INTRODUCTION

Warfarin, an oral anticoagulant (OAC), is widely used to treat and prevent thromboembolism. Warfarin therapy requires periodic prothrombin time measurements and thrombotests to assess international normalized ratios (INRs). The drug takes 2–3 d. Warfarin treatment may be limited by drug–drug interactions or food effects.\(^1\,^2\) Dabigatran, rivaroxaban, apixaban, and edoxaban, which are direct OACs (DOACs), have been widely used in recent years because they do not require frequent monitoring tests, and in addition to their immediate onset of efficacy, they are less susceptible to the effects of foods and concomitant drug use than warfarin.\(^2\,^3\)

Serious adverse events of OACs include intracranial bleeding and gastrointestinal bleeding, which reportedly occurs at rates of 1.45 and 0.70%, and 2.02 and 2.56% for warfarin and DOACs, respectively, and it can be fatal.\(^4\) Held rates of 1.45 and 0.70%, and 2.02 and 2.56% for warfarin and \(^1\,^2\) dabigatran, rivaroxaban, drug interactions or food effects.

The drug takes international normalized ratios (INRs). The drug takes 2–3 d. Warfarin treatment may be limited by drug–drug interactions or food effects. Warfarin increases the risk of gastrointestinal bleeding when used in combination with aspirin \(^8\) or NSAIDs, \(^9\) as well as the risk of major bleeding when combined with antiplatelet agents and dabigatran \(^10\) or rivaroxaban and NSAIDs. \(^11\) A case report mentioned that the INRs increased to 4.5 in concomitant use of warfarin and miconazole, a CYP inhibitor, contraindicating their combined use. \(^12\) Moreover, significantly increased bleeding risk with dabigatran, rivaroxaban, and apixaban in combination with amiodarone, fluconazole, rifampicin, and phenytoin has been reported. \(^13\) Selective serotonin reuptake inhibitors used for depression increase the risk of bleeding in OAC users due to their antiplatelet action as a secondary pharmacological effect. \(^14\) Thus, it is crucial to investigate the pharmacological effects of drugs and their pharmacokinetics in relation to their interaction with OACs.

Therefore, we conducted a nested case-control study to com-
prehensively explore drugs that affect the risk of bleeding when combined with OACs in patients who were newly prescribed OACs, utilizing large-scale health insurance claims data.

MATERIALS AND METHODS

Study Design  We conducted a nested cohort case-control study of patients who were first prescribed OACs between January 2005 and June 2017, using a Japanese health insurance claims database from JMDC Inc. (Tokyo, Japan). The case and control groups were patients with and without bleeding events. We evaluated whether concomitant medications affected the bleeding risk of OAC users (Fig. 1).

Data Source  In this study, we used health insurance claims data from JMDC Inc. The JMDC database contains anonymized information about workers and their family members, covering more than 400,000 individuals. The data comprise demographic characteristics (e.g., age and sex), procedures, disease diagnoses coded using the International Classification of Disease, 10th Revision (ICD-10), and prescribed drugs (daily dose, dose unit, number of days of administration per prescription, dosage) coded using the Anatomical Classification of Pharmaceutical Products of the European Pharmaceutical Market Research Association. The database tracks individual information and treatment history when different hospitals and pharmacies are visited.

Study Subjects and Observation Periods  We identified patients who had been newly prescribed OACs, including warfarin and DOACs, such as dabigatran, rivaroxaban, apixaban, and edoxaban, between January 2005 and June 2017. New OAC users were defined as those individuals with no prescription record for longer than two months before the first OAC prescription in the database. We excluded patients diagnosed with cancer, patients with a history of bleeding before the first OAC prescription, and patients with different OACs prescribed on the same day.

We defined the periods of continuous OAC administration as the observation periods. Interruption was defined as a gap of \( \geq 2 \) months between consecutive prescriptions. Therefore, the observation periods were from the first prescription for OACs to the bleeding event, interruption of OACs, change to other OACs, censoring for loss to follow-up, or the end of the study period (June 2017), whichever came first.

Identification of Case and Control Groups  The case group included patients who experienced bleeding events during the observation period. Bleeding events included intracranial bleeding, upper and lower gastrointestinal bleeding, and bleeding from other sources. These OAC-related bleeding events were defined as bleeding that occurred up to one month following the end of continuous OAC administration. The date of the first bleeding event was the index date; gastrointestinal bleeding was defined as bleeding occurrence if the ICD-10 code and medical procedure code were recorded on the same date. Intracranial hemorrhage and other hemorrhages may be treated conservatively. Therefore, bleeding occurrence was defined if only the ICD-10 code was recorded. Intracranial hemorrhage was defined as non-traumatic hemorrhage (ICD-10 codes: I60-I62). The following ICD-10 codes and medical procedure codes were used to identify upper gastrointestinal bleeding occurrences. ICD-10 codes: esophageal bleeding (K226, K228, and I850) and gastric and duodenal bleeding (K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K282, K284, K286, K290, K571, I864, K920, and K922), and medical procedure codes: esophagus fiberscope (D306), stomach and duodenum fiberscope (D308), esophageal and gastric varices surgery (K532-0), esophageal varices surgery (K532-2), laparoscopic esophageal varices surgery (K532-3), endoscopic esophageal and gastric vein ligation (K533-2), gastric vessel ligation (K646), endoscopic gastrointestinal hemostasis (K654), and local ethanol injection (J017). The following ICD-10 codes and medical procedure codes were used to identify lower gastrointestinal bleeding occurrences. ICD-10 codes: small and large bowel bleeding (K270, K272, K274, K276, K280, K282, K284, K573, K625, K625, K921, and K922) and medical procedure codes: small bowel fiberscope (D310), small bowel endoscopy (D310), rectum fiberscope (D312), colonoscopy (D313), sigmoid colon fiberscope (D313), descending and transverse colon fiberscope (D313), ascending colon and cecum fiberscope (D313), endoscopic gastrointestinal hemostasis (K654), small

