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(Degree)

博士 (保健学)

(Date of Degree)

2024-03-25

(Date of Publication)

2025-03-01

(Resource Type)

doctoral thesis

(Report Number)

甲第8908号

(URL)

<https://hdl.handle.net/20.500.14094/0100490133>

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博 士 論 文

Analysis of post-extraction bleeding in patients taking antithrombotic therapy using data from the longevity improvement and fair evidence study

(レセプトデータを用いた抗血栓療法患者における

抜歯後出血の分析:LIFE Study)

令和 6 年 1 月 9 日

神戸大学大学院保健学研究科保健学専攻

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Analysis of post-extraction bleeding in patients taking antithrombotic therapy using data from the Longevity Improvement and Fair Evidence study

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Abstract

Introduction: Several studies have investigated post-extraction bleeding in patients on antithrombotic therapy, but most included a small sample size. This study aimed to analyze post-extraction bleeding in patients on antithrombotic therapy using data from a large database.

Methods: Claims data of National Health Insurance and Late-Stage Elderly Healthcare System enrollees who underwent tooth extraction between October 2014 and March 2019 (n=107,767) in a large multiregional cohort study (Longevity Improvement and Fair Evidence study) were included. Antithrombotic therapy was determined based on drug codes at the time of tooth extraction (classified into six groups: no antithrombotic, single antiplatelet, dual antiplatelet, Direct Oral Anticoagulant, warfarin, and combined antiplatelet and anticoagulant therapies). Outcome was defined as the presence of "post-extraction bleeding" as a receipt disease name in the same month as tooth extraction. To examine the association between antithrombotic therapy and post-extraction bleeding in detail, multiple logistic regression analysis was performed with post-extraction bleeding as the objective variable; each antithrombotic therapy as the explanatory variable; and age, sex, and comorbidities as adjustment variables.

Results: Antithrombotic therapy was administered in 14343 patients (13.3%), and post-extraction bleeding was observed in 419 patients (0.4%). The rate of post-extraction bleeding was significantly lower in the no antithrombotic therapy group or in the single antiplatelet group than in the other groups (odds ratio: 2.00–9.02).

Conclusion: The frequency of post-extraction bleeding is high in patients on anticoagulation or dual antithrombotic therapy. Therefore, careful preparation before extraction is necessary in these patients.

Introduction

Tooth extraction is the most frequently performed oral surgical procedure¹. The main complications after tooth extraction include swelling, pain, infection, and bleeding². Of these, bleeding is the most urgent to deal with and sometimes requires additional treatment, such as re-hemostasis or hospitalization³.

There has been much discussion regarding the causes of post-extraction bleeding. In particular, with regard to antithrombotic therapy, which is commonly used in the elderly, "the guidelines for patients on antithrombotic therapy requiring dental extraction"⁴ have been established in Japan, and many other clinical guidelines have been reported in various other countries^{5),6),7}. Generally, antithrombotic therapy is recognized as a major risk factor for post-extraction bleeding. Several studies^{8),9),10),11} have reported on the risk of post-extraction bleeding focusing on the type of antithrombotic therapy; however, most were conducted on a small scale. Furthermore, the probability of bleeding was variable, ranging from 0 to 66.7%¹¹. In addition, there are many classifications of the number and types of drugs used in antithrombotic therapy, for example, antiplatelet drugs are mainly used to prevent thrombus formation in the arterial system, while anticoagulants are used to prevent thrombus formation in the venous system. As different types of antithrombotic therapy have varying mechanisms of action, each type should be considered separately. Detailed discussion on the effects of different types of antithrombotic therapy on post-

extraction bleeding is lacking, and it is difficult to apply the previously reported information to clinical practice, such as for patient explanation and presurgical management.

Accordingly, this study aimed to identify the prevalence of post-extraction bleeding using claims data, with particular attention to the type of antithrombotic therapy, and to investigate the frequency and trends of post-extraction bleeding for each type of therapy.

