BLED score.

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6 3 Preoperative identification of patients at high risk of post-extraction bleeding could facilitate
7 appropriate preparations prior to performing tooth extraction. Therefore, we examined whether
8 the HAS-BLED score was useful in predicting post-extraction bleeding in patients on warfarin
9 therapy.
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14 7 15 8 **MATERIAL AND METHODS**

16 9 Study design

17 10 This was a retrospective cohort study.
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23 12 Study population and eligibility criteria

24 13 The study subjects were included from 258 sequential inpatient cases at the Department of Oral
25 and Maxillofacial Surgery, Tokyo Women's Medical University, who underwent tooth extraction
26 between January 1, 2010 and December 31, 2012, while receiving a maintenance dose of
27 warfarin. As a general rule, we performed inpatient tooth extraction in patients taking warfarin.
28 Concomitant antiplatelet agents were continued at the maintenance dose. The exclusion criteria
29 were as follows: 1) patients younger than 20 years in age at the time of hospital admission; 2) the
30 presence of comorbid blood diseases; and 3) a prothrombin time-international normalized ratio
31 (PT-INR) level of ≥ 3.1 , as indicated by blood tests performed on the day of the tooth extraction.
32 Patients underwent follow-up examinations for 1 month after discharge. The doctors' and nurses'
33 records obtained from the medical examination records were registered in a database along with
34 the results of the clinical tests. When the same patient was hospitalized and underwent tooth
35 extraction more than once during the study period, all instances were included in the analysis.
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48 26 Tooth extraction procedure

49 27 Each patient's primary physician was consulted preoperatively regarding the general medical
50 status and the use of anticoagulants. When acute symptoms, such as periodontal abscesses, apical
51 periodontitis, or pericoronitis were present around the tooth to be extracted, antibiotics were
52 administered for at least 3 days and anti-inflammation procedures, such as incision and drainage,
53 were performed as necessary. During the tooth extraction, electrocardiograms, blood pressure,
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1 pulse rate, and percutaneous oxygen saturation levels were monitored. For local anesthesia, 1.8–
2 3.6 ml of 2% lidocaine containing 1/80,000 units of epinephrine was administered. Tooth
3 extraction was performed with minimal invasion. When multiple teeth were indicated for
4 extraction and comprised within 1/3 of the jaw area, all the teeth were extracted in one procedure.
5 When the teeth comprised over 1/3 of the total jaw area, multiple teeth were extracted in one
6 procedure if the procedure was expected to take <30 min, while at the same time considering the
7 age of the patient and any comorbid diseases. After extraction, curettage of inflammatory
8 granulation tissue around the wound border was performed, a hemostatic gelatin sponge was
9 inserted into the socket (Spongel, Astellas Pharma Inc.), and suturing was performed to reduce
10 the size of the wound border. The patient was requested to bite down on a piece of absorbent
11 cotton for 20 min after completion of the tooth extraction in order to achieve pressure hemostasis.
12 At 30 min after the tooth extraction, the patient was examined to confirm that the bleeding had
13 stopped. After extraction, patients were instructed to avoid strong or frequent gargling and to rest
14 as much as possible. Post-extraction meals were comprised of rice gruel. In patients with a high
15 risk of developing infective endocarditis²⁴, intravenous antibiotics were administered before
16 surgery and oral antibiotics were administered for 3 days after the tooth extraction. For patients
17 with heart disease on anticoagulant therapy who did not require infectious endocarditis
18 prophylaxis, oral antibiotics were administered for 3 days following tooth extraction. Five doses
19 of analgesics, which comprised loxoprofen sodium or acetaminophen, were prescribed as a
20 medication when pain was experienced.

21 Post-extraction Bleeding

22 Patients who had bleeding but in whom hemostatic procedures were not deemed necessary were
23 instructed to get adequate rest and refrain from excessive gargling. Regular follow-up
24 examinations were performed. When patients had mild bleeding and oozing, the patient was
25 requested to bite down for 20 min on a piece of gauze or absorbent cotton placed on the tooth
26 extraction wound in order to achieve pressure hemostasis. These patients who did not require
27 medical treatment for post-extraction bleeding were categorized into the non-post-extraction
28 bleeding group.

29 Patients who had bleeding on examination after the tooth extraction and who underwent some
30 form of medical hemostatic procedure were categorized into the post-extraction bleeding group.
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3 1 The hemostatic procedures that were performed in accordance with the decision of the
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5 2 examining oral surgeon are described below. In cases of moderate to severe bleeding, which
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7 3 were difficult to resolve using primary hemostasis alone, the local dental anesthetic epinephrine,
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9 4 which has vasoconstrictive effects, was infiltrated at a dose of 1.0–1.8 ml around the tooth
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11 5 extraction wound. Pressure was then applied to the wound by asking the patient to bite down on
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13 6 a piece of gauze or absorbent cotton. When it was determined that the bleeding could not
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15 7 sufficiently be halted by pressure hemostasis alone, the area was additionally filled with local
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17 8 hemostatic agents or additional suturing of the wound was performed as necessary. For cases of
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19 9 repeated bleeding or prolonged exudative bleeding after hemostatic procedures, a hemostatic
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21 10 splint was fabricated to cover the wound. This was fitted after applying a cavity lining with a
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23 11 periodontal pack or denture-based tissue conditioner.
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26 13 Bleeding risk factors for tooth extraction