Fig. 1. Study Design

Cases were defined as persons diagnosed with bleeding (intracranial bleeding, gastrointestinal bleeding, and other bleeding) and were matched with 1–4 control subjects on OACs of the same kind, initiation year of OAC use, age (± 5 years), and sex. The index date of cases was defined as the date of the first diagnosis of bleeding during the observation period. Controls were assigned an index date corresponding to the OAC prescription duration of their matched cases. The bleeding risk associated with exposure to concomitant medications within 30d of the event/index date was evaluated.
bowel colonicostomy (K722), and local ethanol infusion (J017). The following ICD-10 codes were used to identify other bleeding occurrences. ICD-10 codes: hemorrhagic anemia (D500 and D62), ocular hemorrhage (H313, H356, H431, and H450), pericardial hematoma (I312), hemotherox (J942), intra-abdominal hemorrhage (K661), spinal cord hemorrhage (G951), nasopharyngeal and pulmonary airway hemorrhage (R04), and genital hemorrhage and hematuria (R31).

A matched control group was randomly selected from the patients who did not experience bleeding events during the observation period. A one-to-four matching was applied to cases and control subjects in four categories: type of OACs, year of first prescription, age (±5 years), and sex. The index date for the control subjects was set as the duration of OAC prescription in the corresponding matched cases.

Definitions of Concomitant Medication Exposure To explore the effects of concomitant medications on the bleeding risk of OAC users, exposure was defined as medications concomitant with OACs in the 30d prior to the index date. We counted medications concomitant with OACs in both the case and control groups. Exposure to oral medicines to be taken as needed and to external medications were excluded, and oral and injectable medications were included in the analysis.

Identification of Potential Confounding Variables The following potential confounding variables were extracted: age, sex, and comorbidities prior to the index date. In both the case and control groups, the Charlson comorbidity score, which represents disease severity and is an index used for patients with atrial fibrillation undergoing anticoagulation, the HAS-BLED score, which assesses the risk of developing hemorrhage, and the CHA2DS2-VASc score, which assess the risk of developing stroke, were calculated. In this study, all malignant tumors cases, including metastatic solid tumors, were excluded; therefore, the Charlson comorbidity score was calculated to a maximum of 25 points. The CHA2DS2-VASc Score was defined by assigning 1 point for congestive heart failure, hypertension, diabetes mellitus, vascular disease, female, and age range between 65 to 74 and 2 points for history of stroke/transient ischemic attack (TIA)/thromboembolism and age 75 or older, and the score was calculated to a maximum of 9 points. Similarly, we determined a CHADS2 score for each patient by assigning 1 point for age 75 or older, hypertension, diabetes mellitus, and heart failure and 2 points for previous stroke or transient ischemic attack, with a maximum score of 6 points. We also defined a modified HAS-BLED score for each patient by assigning 1 point for the following conditions and summing the points: hypertension, renal disease, hepatic disease, stroke, major bleeding event, age 65 and above, concomitant use of NSAIDs or antplatelet agents, and alcohol consumption. The score was calculated to a maximum of 7 points because the claim data provided by JMDC does not include information of INR and patients with a history of bleeding were excluded from this study. Comorbidities included gastrointestinal disease, stroke/TIA, thromboembolism, vascular disease, hepatic disease, renal disease, hypertension, diabetes, heart failure, and alcoholism, which are bleeding risk factors. These factors are also used to calculate the HAS-BLED, CHA2DS2-VASc, and CHADS2 scores.

Statistical Analysis To identify variables affecting the bleeding risk of OACs, we first divided the OAC users into patients prescribed warfarin and those prescribed DOACs. Univariate logistic regression analysis was performed to screen variables (patient background, comorbidities, and concomitant drug use) associated with the presence or absence of bleeding events in warfarin users and DOAC users. Variables with a p value <0.05 in the univariate analysis were selected and evaluated using multivariate models to identify the influencing factors independently associated with bleeding among both warfarin and DOAC users after adjusting for contributions of other variables. Considering multiple co-linearity, the Charlson comorbidity, HAS-BLED, CHA2DS2-VASc, and CHADS2 scores were not used, and covariates of each score were used for the selected items in multivariable logistic regression analysis. In the univariate and multivariate logistic regression models, adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated. p-Values <0.05 were considered to indicate statistical significance. The suitability of logistic regression models used in this study was confirmed by chi-squared goodness-of-fit and Hosmer–Lemeshow tests. SAS Enterprise Guide version 7.13, IBM SPSS Statistics version 23.0, and R Studio version 3.0 were used for statistical analysis.