Materials and Methods

Study database

This study was conducted using a database generated by the Longevity Improvement and Fair Evidence (LIFE) study. The LIFE study is a longitudinal cohort study that collected and linked administrative claims data and health checkup data of residents from the participating municipalities^{12),13)}¹⁴. The municipalities were 13 cities and towns in Fukuoka Prefecture, with population sizes ranging from about 35,000 to 301,000 and an average population of 80,766. The municipality's population density was 665-3,464 persons/km², with an average of 1,687 persons/km². The database includes information of the national health insurance enrollees (mainly comprising retirees aged ≤ 74 years, self-employed people, non-regularly employed people, and primary industry workers), Latter-Stage Elderly Healthcare System enrollees (comprising all residents aged ≥ 75 years), and long-term care insurance enrollees (comprising residents aged ≥ 65 years with certified care needs) from April 2014 onward. The study protocol was approved by the Kyushu University institutional ethics committee (approval number 2021-399). The LIFE study is conducted under individual agreements between Kyushu University and each

participating municipality. Each participating municipality provides opt-out opportunities for those who do not wish to participate in the study. The LIFE study receives and stores data that these municipalities agree to share.

Study design, setting, and participants

This study is a cross-sectional study. Data of 362,919 patients (13 municipalities) who underwent extraction between October 2014 and March 2019 were evaluated. Patients with multiple extractions were included only for the first extraction. Patients who were prescribed Direct Oral Anticoagulant (DOAC) and warfarin in the same month (n=25) were excluded. After applying these criteria, data of 107,767 patients were included in the final analysis. (**Figure 1.**)

Variables

Post-extraction bleeding

The presence of post-extraction bleeding was defined by the injury/illness name "post-extraction bleeding" (claim code: 5258013) in the receipt of the same month in which the tooth extraction was performed. In the guideline⁴, post-extraction bleeding is defined as "bleeding again after the tooth extraction is completed, from 30 min to several days after the tooth extraction." The extraction sites were anterior tooth (practice code: 310000210), molar (310000310), and wisdom tooth sites (310000510).

Antithrombotic therapy

The type of antithrombotic therapy was determined from the drug codes in the receipt data at the time of the extraction procedure. We extracted data on 278 antiplatelet drugs,

16 DOACs, and 19 warfarin-based drugs from the drug codes. As reported in a previous study¹⁵, the patients were classified into the following six groups based on the type of antithrombotic therapy: no antithrombotic therapy, single antiplatelet drug, dual antiplatelet drugs, anticoagulant drug (DOAC), anticoagulant drug (warfarin), and combined antiplatelet–anticoagulant drugs.

Demographic and clinical variables

The following demographic and clinical variables were obtained from receipt data at the time of the extraction procedure: age, sex, information on difficult extractions (extractions with root separation or alveolar trimming; practice code: 310000410), the number of teeth extracted per month and comorbidities. Important comorbidities (hypertension, liver disease, renal disease, stroke, and coagulopathy) that could be related to post-extraction bleeding were selected by referring to the existing bleeding risk assessment batteries, including the Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol Concomitantly (HAS-BLED) score¹⁶; Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score¹⁷; Outcomes Registry for Better Informed Treatment (ORBIT) score¹⁸; and the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria¹⁹. Charlson Comorbidity Index (CCI) was calculated to assess all comorbidities. Higher CCI score implied that the patient had more comorbidities²⁰.

Statistical analysis

We calculated the mean and standard deviation (SD) for age and CCI, and number (n) and percentage (%) for other variables to describe the demographic and clinical characteristics

of patients. To compare the characteristics between the patients with and without post-extraction bleeding, we conducted t-tests and Wilcoxon rank sum tests for continuous variables and chi-square tests for binary variables.

We first calculated the percentage of post-extraction bleeding in each antithrombotic therapy group. Multiple logistic regression analysis was performed to examine the impact of antithrombotic therapy on post-extraction bleeding. The dependent variable was the presence of post-extraction bleeding; independent variable was antithrombotic therapy (no antithrombotic therapy: reference); and adjustment variables were age, sex, CCI, and the presence of each comorbidity (hypertension, liver disease, renal disease, stroke, and coagulopathy)^{16,17,18,19}. In addition, to perform a detailed analysis among patients who received antithrombotic therapy, multiple logistic regression analysis was performed as a sub-analysis using the data of patients on single antiplatelet drug as a reference. Odds ratios (OR) and 95% confidence intervals (95%CI) were calculated.