28 14 The details of extracted teeth, surgical procedure, bleeding tendency, and the use of concomitant
29
30 15 antiplatelet agents were investigated as possible factors affecting post-extraction bleeding.
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32 16 Details regarding the extracted teeth, extraction site (maxilla/mandible), type of teeth
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34 17 (incisor/premolar/molar/wisdom), and stability of teeth were examined. Teeth exhibiting alveolar
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36 18 bone resorption of at least 2/3 of the tooth root length, as determined by preoperative X-rays, or
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38 19 teeth found to have clinical grade III instability were defined as having poor stability. The
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40 20 surgical procedure was classified into simple extraction and surgical extraction. For surgical
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42 21 extraction, the strategy followed was to make an incision into the gingiva, detach and turn over
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44 22 the muco-periosteal flap, and extract the tooth after cutting off the alveolar bone or root
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46 23 separation. All other extractions were defined as simple extractions. With respect to the bleeding
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48 24 tendency, the PT-INR value and platelet count were examined.
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51 26 HAS-BLED score

52 27 The HAS-BLED score was evaluated according to the European Society of Cardiology
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54 28 guidelines²³ (Table 1) and is described below. Patients with a systolic blood pressure of
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56 29 ≥ 160 mmHg, which was measured on arrival at the hospital, were categorized as having
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58 30 “hypertension.” Patients were categorized as having “abnormal renal or liver function” based on

1 the following conditions: 1) patients receiving hemodialysis or those who had a kidney
2 transplant; 2) patients with a serum creatinine level of ≥ 2.26 mg/dl in the most recent blood test;
3 3) patients exhibiting chronic liver disease, such as liver cirrhosis, and bilirubin levels of at least
4 two times the normal upper limit; and 4) patients with at least three times the normal upper limit
5 of either alanine transaminase, aspartate aminotransferase, or alkaline phosphatase levels.
6 Patients were categorized as having “stroke” or “bleeding” based on the information obtained
7 from the medical interviews on admission to the hospital. “Labile INRs” were described as
8 unstable/high INRs or poor time in therapeutic range (e.g., $<60\%$). Patients who were ≥ 65 years
9 in age at the time of tooth extraction were categorized as “elderly.” Patients with long-term
10 administration of antiplatelet agents or non-steroidal anti-inflammatory drugs (NSAIDs) or
11 patients with alcohol dependency were categorized into “drug and alcohol” group. One point was
12 allocated for each of these categories with a possible full score of nine points.

13 14 Selection of representative teeth

15 Of the sequential cases in this study, some patients had duplicate tooth extractions at different
16 time periods; however, the age of the patient, PT-INR values, and the tooth extraction site were
17 different for each extraction. In cases of extraction of multiple teeth in the same patient, each
18 period was treated as independent data with the representative tooth following the procedure.
19 The most posterior tooth was selected as the representative tooth, and in cases of multiple
20 posterior teeth, the upper tooth or the tooth showing the best stability was selected.

21 22 Statistical analyses

23 Statistical analysis involved processing the data of the patient with the representative tooth.
24 Univariate and multivariate logistic analyses were applied to analyze the bleeding risk factors for
25 the tooth extraction data with the presence/absence of post-extraction bleeding as the response
26 variable and the bleeding risk factor as the explanatory variable. Two variable values were used
27 to describe the tooth extraction site (maxilla/mandible), four variable values were used to
28 describe the type of teeth (incisor/premolar/molar/wisdom), two variable values were used to
29 describe the stability of teeth (good/poor), and two variable values were used to describe the
30 surgical procedure (simple/surgical extraction). For the PT-INR value and platelet count, the
31 actual measured values were analyzed as continuous variables, and the HAS-BLED score was

1 used in the analysis as both a continuous and a nominal variable. Concomitant antiplatelet agents
2 were evaluated as two variable values (yes/no). During logistic analysis, we calculated the risk
3 ratio (RR), 95% confidence interval (CI), and *P* value. The RR was calculated as the ratio of
4 “maxilla” to “mandible” for the site, the tooth type within the anterior teeth for the type of teeth,
5 “good” to “poor” for the condition of the periodontium, and from “surgical” to “simple” for the
6 surgical procedure. The RR for the HAS-BLED score was calculated for each level. For
7 concomitant antiplatelet agents, the RR of “yes” to “no” was calculated. In the multivariate
8 analysis, RRs were combined to create post-extraction bleeding analysis models. For each model,
9 we plotted the receiver operating characteristic (ROC) curve and calculated the area under the
10 curve (AUC) in addition to the *P* value and 95% CI for the C-statistical model overall. Many
11 screening tools have used a C-statistical value of ≥ 0.70 . We used the C-statistic for comparisons
12 between each model. Model 1 was constructed from the extracted tooth state, surgical procedure,
13 and bleeding tendency. Model 2 was constructed from the HAS-BLED score only. Model 3 was
14 constructed by adding the HAS-BLED score to Model 1. Model 4 was constructed by adding
15 concomitant antiplatelet agents as an explanatory variable to Model 1. Data were analyzed with
16 the use of JMP Pro 11 software (2014 SAS Institute Inc., US) with a two-tailed alpha level of
17 0.05.