Ethical Considerations This study was approved by the Ethical Review Board for Clinical Research at Tokyo University of Science (Approval No. 20003).

RESULTS

Study Subjects In total, 7241 patients met the eligibility criteria for this study, from whom 554 cases with bleeding events and 1337 matched controls were randomly selected. Among warfarin-prescribed patients, there were 327 cases and 814 controls, whereas among DOAC-prescribed patients, there were 227 cases and 523 controls (Fig. 2). A breakdown of the OAC users is shown in Table 1.

Comparison of Characteristics of Cases and Controls among Patients Prescribed Warfarin Among the warfarin-prescribed patients, sex, gastrointestinal diseases, stroke/TIA, vascular diseases, renal diseases, diabetes mellitus, heart failure, and alcoholism showed significant differences between the case and control groups in the univariate logistic regression analysis. There were 441 concomitant medicines that were prescribed in the 30d prior to the index date in both case and control groups, 30 of which exhibited significant differences in sex, gastrointestinal diseases, stroke/TIA, vascular diseases, hepatic diseases, and alcoholism between the case and control groups. There were 272 medicines that were co-prescribed in the 30d prior to the index date in both case and control groups, 10 of which showed significant effects on bleeding risk in the univariate logistic regression analysis. Mean Charlson comorbidity, HAS-BLED, CHADS2, and CHA2DS2-VASc scores were all significantly higher in the case group (Table 2).

Comparison of Characteristics of Cases and Controls among Patients Prescribed DOACs Among the DOAC-prescribed patients, the univariate logistic regression analysis revealed significant differences in sex, gastrointestinal diseases, stroke/TIA, vascular diseases, hepatic diseases, and alcoholism between the case and control groups. There were 272 medicines that were co-prescribed in the 30d prior to the index date in both case and control groups, 10 of which showed significant differences in univariate logistic regression analysis. Mean Charlson comorbidity, HAS-BLED, CHADS2, and CHA2DS2-VASc scores were all higher in the case group (Table 3).

Concomitant Drugs Affecting Bleeding Risk in Warfarin-Prescribed Patients In warfarin-prescribed patients, multi-
Bivariate logistic regression analysis showed that in combination with warfarin, ATP (aOR, 4.58; 95% CI, 1.19–17.68; \( p = 0.027 \)) and sarpogrelate (aOR, 5.71; 95% CI, 1.05–31.15; \( p = 0.044 \)) significantly increased the bleeding risk. In contrast, amlodipine significantly reduced the bleeding risk (aOR, 0.64, 95% CI: 0.41–0.98; \( p = 0.042 \)) (Table 4).

**Concomitant Drugs Affecting Bleeding Risk in DOAC-Prescribed Patients** In DOAC-prescribed patients, multivariate logistic regression analysis showed that concomitant medications that significantly increased the bleeding risks of DOACs were insulin glargine (aOR, 8.71; 95% CI, 1.63–46.64; \( p = 0.011 \)), alprazolam (aOR, 12.09; 95% CI, 1.03–141.47; \( p = 0.047 \)), and telmisartan (aOR, 4.87; 95% CI, 1.84–12.9; \( p = 0.001 \)). In contrast, bleeding risks were significantly reduced by combination with nifedipine (aOR, 0.25; 95% CI, 0.07–0.94; \( p = 0.041 \)) or bisoprolol (aOR, 0.51; 95% CI: 0.33–0.80; \( p = 0.003 \)) (Table 5).

**DISCUSSION**

This comprehensive nested case-control study in OAC users based on large-scale health insurance claims data showed that combinations of warfarin with amlodipine and of DOACs with nifedipine or bisoprolol were associated with decreased risk of bleeding, whereas telmisartan was associated with an increased risk of bleeding when combined with DOACs. Importantly, these results suggested that several types of antihypertensive medications have an opposite effect on the risk of bleeding of OACs.