Statistical significance was set at $P < 0.05$. All statistical analyses were performed using R studio v 4.0.4. (R Foundation for Statistical Computing, Vienna, Austria)

Results

Participants and variables

The mean age of the 107,767 patients in the final analysis was 68.3 ± 14.3 years, and 59,466 (55.2%) were women. Post-extraction bleeding was observed in 419 (0.4%) patients. Demographic and clinical variables are shown in **Table 1**. The group with post-extraction bleeding included older patients with a higher CCI, and a higher percentage of patients with hypertension, liver disease, renal disease, and coagulopathy compared with

the group without post-extraction bleeding.

Frequency of post-extraction bleeding for each antithrombotic therapy

Antithrombotic therapy was administered in 14,343 patients (13.3%). The frequency of post-extraction bleeding was 0.3% in the no antithrombotic therapy group, 0.6% in the single antiplatelet group, 1.3% in the dual antiplatelet drugs group, 1.7% in the DOAC group, 1.9% in the warfarin group, and 2.8% in the combined antiplatelet–anticoagulant drugs group (**Figure 2**).

Association between each antithrombotic therapy group and post-extraction bleeding

The results of multiple logistic regression analysis are shown in **Table 2**. Regardless of the type of antithrombotic therapy, rate of post-extraction bleeding in groups with antithrombotic therapy was significantly higher than those in the no antithrombotic therapy group (OR [95%CI]: single antiplatelet drug, 2.00 [1.43–2.77]; dual antiplatelet drugs, 4.63 [2.90–7.41]; DOAC, 5.48 [3.84–7.83]; warfarin, 5.93 [4.14–8.48]; combined antiplatelet-anticoagulant drugs, 9.02 [5.79–14.0]). The results of multiple logistic regression analysis with the single antiplatelet drug group as reference are shown in **Table 3**. Compared to the single antiplatelet drug group, the other antithrombotic therapy groups had a significantly higher rate of post-extraction bleeding (OR [95%CI]: dual antiplatelet drugs, 2.33 [1.34–3.91]; DOAC, 2.76 [1.76–4.29]; warfarin, 2.98 [1.91–4.63], combined antiplatelet–anticoagulant drugs, 4.53, [2.68–7.48]).

Discussion

In this study, we used claims data to examine the prevalence of post-extraction bleeding

and the relationship of antithrombotic therapy type with post-extraction bleeding. The findings showed that post-extraction bleeding was present in 0.4% of all patients, with a significantly higher rate in the patients who had received antithrombotic therapy than those who did not. Among the types of antithrombotic therapy, the rate of post-extraction bleeding was the highest in the combined antiplatelet–anticoagulant drugs group, followed by, in decreasing order, anticoagulant, dual antiplatelet drugs, and single antiplatelet drug groups. Among antithrombotic therapies, the rate of post-extraction bleeding was found to be significantly higher among patients who were taking two antithrombotic drugs or anticoagulants.

More than 10 years have passed since the publication of the "guidelines for patients on antithrombotic therapy requiring dental extraction"⁴ by the Japanese Society of Dentistry for Medically Compromised Patients, Japanese Society of Oral and Maxillofacial Surgeons, and Japanese Society of Gerodontology. Although the current guidelines recommend tooth extraction under continued antithrombotic therapy, there are many unknowns regarding the compliance rate with the guidelines and the impact of different types of antithrombotic therapy. The strength of this study is that it is the first to examine post-extraction bleeding using a large database and to classify antithrombotic therapies in detail to determine the frequency of post-extraction bleeding. We believe that our study findings will allow appropriate treatment planning to reduce the risk of post-extraction bleeding in daily clinical practice.