18 19 Ethics

20 This study was approved by the ethical review board of the Tokyo Women’s Medical University
21 (approval number: 3079). The first and second authors take complete responsibility for the
22 integrity of the data and the accuracy of the data analysis.

23 24 RESULTS

25 A total of 462 extracted teeth in 258 patients (males: 157, females: 101) were analyzed. Post-
26 extraction bleeding was observed in 21 patients (8.1%). Hemostasis with a localized hemostatic
27 procedure was performed in all the cases of post-extraction bleeding and no patients died
28 because of hemorrhage.

29 30 Patient characteristics

31 Post-extraction bleeding was noted in 21 patients (males: 14, females: 7; mean age: $63.4 \pm$

1 13.2 years). Table 2 shows the underlying diseases for which anticoagulant therapy was
2 prescribed. The mean warfarin dosage was 3.9 ± 1.4 mg, and the median (25th percentile, 75th
3 percentile) PT-INR was 2.1 (1.8, 2.5). The mean platelet count was $16.8 \pm 5.3 \times 10^4/\mu\text{l}$. Eleven
4 patients were taking only warfarin, and 10 patients were taking an antiplatelet agent in addition
5 to warfarin. Aspirin was administered as the antiplatelet agent in all cases.

6 The non-post-extraction bleeding group included 237 patients (males: 143, females: 94; mean
7 age: 66.6 ± 13.7 years). The underlying diseases for which anticoagulant therapy was prescribed
8 are shown in Table 2. The mean warfarin dosage was 3.2 ± 1.3 mg. The median (25th percentile,
9 75th percentile) PT-INR was 2.0 (1.8, 2.3). The mean platelet count was $18.2 \pm 5.8 \times 10^4/\mu\text{l}$. A
10 total of 174 patients were taking only warfarin, and 63 patients were taking warfarin and an
11 antiplatelet agent. Table 2 shows a breakdown of the antiplatelet agents. Seven patients who were
12 taking two types of antiplatelet agents were all categorized into the non-post-extraction bleeding
13 group. Between the two groups, a statistically significant difference was noted for the warfarin
14 dosage; however, no significant difference was noted for PT-INR. In addition, no significant
15 differences were noted for age, sex, platelet count, or concomitant antiplatelet agent use.

17 **Details of the extracted tooth**

18 In the post-extraction bleeding group, the maxilla was the tooth extraction site in 14 cases and
19 the mandible was that in 7 cases. For the non-post-extraction bleeding group, the maxilla was the
20 tooth extraction site in 122 cases and the mandible was that in 115 cases. No significant
21 differences were noted between the two groups ($P = 0.254$, Fisher's exact test; Table 3).

22 **Results for tooth type**

23 The numbers of incisor, premolar, molar, and wisdom teeth were 1, 2, 9, and 9, respectively, for
24 the post-extraction bleeding group, and 36, 65, 89, and 47, respectively, for the non-post-
25 extraction bleeding group. A statistically significant difference was noted between the two
26 groups ($P = 0.039$, Fisher's exact test; Table 3).

27 In the post-extraction bleeding group, 17 cases showed good stability of teeth, whereas 4 cases
28 showed poor stability. In the non-post-extraction bleeding group, 158 cases showed good
29 stability, whereas 79 cases showed poor stability. No statistically significant difference was
30 noted between the two groups ($P = 0.227$, Fisher's exact test; Table 3).

31 **Extraction procedure**

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3 1 In the post-extraction bleeding group, the selected extraction procedure was simple extraction in
4 17 cases and surgical extraction in 4 cases. In the non-post-extraction bleeding group, the
5 2
6 3 selected extraction procedure was simple extraction in 165 cases and surgical extraction in 72
7 4
8 5 cases. No significant differences were noted between the two groups ($P = 0.328$, Fisher's exact
9 6
10 7 test; Table 3).

11 6 Number of teeth extracted per operation

12 7 The number of teeth extracted per operation was 1.7 ± 0.6 in the post-extraction bleeding group
13 8
14 9 and 1.8 ± 1.1 in the non-post-extraction bleeding group. There were no cases of multiple
15 10
16 11 extractions of four or more teeth in the post-extraction bleeding group. No significant difference
17 12
18 13 was noted between the two groups with respect to the number of teeth extracted per operation
19 14
20 15 ($P = 0.576$, Student's t-test; Table 3).

21 13 HAS-BLED score

22 14 The highest HAS-BLED score obtained was three points. The mean score was 1.3 ± 0.9 in the
23 15
24 16 post-extraction bleeding group and 1.2 ± 0.8 in the non-post-extraction bleeding group. No
25 17
26 18 statistically significant difference was noted between the two groups ($P = 0.467$, Student's t-test;
27 19
28 20 Table 4).

29 19 Statistical examination

30 20 Univariate analysis demonstrated statistically significant differences between the wisdom teeth
31 21
32 22 and incisors ($RR = 8.894$, $P = 0.027$) and between concomitant antiplatelet agents (yes/no) (RR
33 23
34 24 $= 2.511$, $P = 0.500$). RR was ≤ 1 for the surgical procedure and platelet count. No statistically
35 25
36 26 significant difference was noted between a HAS-BLED score of ≥ 3 and a HAS-BLED score of
37 27
38 28 ≤ 2 ($RR = 1.362$, $P = 0.7033$; Table 5).