We found that the bleeding risk of OACs might be reduced with concomitant use of the antihypertensive drugs amlodipine, nifedipine, and bisoprolol. Although no reports have validated changes in bleeding risk with warfarin in combination with amlodipine and DOACs in combination with nifedipine or bisoprolol, hypertension is considered a significant risk factor for major bleeding during antithrombotic therapy. 33–35) A
Table 2. Comparison of Characteristics of Cases and Controls among Patients Prescribed Warfarin

| Risk factors (%)                  | Cases (n = 327) | Controls (n = 814) | p-Value |
|-----------------------------------|----------------|--------------------|---------|
| Sex                               |                |                    |         |
| Male                              | 267 (81.7)     | 712 (87.5)         | 0.011*  |
| Female                            | 60 (18.3)      | 102 (12.5)         |         |
| Age (mean ± standard deviation)   | 54.6 ± 8.5     | 54.3 ± 8.1         | 0.691   |
| Comorbidity                       |                |                    |         |
| Gastrointestinal disease          | 268 (82.0)     | 545 (67.0)         | 0.000*  |
| Stroke/TIA                        | 128 (39.1)     | 178 (21.9)         | 0.000*  |
| Thromboembolism                   | 32 (9.8)       | 62 (7.6)           | 0.229   |
| Vascular disease                  | 244 (74.6)     | 489 (60.1)         | 0.000*  |
| Hepatic disease                   | 150 (45.9)     | 326 (40.0)         | 0.072   |
| Renal disease                     | 93 (28.4)      | 156 (19.2)         | 0.001*  |
| Hypertension                      | 225 (68.8)     | 551 (67.7)         | 0.715   |
| Diabetes                          | 233 (71.3)     | 528 (64.9)         | 0.039*  |
| Heart failure                     | 225 (68.8)     | 498 (61.2)         | 0.016*  |
| Alcoholism                        | 13 (4.0)       | 14 (1.7)           | 0.028*  |
| Score                             |                |                    |         |
| Charlson Comorbidity score        | 4.3 ± 2.4      | 3.1 ± 2.1          | 0.000*  |
| HAS BLED score                    | 2.4 ± 1.3      | 2.0 ± 1.2          | 0.000*  |
| CHADS2 score                      | 2.9 ± 1.5      | 2.4 ± 1.3          | 0.000*  |
| CHA2DS2 VASc score                | 4.0 ± 1.7      | 3.3 ± 1.7          | 0.000*  |
| Concomitant medications           |                |                    |         |
| Gastrointestinal and metabolic medications |      |                    |         |
| Atropine                          | 13 (4.0)       | 12 (1.5)           | 0.012*  |
| Famotidine                        | 51 (15.6)      | 85 (10.4)          | 0.016*  |
| Dimethicone                       | 11 (3.4)       | 9 (1.1)            | 0.012*  |
| Metoclopramide                    | 15 (4.6)       | 18 (2.2)           | 0.034*  |
| Rebamipide                        | 30 (9.2)       | 44 (5.4)           | 0.021*  |
| Magnesium oxide                   | 29 (8.9)       | 43 (5.3)           | 0.026*  |
| Sennoside                         | 17 (5.2)       | 18 (2.2)           | 0.010*  |
| Picosulfate                       | 9 (2.8)        | 6 (0.7)            | 0.012*  |
| Bifidobacterium bifidum           | 8 (2.4)        | 4 (0.5)            | 0.008*  |
| Clostridium butyricum             | 6 (1.8)        | 4 (0.5)            | 0.040*  |
| Sodium bicarbonate                | 26 (8.0)       | 32 (3.9)           | 0.006*  |
| Nervous system medications        |                |                    |         |
| Carbamazepine                     | 4 (1.2)        | 1 (0.1)            | 0.039*  |
| Cardiovascular medications        |                |                    |         |
| ATP                               | 7 (2.1)        | 4 (0.5)            | 0.018*  |
| Amlodipine                        | 36 (11.0)      | 129 (15.8)         | 0.037*  |
| Isosorbide mononitrate            | 9 (2.8)        | 8 (1.0)            | 0.033*  |
| Olprinone                         | 6 (1.8)        | 3 (0.4)            | 0.023*  |
| Metildigoxin                      | 6 (1.8)        | 36 (4.4)           | 0.042*  |
| Medications for blood and hematopoietic organs |    |                    |         |
| Carbazochrome                     | 18 (5.5)       | 16 (2.0)           | 0.002*  |
| Sarpgrelate                       | 5 (1.5)        | 2 (0.2)            | 0.028*  |
| Menatetrenone                     | 9 (2.8)        | 4 (0.5)            | 0.004*  |
| Fresh frozen human plasma         | 11 (3.4)       | 11 (1.4)           | 0.031*  |
| Human red blood cell              | 19 (5.8)       | 17 (2.1)           | 0.002*  |
| Infusion solution                 |                |                    |         |
| Amino acid · sugar · electrolyte · vitamin | 9 (2.8) | 8 (1.0) | 0.033* |
| Manganese chloride · zinc sulfate hydrate | 6 (1.8) | 1 (0.1) | 0.012* |
| Acetic acid maintenance solution (with glucose) | 6 (1.8) | 3 (0.4) | 0.023* |
| Antibacterial medications        |                |                    |         |
| Piperacillin                      | 4 (1.2)        | 1 (0.1)            | 0.039*  |
| NSAIDs                            |                |                    |         |
| Diclofenac                        | 5 (1.5)        | 2 (0.2)            | 0.028*  |
| Other medications                 |                |                    |         |
| Hydrocortisone succinate ester sodium | 5 (1.5) | 2 (0.2) | 0.028* |
| Pronase                           | 6 (1.8)        | 3 (0.4)            | 0.023*  |
| Polystyrene sulfonic acid calcium | 6 (1.8)        | 4 (0.5)            | 0.040*  |

*p < 0.05.
possible reason for the reduced risk of OAC-induced bleeding is that the antihypertensive effect of these drugs suppressed the risk of bleeding.