The rate of post-extraction bleeding in this study was lower than that reported in the previous studies^{8),9),10),21),22}. This inconsistency may be because of the difference in the

definition of post-extraction bleeding between the present study and previous studies. Furthermore, few previous studies have investigated populations of more than 1000 patients, and it is possible that observer bias, or the small sample size, may be the cause for inconsistency. However, the sequential relationship of the incidence of post-extraction bleeding in each antithrombotic therapy group itself was consistent with the major guidelines^{5),6),7} issued by the U.S. and U.K., and findings of a previous systematic review of post-extraction bleeding in antithrombotic therapy^{11),23}. Additionally, shifting the perspective to generalized bleeding events, a study that enrolled more than 4000 Japanese patients¹⁵ and a 7000-patient study on the incidence of systemic bleeding complications during antithrombotic therapy reported that the effect of DOAC was equal to or less than warfarin²⁴. The trend of post-extraction bleeding in the present study was almost consistent with these findings.

In addition, to investigate the detailed impact of each type of antithrombotic therapy, we performed an analysis using the single antiplatelet drug group as a reference. The present study findings clearly showed that the two antiplatelet drug groups and combined antiplatelet and anticoagulant group had significantly higher rates of post-extraction bleeding than the single antiplatelet drug group. A systematic review^{25),26} on post-extraction bleeding and post-oral minor surgery bleeding in patients taking dual antiplatelet drugs suggests that, similar to the present study, the risk of postoperative bleeding is higher in patients taking dual antiplatelet drugs. There are no reviews on post-extraction bleeding in combination therapy with antiplatelet-coagulant drugs and only one observational study²⁷. Further evidence is needed due to the paucity of previous studies.

Furthermore, in our study, the rate of post-extraction bleeding was significantly higher in the anticoagulant (DOAC/warfarin) group than that in the single antiplatelet drug group. A previous study²⁸ found a significant increase in delayed post-extraction bleeding under continuous DOAC administration. The difference in the mechanism of action of antiplatelet drugs and poor secondary hemostasis may have led to greater post-extraction bleeding than in the single antiplatelet drug group. Regarding the type of anticoagulant, several studies^{9),10),29} have compared post-extraction bleeding with continuous DOAC and warfarin administration, respectively, and none found significant differences between the two drugs, and the same trend was observed in the present study.

Overall, the findings of this study suggest that post-extraction bleeding was maintained at a low rate of 2.8% or less in all groups. Assuming that the findings of this study were obtained under conditions in compliance with the Japanese guidelines⁴, there would be no objection to the extraction of teeth under continued antithrombotic therapy. However, considering the finding of each antithrombotic therapy type, it is necessary to take thorough precautions against post-extraction bleeding, such as tooth extraction under hospitalization and careful hemostatic treatment in patients taking anticoagulants (both DOAC and warfarin) or dual antithrombotic drugs. In the clinical settings, trade-off of ischemic and bleeding events should be considered. At present, it may be advisable to emphasize the thrombotic and embolic risks^{30),31),32} of discontinuing antithrombotic therapy and to continue antithrombotic therapy and take thorough precautions against post-extraction bleeding.

This study had some limitations. First, the information was obtained only from receipts, and the possible factors³³ of post-extraction bleeding, such as local condition of the extraction site, presence of inflammation, surgeon's experience, and hemostatic method, were unknown. However, these factors are not related to the type of antithrombotic therapy, which is an exposure factor; therefore, they were not considered a priority for adjustment in this analysis. Second, the definition of the outcome of post-extraction bleeding might be not standardized among surgeons. Various types of post-extraction bleeding were considered, including bleeding controlled by gauze compression, bleeding that required a return visit for hemostasis, occurring immediately after extraction, and that occurring several days after extraction. Although the validity of the disease name "post-extraction bleeding" in the receipt data has not been verified in the previous studies, it can be considered as "bleeding to the extent that it was necessary to register post-extraction bleeding as a disease name in the receipt," that is, bleeding that involved an event in which the patient became troubled and visited a medical institution, or bleeding that required procedures, such as suturing or interventions that were not a part of a prior treatment plan. From this perspective, the outcome of this study can be considered "clinically significant bleeding", and the fact that the frequency of post-extraction bleeding was within the range reported in previous studies suggests that the sampling method was valid. Third, it is unclear whether antithrombotic therapy was continued or discontinued prior to tooth extraction, and if so, how well it was controlled. Japanese guidelines⁴ recommend that, in principle, teeth should be extracted while antithrombotic therapy is continued, and since the data in this study were obtained several years after the guidelines were established, it is highly likely that they are in line with the guidelines to some extent. Fourthly, Japan's public health insurance system is generally divided into