39 29 No statistically significant differences were noted within multivariate analysis for any of the
40 30
41 31 parameters in Models 1, 2, or 3. In Model 4, a statistically significant difference was noted for
42 32
43 33 antiplatelet agents (yes) in the non-post-extraction bleeding group ($RR = 2.881$, $P = 0.035$; Table
44 34
45 35 6). The AUCs for Models 1, 3, and 4 were 0.7, with a statistically significant difference noted
46 36
47 37 only in Model 4. The AUC for Model 2 was the lowest at 0.5, and a statistically significant
48 38
49 39 difference was noted between Models 2 and 3 ($P = 0.004$; Table 7).

50 31

Discussion

Our investigation of 258 tooth extraction patients indicated that post-extraction bleeding occurred in 21 patients (8%), in 39 of the total 462 extracted teeth (8%). In all the cases of post-extraction bleeding, hemostasis was possible with localized hemostatic procedures. The HAS-BLED score alone could not predict post-extraction bleeding. On considering all the risk factors for post-extraction bleeding statistically, concomitant antiplatelet agent use was a risk factor. It has been reported that the incidence of bleeding in an anticoagulation group was the same (approximately 6%–7%) as in an anticoagulation withdrawal group²⁵. The post-extraction bleeding in this study was in accordance with this report.

Many cases of tooth extraction that have been performed while continuing anticoagulant therapy have been reported^{1, 7-18, 26, 27}. However, in the clinical setting, it is not uncommon to encounter post-extraction bleeding during tooth extraction in cases with an optimal INR value range. In a multicenter large-scale study, Iwabuchi et al.²⁸ reported that the risk factors for post-extraction bleeding in patients taking warfarin were age, PT-INR, and inflammation at the extraction site. To date, although many reports did not include cases of surgical extraction, such as the extraction of wisdom teeth and impacted teeth, these types of surgical extraction are often performed in the clinical setting. Therefore, this study targeted cases that were managed in the optimal treatment range and concurrently investigated all cases of tooth extraction, including the extraction of wisdom teeth, impacted teeth, and multiple teeth.

Various methods of hemostasis have been reported for cases of tooth extraction performed while continuing warfarin therapy. These include pressure hemostasis alone, wound suturing, and the application of local hemostatic agents^{2, 29-31}. To implement hemostasis, we placed a hemostatic gelatin sponge in the extraction socket and routinely conducted pressure hemostasis using absorbent cotton with suturing of the wound. Patients were examined 30 min after tooth extraction to confirm whether the bleeding had stopped. Hemostasis was determined to have been sufficient in all cases. As all patients underwent tooth extraction on an inpatient basis, the patient could rapidly be examined by an oral surgeon or a nurse and could receive early diagnosis and appropriate treatment if post-extraction bleeding was suspected. However, although the patients were examined, many did not require hemostatic treatment. Of the patients who exhibited post-extraction bleeding, no systemic hemostatic treatment, such as blood transfusion, was required in any of the cases.

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3 1 The HAS-BLED score is used in cardiology to evaluate the risk of hemorrhage in patients with
4 adequate anticoagulation. It would be highly significant if the HAS-BLED score could be used to
5 predict the risk of post-extraction bleeding, and therefore, we evaluated its use in this study. We
6 found that the highest HAS-BLED score was three points. A score of one point was the most
7 commonly achieved score among the 137 patients (53%). The commonest risk factor was age
8 (174 patients; 67%). No significant difference was noted for the mean HAS-BLED score
9 between the post-extraction bleeding and non-post-extraction bleeding groups. The European
10 Society of Cardiology has proposed that a HAS-BLED score ≥ 3 indicates a high risk of
11 hemorrhagic complications. In the cases of post-extraction bleeding, we compared patients with
12 a HAS-BLED score of three or higher with those having a score of two or lower but did not
13 detect any statistically significant difference (univariate analysis; RR = 1.362, $P = 0.703$).
14 Multivariate analysis indicated that there was little risk associated with the score increasing by
15 one (Table 6). The AUC for the HAS-BLED score alone (Model 2) was 0.55, which was the
16 lowest for all of the models that we constructed. In Model 3, to which the details of extracted
17 teeth were added to the HAS-BLED score, AUC was 0.745, suggesting that this model is useful
18 for predicting post-extraction bleeding. However, a statistically significant difference was noted
19 for Model 2 versus Model 3 ($P = 0.004$), indicating that the HAS-BLED score alone was
20 insufficient for predicting post-extraction bleeding.

21 As bleeding risk factors for tooth extraction, investigation of the conditions of the individual
22 teeth extracted indicated that the post-extraction bleeding risk was five to six times higher for
23 wisdom teeth compared with that for anterior teeth. The extraction site and stability had little
24 effect. Although no differences were observed for the number of teeth extracted in one treatment,
25 there were no cases of multiple extractions of four or more teeth in the post-extraction bleeding
26 group. Although we predicted that surgical extraction was a risk factor for post-extraction
27 bleeding, the results indicated that surgical extraction hardly had any effect on post-extraction
28 bleeding (RR = 0.539, $P = 0.256$).