However, hemorrhage risk associated with the use of telmisartan, which also has an antihypertensive effect, is significantly increased in combination with DOACs (namely rivaroxaban and apixaban) (aOR, 4.87; 95% CI, 1.84–12.91). Telmisartan inhibits digoxin efflux to the intestinal lumen through a P-gp-inhibitory effect. As elimination of rivaroxaban and apixaban, the substrate of P-gp, is inhibited due to their inhibitory effect on P-gp, it is possible that telmisartan would increase the blood levels of these two drugs via P-gp-mediated interactions, which may have increased the risk of hemorrhage.

The bleeding risk of warfarin was elevated with concomitant use of ATP and sarpogrelate. ATP causes cerebral blood vessels to dilate and enhances blood flow, which seems to increase the risk of bleeding. Warfarin reportedly increases the risk of bleeding with concomitant use of antiplatelet drugs, and sarpogrelate is considered to increase the risk of bleeding with concomitant use due to its antiplatelet effect. In addition, the bleeding risks of DOACs were elevated in combination with insulin glargine and alprazolam. However, the insulin glargine- and alprazolam-related risks may not reflect the exact risks due to the small number of patients included in the analysis.

The combined use of antiplatelet agents and OACs has been reported to increase bleeding risks. Nonetheless, we did not find elevated bleeding risks of OACs users with concomitant use of antiplatelet agents other than sarpogrelate. Gastric acid suppressants such as proton-pump inhibitors (PPIs) and H₂ blockers reduce the risk of upper gastrointestinal bleeding in combination with OACs. In this study, concomitant medications were examined individually in combination with OACs, and the percentage of patients on antiplatelet medications in the case and control groups who received PPIs was greater than 55%. The percentage of users of either PPIs or H₂ blockers was found to be approximately 65% (data not shown).

### Table 3. Comparison of Characteristics of Cases and Controls among Patients Prescribed DOACs

| Risk factors (%) | Cases (n = 227) | Controls (n = 523) | p-Value |
|------------------|----------------|-------------------|--------|
| **Sex**          |                |                   |        |
| Male             | 183 (80.6)     | 455 (87.0)        |        |
| Female           | 44 (19.4)      | 68 (13.0)         | 0.025* |
| **Age** (mean ± standard deviation) | 58.5 ± 7.9 | 58.3 ± 7.4 | 0.65  |
| **Comorbidity**  |                |                   |        |
| Gastrointestinal disease | 166 (73.1) | 329 (62.9) | 0.007* |
| Stroke/TIA       | 76 (33.5)      | 101 (19.3)        | 0.000* |
| Thromboembolism  | 9 (4.0)        | 24 (4.6)          | 0.702  |
| Vascular disease | 151 (66.5)     | 293 (56.0)        | 0.007* |
| Hepatic disease  | 121 (53.3)     | 209 (40.0)        | 0.001* |
| Renal disease    | 56 (24.7)      | 104 (19.9)        | 0.142  |
| Hypertension     | 167 (73.6)     | 365 (69.8)        | 0.295  |
| Diabetes         | 176 (77.5)     | 391 (74.8)        | 0.417  |
| Heart failure    | 153 (67.4)     | 362 (69.2)        | 0.623  |
| Alcoholism       | 10 (4.4)       | 8 (1.5)           | 0.024* |

| Score            |                |                   |        |
| Charlson Comorbidity score | 3.6 ± 1.9 | 3.0 ± 2.0 | 0.000* |
| HAS BLED score   | 2.3 ± 1.3      | 1.9 ± 1.2        | 0.000* |
| CHADS₂ score     | 2.9 ± 1.3      | 2.5 ± 1.3        | 0.001* |
| CHA₂DS₂ VASc score | 4.0 ± 1.6 | 3.5 ± 1.6 | 0.000* |

| Concomitant medications |                |                   |        |
| Gastrointestinal and metabolic medications |                |                   |        |
| Insulin glargine     | 6 (2.6)        | 2 (0.4)           | 0.017* |
| Sennoside            | 4 (1.8)        | 1 (0.2)           | 0.046* |
| Picosulfate          | 8 (3.5)        | 4 (0.8)           | 0.012* |
| Bifidobacterium bifidum | 5 (2.2) | 2 (0.4) | 0.035* |
| Nervous system medications |            |                   |        |
| Alprazolam            | 4 (1.8)        | 1 (0.2)           | 0.046* |
| Cardiovascular medications |             |                   |        |
| Telmisartan           | 12 (5.3)       | 9 (1.7)           | 0.010* |
| Nicardipine           | 6 (2.6)        | 2 (0.4)           | 0.017* |
| Nifedipine            | 3 (1.3)        | 23 (4.4)          | 0.046* |
| Bisoprolol            | 39 (17.2)      | 132 (25.2)        | 0.016* |
| Isosorbide dinitrate  | 6 (2.6)        | 3 (0.6)           | 0.030* |

*p < 0.05.
Pogrelate did not increase the bleeding risk of OACs in this study.