three categories: "National Health Insurance enrollees" "Employee Health Insurance" and "Latter-Stage Elderly Healthcare System enrollees". The database of this study includes "National Health Insurance enrollees" and "Latter-Stage Elderly Healthcare System enrollees", but does not include "Employee's Health Insurance" enrollees. Thus, the distribution is biased toward older ages. However, as the antithrombotic therapies studied in this study were often administered to elderly patients, the effect of this bias is likely to be relatively small. Finally, although this study was based on a large data set, it used information from few municipalities. Future studies should include data from municipalities in a broader geographic area.

Conclusion

In this large database analysis, post-extraction bleeding was observed in 0.4% of patients. Post-extraction bleeding occurred more frequently in patients taking anticoagulants or dual antithrombotic drugs than in patients not taking any antithrombotic drugs or those taking a single antiplatelet drug. The findings suggest the need for thorough measures to prevent post-extraction bleeding, such as tooth extraction under hospitalization and careful hemostatic treatment, in patients taking anticoagulant or dual antithrombotic drugs.

Acknowledgements

We thank the staff of Kobe University and Kyusyu University for their kindness and collaboration. All authors approve the manuscript to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

This work was supported by grants provided by the Japan Science and Technology Agency (JST) Fusion Oriented Research for disruptive Science and Technology (FOREST) Program (Grant Number: JPMJFR205J) and the Japan Society for the Promotion of Science (JSPS) Grants-in-Aid for Scientific Research (KAKENHI) Program (Grant Numbers: JP20H00563 and JP19K21590).

Conflict of Interest

The authors declare no conflict of interest.

Data Accessibility Statement

The data used in this study were acquired under agreements between Kyushu University and the participating municipalities, which stipulate that the data can only be used by authorized research institutions and cannot be shared with third parties. However, research institutions that have entered into agreements with the authorized research group in Kyushu University may access the data.