29 Effects of warfarin can be possibly affected by the interactions between meals and medicine and
30 by the general state of the patient. Therefore, in this study, to accurately determine the
31 anticoagulation state directly before tooth extraction, all blood tests were performed before
breakfast on the tooth extraction day or the first tooth extraction day if tooth extraction was
planned on consecutive days. Although post-extraction bleeding cases were receiving high doses

1 of warfarin, no difference was observed in PT-INR values. There were no cases classified as
2 having labile INRs. Accordingly, the PT-INR value was investigated using actual measured
3 values as the continuous variable. There were no statistically significant differences noted for
4 PT-INR values by either univariate or multivariate analyses ($P \geq 0.1$), suggesting that the PT-
5 INR value had little effect on post-extraction bleeding in patients on anticoagulant therapy while
6 being managed within the optimal treatment range.

7 There has been no fixed consensus regarding the concomitant use of warfarin and antiplatelet
8 agents because some reports have indicated that these increase the risk of post-extraction
9 bleeding^{1,32}), whereas other reports have suggested that antiplatelet agents have little effect^{16,19}).
10 In this study, the incidence of post-extraction bleeding was 13.7% with concomitant antiplatelet
11 drugs and 5.9% with warfarin alone. Both the univariate and multivariate analyses indicated that
12 the use of concomitant antiplatelet agents was a significant factor affecting post-extraction
13 bleeding. It has been reported that the concomitant use of two antiplatelet agents significantly
14 increases the frequency of intracranial hemorrhaging³³). Furthermore, a prospective observational
15 study of hemorrhagic complications in Japanese cerebral infarction patients³⁴) found that
16 compared with patients taking only one antiplatelet agent, those taking two or three antiplatelet
17 agents along with warfarin clearly exhibited higher annual onset rates of intracranial
18 hemorrhaging. These results suggest that concomitant antiplatelet agents are a risk factor for
19 post-extraction bleeding.

20 The limitations of the present study include the fact that the data were obtained only at a single
21 facility and that outpatients were not included in the subjects that we investigated. In our facility,
22 there were many patients with cardiovascular diseases, particularly post-operative valve
23 replacement patients at approximately 50%. Furthermore, because patients with a PT-INR of
24 ≥ 3.1 during the blood testing performed on the day of tooth extraction were excluded, the current
25 study included patients whose anticoagulant therapy was well managed. Therefore, our subjects
26 were not exactly representative of generalized cases of tooth extraction patients taking warfarin.
27 Moreover, because this was a retrospective study, we believe that a large-scale, prospective,
28 cohort study, including outpatient tooth extraction cases, needs to be conducted in the future.

29 Moreover, we could not examine drug interaction effects because our subjects included patients
30 who received intravenous antibacterial agents and patients who received oral antibacterial agents.
31 Warfarin has a number of drug interactions. Holbrook et al.³⁵) stated that anti-infective agents,

1 lipid-lowering drugs, NSAIDs, including COX-2 selective NSAIDs, selective serotonin reuptake
2 inhibitors, amiodarone, omeprazole, fluorouracil, and cimetidine enhance the anticoagulation
3 effects of warfarin. It has been suggested that changing to alternative drugs that have a smaller
4 interactive effect with warfarin should be considered. However, some reports have stated that in
5 most stable anticoagulant therapy patients, exposure to antibacterial agents did not cause clinical
6 problems³⁶); furthermore, other reports have found that NSAIDs and antibacterial agents often
7 increased warfarin effects only in cases of long-term administration¹⁸). We also believe that the
8 short-term or low-dose administration of NSAIDs or antibacterial agents does not cause any
9 prolongation of clinically problematic PT-INR.

10 Of the models that we created in this study, Model 4 exhibited the highest predictive ability for
11 post-extraction bleeding (AUC = 0.76, $P = 0.0309$). However, because there were no significant
12 differences observed between Models 1 or 3 versus Model 4, we were unable to construct an
13 optimal model for predicting post-extraction bleeding. To increase model precision, it may be
14 beneficial to add other factors, such as the surgeon's skill (e.g., years of experience or time
15 required for one tooth extraction), which were not included in our current investigation.
16 Furthermore, the addition of all extraction data from outpatients to the analysis set is necessary to
17 conduct a multilevel analysis.

18 Finally, all the patients who had post-extraction bleeding achieved hemostasis with localized
19 hemostatic procedures, and no systemic hemostatic treatment was required. There was no case
20 that warranted extended hospitalization because of post-extraction bleeding. In agreement with
21 our results, Wahl et al.²⁵) stated that bleeding complications requiring more than local hemostatic
22 measures after dental surgery were exceedingly rare. To avoid the onset of fatal
23 thromboembolism⁶), there is no need to pause or interrupt warfarin therapy for tooth extraction.
24 A special environment for the post-extraction bleeding procedure is not necessary. If the
25 conditions are adequately prepared, we believe that tooth extraction in a patient on warfarin
26 therapy is possible in a private office.

27 28 **CONCLUSIONS**

29 1. We investigated post-extraction bleeding for all types of tooth extractions, including impacted
30 teeth, in patients taking warfarin. Minor post-extraction bleeding was observed in 8% of patients;
31 however, no patients required more than local measures for hemostasis.