The mean Charlson comorbidity, HAS-BLED, CHADS<sub>2</sub>, and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were all higher among cases than among controls in patients prescribed warfarin or DOACs. This likely is because patients in the case group had comorbidities that are expected to increase the bleeding risk, such as diabetes mellitus, which is often accompanied by renal and hepatic diseases and vascular disorders. In addition, several underlying diseases may be associated with the use of more concomitant medications, and drug interactions are likely to cause bleeding. To avoid multicollinearity, confounding in the case and control groups was adjusted for diseases to calculate HAS-BLED, CHADS<sub>2</sub>, and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores.

The limitations of this study include the lack of validation of bleeding events due to the use of an anonymized large data set and the lack of information on adherence and over-the-counter medication use due to the characteristics of the data. In addition, the dosages of OACs and concomitant medications were not investigated, and the patients included in the analysis were relatively young. Further investigations into the dosage and risks of hemorrhage in older age groups are warranted. Moreover, it has been reported that sex does not affect bleeding risk in anticoagulation therapy<sup>41</sup>; however, given the high male-to-female patient ratio in this study, future studies should consider using databases that have a more balanced sex ratio.

In conclusion, this study comprehensively explored drugs

### Table 4. Concomitant Medications Affecting Bleeding Events in Patients Prescribed Warfarin

| Ingredient name                                      | Adjusted OR (95% CI) | p-Value |
|------------------------------------------------------|----------------------|---------|
| **Gastrointestinal and metabolic medications**       |                      |         |
| Atropine                                             | 1.68 (0.62–4.57)     | 0.31    |
| Famotidine                                           | 0.94 (0.60–1.46)     | 0.77    |
| Dimethicone                                          | 0.96 (0.28–3.31)     | 0.942   |
| Metoclopramide                                       | 1.00 (0.40–2.52)     | 0.999   |
| Rebamipide                                           | 1.29 (0.74–2.26)     | 0.364   |
| Magnesium oxide                                      | 1.06 (0.60–1.88)     | 0.842   |
| Sennoside                                            | 1.40 (0.59–3.34)     | 0.446   |
| Picosulfate                                          | 2.00 (0.54–7.48)     | 0.302   |
| Bifidobacterium bifidum                              | 2.86 (0.66–12.44)    | 0.162   |
| Clostridium butyricum                                | 3.81 (0.86–16.93)    | 0.079   |
| Sodium bicarbonate                                   | 0.64 (0.29–1.43)     | 0.276   |
| **Nervous system medications**                       |                      |         |
| Carbamazepine                                        | 6.69 (0.62–72.19)    | 0.117   |
| **Cardiovascular medications**                       |                      |         |
| ATP                                                  | 4.58 (1.19–17.68)    | 0.027*  |
| Amiodipine                                           | 0.64 (0.41–0.98)     | 0.042*  |
| Isosorbide mononitrate                               | 2.12 (0.77–5.81)     | 0.144   |
| Olprinone                                            | 2.63 (0.43–16.01)    | 0.294   |
| Metildigoxin                                         | 0.51 (0.20–1.27)     | 0.148   |
| **Medications for blood and hematopoietic organs**   |                      |         |
| Carbazochrome                                        | 1.81 (0.62–5.25)     | 0.275   |
| Sarpogrelate                                         | 5.71 (1.05–31.15)    | 0.044*  |
| Menatetrenone                                        | 3.62 (0.77–16.97)    | 0.102   |
| Fresh frozen human plasma                            | 0.30 (0.05–1.71)     | 0.174   |
| Human red blood cell                                 | 1.65 (0.48–5.60)     | 0.425   |
| **Infusion solution**                                |                      |         |
| Amino acid·sugar·electrolyte·vitamin                 | 0.69 (0.18–2.69)     | 0.598   |
| Manganese chloride·zinc sulfate hydrate              | 7.07 (0.61–81.49)    | 0.117   |
| Acetic acid maintenance solution (with glucose)      | 3.92 (0.69–22.38)    | 0.124   |
| **Antibacterial medications**                        |                      |         |
| Piperacillin                                          | 1.35 (0.09–20.98)    | 0.828   |
| **NSAIDs**                                           |                      |         |
| Diclofenac                                           | 3.95 (0.64–24.30)    | 0.139   |
| **Other medications**                                |                      |         |
| Hydrocortisone succinate ester sodium                | 1.86 (0.20–16.87)    | 0.582   |
| Pronase                                              | 5.20 (0.85–31.95)    | 0.075   |
| Polystyrene sulfonic acid calcium                    | 3.06 (0.70–13.50)    | 0.139   |