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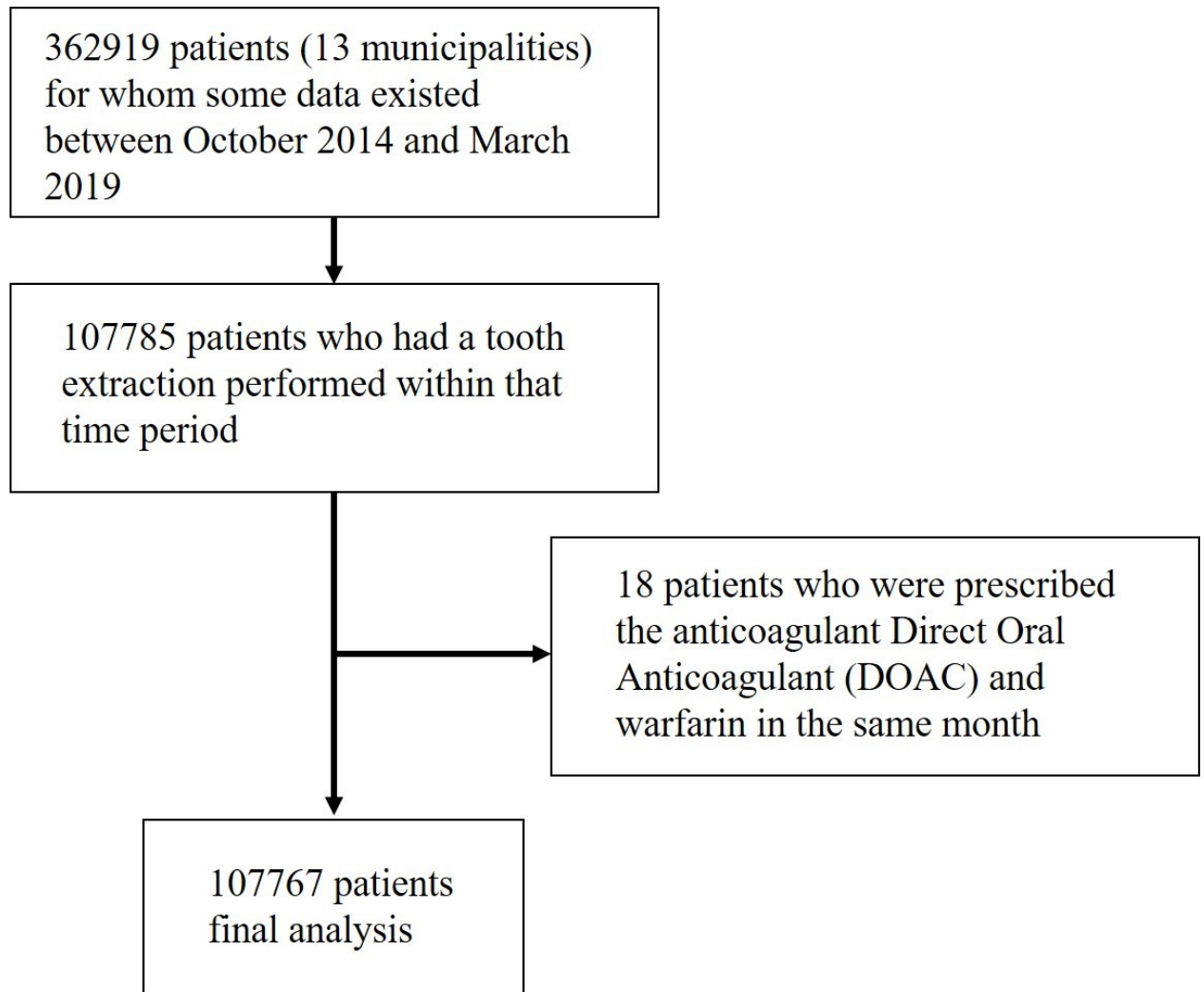