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4 1 2. The HAS-BLED score alone could not predict post-extraction bleeding in patients taking
5 2 warfarin.

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7 3 3. The use of concomitant antiplatelet agents was a risk factor for post-extraction bleeding. More
8 4 care must be taken regarding post-extraction bleeding in cases undergoing concomitant use of
9 5 antiplatelet drugs than in those on warfarin alone.
10
11 6

14 7 **Acknowledgments**

15 8 We would like to extend our gratitude and thanks to the professors at the Department of Oral and
16 9 Maxillofacial Surgery at Tokyo Women's Medical University who offered their kind cooperation
17 10 during this study.
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19

21 11 **Contributors**

22 12 TA and TK were involved in the planning of the study concept and design. TK wrote the draft of
23 13 the manuscript. KH and TK were involved in the statistical analysis. TA and TK reviewed and
24 14 revised the manuscript. All authors have read and approved the final manuscript.
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26
27

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30
31

32 17 **Conflicts of interest**

33 18 The authors have no competing interest to declare regarding this study.
34
35

36 19 **Data sharing statement**

37 20 No additional data are available.
38
39

40 21 **Provenance and peer review**

41 22 Not commissioned; externally peer reviewed.
42
43

44 23 **Open access**

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1 Table 1 HAS-BLED bleeding risk score

risk factor		clinical characteristics
H	Hypertension	uncontrolled, >160mmHg systolic
A	Abnormal renal and liver function (1point each)	presence of chonic dialysis, renal pramsplantation or serum creatinine $\geq 200\mu\text{mol/L}$
		chornic hepatic disease(eg, cirrhosis), bilirubin >2X upper limit of nomal,
		AST/ALT/ALP >3X upper limit of nomal
S	Stroke	previous history
B	Bleeding	bleeding history or predisposition
L	Labile INRs	unstable/high INRs or poor time in therapeutic range (e.g. <60%)
E	Elderly	>65 years
D	Drugs or alcohol (1point each)	concomitantly antiplatelet agents and NSAIDs,
		alcohol excess

- 2 Criteria from the European Society of Cardiology²³⁾ were used., AST=aspartate
 3 aminotransferase, ALT=alanine aminotransferase, ALP=alkaline phosphatase,
 4 NSAIDs=nonsteroidal antiinflammatory drugs

1 Table 2 Patient characteristics

	post-extraction bleeding group	non post-extraction bleeding group	p value	Significant difference	χ^2 value
	N=21	N=237			
	number of patients	number of patients			
Age (mean \pm SD)	63.4 \pm 13.2	66.6 \pm 13.7	0.294 ^a		
Gender(Male/Female)	14/7	143/94	0.646 ^c		0.32
Primary disease					
post Heart Valve Prosthesis Implantation	17	120			
atrial fibrillation	2	76			
cerebral infarction	2	13			
dilated cardiomyopathy	1	9			
myocardial infarction	0	23			
deep vein thrombosis	0	11			
arteriosclerosis obliterans	0	3			
intracardiac thrombus	0	2			
Anticoagulation					
warfarin dose(mg) (mean \pm SD)	3.9 \pm 1.4	3.2 \pm 1.3	0.024 ^a	*	
PT-INR value (mean [25% tile, 75%tile])	2.1[1.8, 2.5]	2.0[1.8, 2.3]	0.330 ^b		
Platelet count($\times 10^4/\mu$ l)	16.8 \pm 5.3	18.2 \pm 5.8	0.298 ^a		
Concomitant antiplatelet agents					
Yes	10	63	0.073 ^c		4.21
Aspirin	10	52			
Ticlopidine	0	8			
ethyl icosapentate	0	6			
Cilostazol	0	2			
Limaprost	0	1			
Dipyridamole	0	1			

2 SD: standard deviation, Multiple factors possible for underlying disease, All seven patients using two
3 types of antiplatelet agents were included in the non post-extraction bleeding group. a; Student's t-test,
4 b;Mann-Whitney U test, c;Fisher's exact test, *:p<0.05

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1 Table 3 Details of extracted teeth

	post-extraction bleeding group	non post-extraction bleeding group	p value	Significant difference	χ^2 value
	N=21	N=237			
	number of patients or mean \pm SD	number of patients or mean \pm SD			
Extraction site					
maxilla	14	122	0.254 ^c		1.79
mandibula	7	115			
Tooth type					
Incisor	1	36	0.039 ^c	*	8.70
premolar	2	65			
molar	9	89			
wisdom	9	47			
Stability of teeth					
good	17	158	0.227 ^c		1.80
poor	4	79			
Extraction procedure					
simple	17	165	0.328 ^c		1.19
surgical	4	72			
Number of teeth extracted in operation	1.7 \pm 0.6	1.8 \pm 1.1	0.576 ^a		
One tooth	8	125	0.188 ^c		9.12
Two tooth	12	65			
Three tooth	1	24			
Four tooth	0	18			
Five tooth	0	3			
Six tooth	0	1			
Seven tooth	0	1			