* p < 0.05. Factors that showed significant differences in univariate logistic regression analysis (sex, gastrointestinal disease, stroke/TIA, vascular disease, renal disease, diabetes, heart failure, alcoholism, and concomitant medications) were selected, and multivariate logistic regression analysis was performed to adjust for confounding factors, and the odds ratio (OR), p-value, and 95% confidence interval (95% CI) were calculated.
that affect the bleeding risks of OACs users by using large-scale insurance claims data. The results indicated that hypotensive drugs might contribute to safety improvement of OACs, whereas P-gp-mediated interactions may increase the risk of bleeding in patients receiving telmisartan in combination with apixaban and rivaroxaban, which are classified as DOACs. Importantly, several types of hypotensive drugs might have an opposite effect on the risk of bleeding owing to their interaction with OACs. Further detailed examinations will contribute to better management of bleeding in patients on OACs.

Acknowledgments This work was supported by the Research Education Fund for Tokyo University of Science.

Conflict of Interest The authors declare no conflict of interest.

REFERENCES

1) Kuruvilla M, Gurk-Turner C. A review of warfarin dosing and monitoring. Proc. Bayl. Univ. Med. Cent., 14, 305–306 (2001).
2) Santarpia G, Curcio A, Sibilio G, Indolfi C. Clinical significance of non-vitamin K antagonist oral anticoagulants in the management of atrial fibrillation. Circ. J., 79, 914–923 (2015).
3) Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace, 15, 625–651 (2013).
4) Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet, 383, 955–966 (2014).
5) Held C, Hylek EM, Alexander JH, Hanna M, Lopes RD, Woydyla DM, Thomas L, Al-Khalidi H, Alings M, Xavier D, Ansell J, Goto S, Ruzyllo W, Rosengvist M, Verheugt FW, Zhu J, Granger CB, Wallentin L. Clinical outcomes and management associated with major bleeding in patients with atrial fibrillation treated with apixaban or warfarin: insights from the ARISTOTLE trial. Eur. Heart J., 36, 1266–1272 (2015).
6) Lip GY, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E, Lane DA, Levi M, Marin F, Palareti G, Kirchhof P, Collet JP, Rubboli A, Poli D, Camm J. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. Europace, 13, 723–746 (2011).
7) Xu T, Yu X, Ou S, Liu X, Yuan J, Tan X, Chen Y. Adherence to antihypertensive medications and stroke risk: a dose–response meta-analysis. J. Am. Heart Assoc., 6, e006371 (2017).
8) Hallas J, Dall M, Andries A, Andersen BS, Aalykke C, Hansen JM, Andersen M, Lassen AT. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. BMJ, 333, 726 (2006).
9) Battistella M, Mamdami MM, Juurlink DN, Rabeneck L, Laupacis A. Risk of upper gastrointestinal hemorrhage in warfarin users treated with nonselective NSAIDs or COX-2 inhibitors. Arch. Intern. Med., 165, 189–192 (2005).
10) Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, Ezekowitz M, Oldgren J, Eikelboom JW, Reilly PA, Yusuf S. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Circulation, 127, 634–640 (2013).
11) Kreutz R, Haas S, Holberg G, Lassen MK, Mantovani LG, Schmidt A, Turpie AG. Rivaroxaban compared with standard thromboprophylaxis after major orthopaedic surgery: co-medication interactions. Br. J. Clin. Pharmacol., 81, 724–734 (2016).
12) Pemberton MN, Oliver RJ, Theaker ED. Miconazole oral gel and drug interactions. Br. Dent. J., 196, 529–531 (2004).
13) Chang SH, Chou JJ, Yeh YH, Chiu MJ, Wen MS, Kuo CT, See LC, Kuo CF. Association between use of non-vitamin K oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation. JAMA, 318, 1250–1259 (2017).
14) Quinn GR, Singer DE, Chang Y, Go AS, Borowsky LH, Udaltsova N, Fang MC. Effect of selective serotonin reuptake inhibitors on bleeding risk in patients with atrial fibrillation taking warfarin. Am. J. Cardiol., 114, 583–586 (2014).
15) “Features of JMDC Claims Database.”. &lt;https://www.jmdc.co.jp/pharma/database.html&gt;, accessed 11 September, 2020.
brillation: contemporary findings in real-life Danish patients. J. Am. Heart Assoc., 6, e004517 (2017).
17) Lip GY, Keshishian A, Kamble S, Pan X, Mardekian J, Horbyuk R, Hamilton M. Real-world comparison of major bleeding risk among non-variceal atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. Thromb. Haemost., 116, 975–986 (2016).
18) "Gastroenterological endoscopy practice guidelines for antithrombotic drug users. (2012 edition)": https://www.jstage.jst.go.jp/article/geo/54/5/2075/pdf, accessed 11 September, 2020.