Figure 1. Participants' selection flowchart

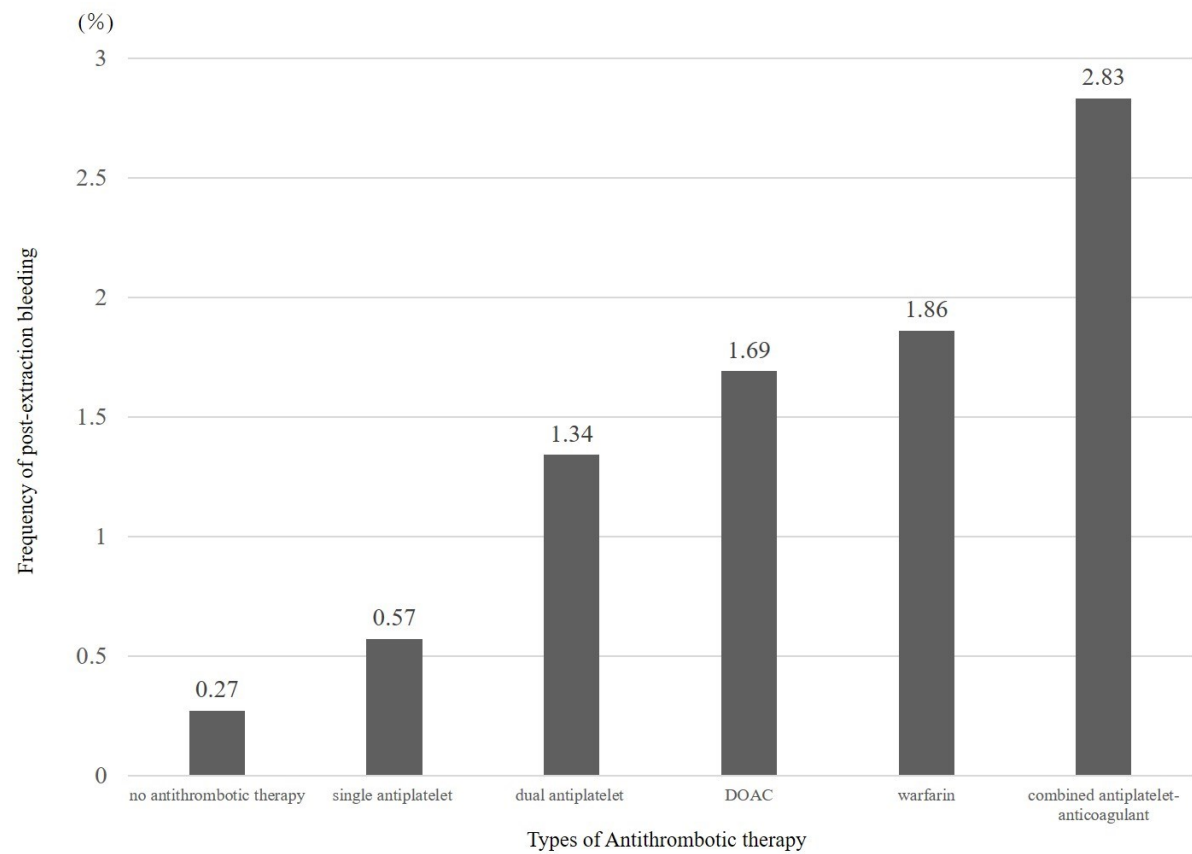


Figure 2. Frequency of post-extraction bleeding for each antithrombotic therapy

Table.1. Characteristics of patients

	Post-extraction bleeding n=419	No post-extraction bleeding n=107348	P-value
age, years	72.7 ± 12.2	68.3 ± 14.3	< 0.01
sex, women	215 (51.3)	59251 (55.2)	0.12
CCI, score	0.76 ± 1.1	0.52 ± 0.9	< 0.01
antiplatelet drug	88 (21.0)	10021 (4.3)	< 0.01
DOAC	47 (11.2)	2572 (2.4)	< 0.01
warfarin	52 (12.4)	2410 (2.2)	< 0.01
hypertension	141 (33.7)	31001 (28.9)	0.03
liver disease	53 (12.6)	9750 (9.1)	0.02
renal disease	17 (4.1)	2064 (1.9)	< 0.01
stroke	42 (10.0)	8348 (7.8)	0.09
coagulopathy	8 (1.9)	298 (0.3)	< 0.01
diagnostic action			0.02
front tooth	89 (21.2)	24194 (22.5)	
molar tooth	313 (74.7)	80927 (75.4)	
wisdom tooth	17 (4.1)	2227 (2.1)	

Note: Data are presented as n (%) or mean ± standard deviation.

Abbreviation: CCI, the Charlson Comorbidity Index; DOAC, Direct Oral Anticoagulant; SD, standard deviation.

Table.2. Association between each antithrombotic therapy group and post-extraction bleeding (ref: no antithrombotic therapy)

	adjusted OR	95%CI
no antithrombotic therapy	ref.	
single antiplatelet drug	2.00	1.43-2.77
dual antiplatelet drugs	4.63	2.90-7.41
DOAC	5.48	3.84-7.83
warfarin	5.93	4.14-8.48
combined antiplatelet-coagulant drugs	9.02	5.79-14.0

Adjusted for age, sex, CCI, hypertension, liver disease, renal disease, stroke, coagulopathy

Abbreviation: DOAC, Direct Oral Anticoagulant; OR, odds ratio; CI, confidence interval

P<0.05 for all

Table.3. Association between each antithrombotic therapy group and post-extraction bleeding (subject: antithrombotic therapy patients, ref: single antiplatelet drug)

	adjusted OR	95%CI
single antiplatelet drug	ref.	
dual antiplatelet drugs	2.33	1.34-3.91
DOAC	2.76	1.76-4.29
warfarin	2.98	1.91-4.63
combined antiplatelet-coagulant drugs	4.53	2.68-7.48

Adjusted for age, sex, CCI, hypertension, liver disease, renal disease, stroke, coagulopathy

Abbreviation: DOAC, Direct Oral Anticoagulant; OR, odds ratio; CI, confidence interval

P<0.05 for all