2 SD: standard deviation, a; Student's t-test, c; Fisher's exact test, *: $p < 0.05$

1 Table 4 HAS-BLED score

	post-extraction bleeding group	non post-extraction bleeding group	p value	Significant difference	χ^2 value
	N=21	N=237			
	mean \pm SD or number of patients	mean \pm SD or number of patients			
HAS-BLED score	1.3 \pm 0.9	1.2 \pm 0.8	0.467 ^a		
0	3	41	0.804 ^c		0.75
1	10	127			
2	6	52			
3	2	17			
4	0	0			
5	0	0			
6	0	0			
7	0	0			
8	0	0			
9	0	0			
risk factor					
H	1	3			
A	1	11			
S	2	38			
B	0	5			
L	0	0			
E	13	161			
D	11	63			

2 SD: standard deviation, a; Student's t-test, c; Fisher's exact test

1 Table 5 Univariate analysis of bleeding risk factor in teeth extraction

	RR	95%CI		p value	significant difference
		lower	Upper		
Extraction site					
maxilla/mandible	1.885	0.756	5.128	0.177	
Tooth type					
premolar/incisor	1.108	0.103	24.300	0.934	
molar/incisor	3.640	0.649	68.346	0.160	
wisdom/incisor	6.894	1.213	130.039	0.027	*
Stability of teeth					
good/poor	2.125	0.756	7.572	0.161	
Extraction procedure					
surgical/simple	0.539	0.151	1.518	0.256	
PT-INR value	1.782	0.597	5.387	0.300	
Platelet count($\times 10^4/\mu\text{l}$)	0.959	0.887	1.037	0.296	
HAS-BLED score					
1/0	1.076	0.312	4.968	0.914	
2/0	1.577	0.391	7.825	0.529	
3/0	1.608	0.199	10.551	0.626	
2/1	1.465	0.477	4.157	0.487	
3/1	1.494	0.218	6.305	0.636	
3/2	1.020	0.140	4.922	0.982	
3/ less than 2	1.362	0.206	5.255	0.703	
Concomitant antiplatelet agents use					
yes/no	2.511	1.001	6.238	0.050	*

2 Criteria from the European Society of Cardiology²³⁾ were used. RR: risk ratio, *:p<0.05

1 Table 6 Multivariate analysis of post-extraction bleeding

	model 1				
	risk ratio	95%CI		p value	significant difference
		lower	upper		
Extraction site					
maxilla/mandible	1.855	0.700	5.286	0.216	
Tooth type					
premolar/incisor	1.118	0.102	24.727	0.928	
molar/incisor	3.468	0.594	65.974	0.188	
wisdom/incisor	5.228	0.850	101.628	0.078	
Stability of teeth					
good/poor	1.790	0.551	6.994	0.344	
Extraction procedure					
surgical/simple	0.624	0.166	1.915	0.425	
PT-INR value	2.078	0.681	6.606	0.204	
Platelet count($\times 10^4/\text{ul}$)	0.970	0.892	1.053	0.461	
HAS-BLED score					
1/0	—	—	—	—	
2/0	—	—	—	—	
3/0	—	—	—	—	
2/1	—	—	—	—	
3/1	—	—	—	—	
3/2	—	—	—	—	
Concomitant antiplatelet agents use					
yes/no	—	—	—	—	

2 Criteria from the European Society of Cardiology²³⁾ were used, *: $p < 0.05$

1 Table 6 continuation

	model 2				
	risk ratio	95%CI		p value	significant difference
		Lower	upper		
Extraction site					
maxilla/mandible	—	—	—	—	
Tooth type					
premolar/incisor	—	—	—	—	
molar/incisor	—	—	—	—	
wisdom/incisor	—	—	—	—	
Stability of teeth					
good/poor	—	—	—	—	
Extraction procedure					
surgical/simple	—	—	—	—	
PT-INR value	—	—	—	—	
Platelet count($\times 10^4/\text{ul}$)	—	—	—	—	
HAS-BLED score					
1/0	1.076	0.312	4.968	0.914	
2/0	1.577	0.391	7.825	0.529	
3/0	1.608	0.199	10.551	0.626	
2/1	1.465	0.477	4.157	0.487	
3/1	1.494	0.218	6.305	0.636	
3/2	1.020	0.140	4.922	0.982	
Concomitant antiplatelet agents use					
yes/no	—	—	—	—	

2 Criteria from the European Society of Cardiology²³⁾ were used, *: $p < 0.05$

1 Table 6 continuation

	model 3				
	risk ratio	95%CI		p value	significant difference
		lower	upper		
Extraction site					
maxilla/mandible	1.914	0.716	5.494	0.198	
Tooth type					
premolar/incisor	1.045	0.095	23.222	0.972	
molar/incisor	3.388	0.579	64.544	0.199	
wisdom/incisor	5.380	0.860	105.301	0.075	
Stability of teeth					
good/poor	1.961	0.588	7.893	0.283	
Extraction procedure					
surgical/simple	0.674	0.177	2.125	0.515	
PT-INR value	2.288	0.727	7.543	0.162	
Platelet count($\times 10^4$ /ul)	0.968	0.889	1.053	0.443	
HAS-BLED score					
1/0	1.197	0.325	5.777	0.798	
2/0	2.271	0.515	12.242	0.284	
3/0	2.338	0.269	16.989	0.410	
2/1	1.897	0.580	5.871	0.279	
3/1	1.954	0.266	9.403	0.463	
3/2	1.030	0.130	5.605	0.975	
Concomitant antiplatelet agents use					
yes/no	—	—	—	—	

2 Criteria from the European Society of Cardiology²³⁾ were used. *: $p < 0.05$

1 Table 6 continuation

	model 4				
	risk ratio	95%CI		p value	significant difference
		lower	upper		
Extraction site					
maxilla/mandible	1.936	0.722	5.585	0.192	
Tooth type					
premolar/incisor	1.159	0.104	25.901	0.906	
molar/incisor	3.730	0.630	71.468	0.164	
wisdom/incisor	5.113	0.804	100.719	0.804	
Stability of teeth					
good/poor	1.916	0.568	7.780	0.304	
Extraction procedure					
surgical/simple	0.670	0.175	2.117	0.509	
PT-INR value	2.687	0.831	9.349	0.107	
Platelet count($\times 10^4$ /ul)	0.970	0.894	1.052	0.465	
HAS-BLED score					
1/0	—	—	—	—	
2/0	—	—	—	—	
3/0	—	—	—	—	
2/1	—	—	—	—	
3/1	—	—	—	—	
3/2	—	—	—	—	
Concomitant antiplatelet agents use					
yes/no	2.881	1.079	7.740	0.035	*

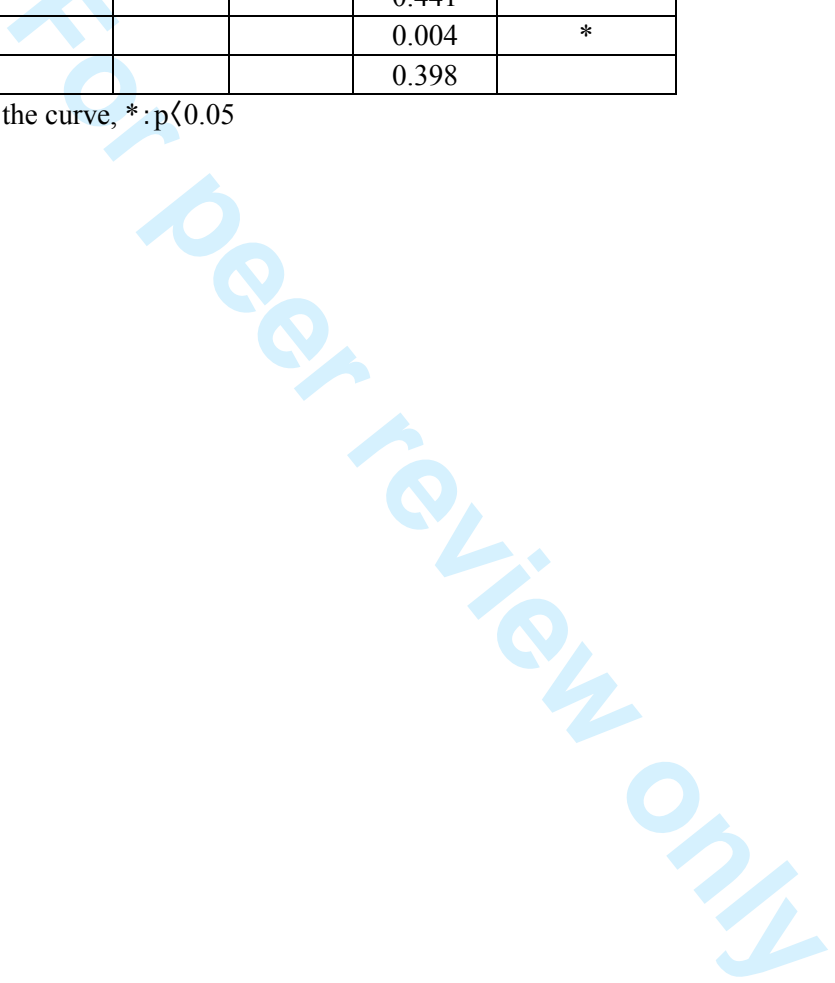
2 Criteria from the European Society of Cardiology²³) were used., *: $p < 0.05$

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1 Table 7 Comparison of the model

	AUC	95%CI		p value	significant difference
		lower	upper		
model 1	0.738	0.630	0.824	0.083	
model 2	0.548	0.425	0.666	0.867	
model 3	0.745	0.632	0.832	0.148	
model 4	0.763	0.650	0.847	0.031	*
model 1vs3				0.727	
model 1vs4				0.441	
model 2vs3				0.004	*
model 3vs4				0.398	

2 AUC; area under the curve, *:p<0.05



STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Check
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 2,3
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 2,3
Methods			
Study design	4	Present key elements of study design early in the paper	Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 3
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 3
		(b) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 3-7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 3-7
Bias	9	Describe any efforts to address potential sources of bias	Page 3
Study size	10	Explain how the study size was arrived at	Page 3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 3-7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 6
		(b) Describe any methods used to examine subgroups and interactions	n/a
		(c) Explain how missing data were addressed	n/a
		(d) If applicable, explain how loss to follow-up was addressed	n/a
		(e) Describe any sensitivity analyses	Page 6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 7-9
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 7-9
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 7-9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and	Page

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(b) Report category boundaries when continuous variables were categorized	Page 7-9
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 7-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 14