19) Takahashi A, Mizutani M, Kawai N, Kawano S, Sato N. Double balloon enteroscopy for diagnosis and treatment of small intestinal hemorrhage. J. Abdom. Emerg. Med., 27, 949–956 (2007).
20) Cappell MS, Friedel D. Acute nonvariceal upper gastrointestinal bleeding: endoscopic diagnosis and therapy. Med. Clin. North Am., 92, 511–550, vii–viii (2008).
21) "Various information of medical fee (2018 edition)”: http://shinryohoshu.mhlw.go.jp/, accessed 11 September, 2020.
22) Pincus D, Gomez T, Hellings C, Zheng H, Paterson JM, Mamdani MM, Juurlink DN. A population-based assessment of the drug interaction between levofloxacin and warfarin. Clin. Pharmacol. Ther., 92, 766–770 (2012).
23) Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC. "Various information of medical fee (2018 edition)”: http://shinryohoshu.mhlw.go.jp/, accessed 11 September, 2020.
24) Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am. J. Epidemiol., 173, 676–682 (2011).
25) Noseworthy PA, Yao X, Abraham NS, Sangaralingham LR, McBlane RD, Shah ND. Direct comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in nonvalvular atrial fibrillation. Chest, 150, 1302–1312 (2016).
26) Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Eur. Heart J., 31, 2369–2429 (2010).
27) Rothendler JA, Rose AJ, Reisman JI, Berlowitz DR, Kazis LE. Choices in the use of ICD-9 codes to identify stroke risk factors can affect the apparent population–level risk factor prevalence and distribution of CHADS2 scores. Am. J. Cardiovac. Dis., 2, 184–191 (2012).
28) Schierning Olsen AM, Lindhardsen J, Gislason GH, McGettigan P, Hatky MA, Fossbøl E, Kaber L, Torp-Pedersen C, Lamberts M. Impact of proton pump inhibitor treatment on gastrointestinal bleeding associated with non-steroidal anti-inflammatory drug use among post-myocardial infarction patients taking antithrombotic therapies: nationwide study. BMJ, 351, h5096 (2015).
29) Chan EW, Lau WC, Leung WK, Mok MT, He Y, Tong TS, Wong IC. Prevention of dabigatran-related gastrointestinal bleeding with gastroprotective agents: a population-based study. Gastroenterology, 149, 586–595.e3 (2015).
30) Ray WA, Chung CP, Murray KT, Smalley WE, Daugherty JR, Dupont WD, Stein CM. Association of proton pump inhibitors with reduced risk of warfarin-related serious upper gastrointestinal bleeding. Gastroenterology, 151, 1105–1112.e10 (2016).
31) Friberg L, Rosengvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur. Heart J., 33, 1500–1510 (2012).
32) Junqueira RM, Duarte EC. Hospitalizations due to ambulatory care-sensitive conditions in the Federal District, Brazil, 2008. Rev. Saude Publica, 46, 761–768 (2012).
33) Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. Am. J. Med., 87, 144–152 (1989).
34) Ishii M, Ogawa H, Uno T, An Y, Iguchi M, Masunaga N, Esato M, Chui YH, Tsuji H, Wada H, Hasegawa K, Abe M, Akao M. Relationship of hypertension and systolic blood pressure with the risk of stroke or bleeding in patients with atrial fibrillation: the fushimi AF registry. Am. J. Hypertens., 30, 1073–1082 (2017).
35) Lotti A, Menenti D, Bianchi S, Latarzi S, Marzucchelli M, Covelli A, Tognarelli A, Perrotta ME, Pampana A, Orlando G, Dell’Amico J, Baratta A, Arena G, Torri T. Role of hypertension and other clinical variables in prognostication of patients presenting to the emergency department with major bleeding events. Crit. Pathw. Cardiol., 17, 139–146 (2018).
36) Kamiyama E, Nakai D, Mikkaichi T, Okudaira N, Okazaki O. Interaction of angiotensin II type 1 receptor blockers with P-gp substrates in Caco-2 cells and hMDR1-expressing membranes. Life Sci., 86, 52–58 (2010).
37) Van Aken H, Fuchstein C, Fitch W, Graham DI. Haemodynamic and cerebral effects of ATP-induced hypotension. Br. J. Anaesth., 56, 1409–1416 (1984).
38) Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadbsoll N, Gislason GH, Folke F, Andersen SS, Schramm TK, Abildstrom SZ, Poulsen HE, Kaber L, Torp-Pedersen C. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation: the Copenhagen Heart Electrocardiogram Database. Arch. Intern. Med., 170, 1433–1441 (2010).
39) Nishio H, Inoue A, Nakata Y. Binding affinity of sarpogrelate, a new antiplatelet agent, and its metabolite for serotonin receptor subtypes. Arch. Int. Pharmacodyn. Ther., 331, 189–202 (1996).
40) Ray WA, Chung CP, Murray KT, Smalley WE, Daugherty JR, Dupont WD, Stein CM. Association of oral anticoagulants and proton pump inhibitor cotherapy with hospitalization for upper gastrointestinal tract bleeding. JAMA, 320, 2223–2230 (2018).
41) Langer S, Cohen N, Kearon C. Influence of sex on risk of bleeding in anticoagulated patients: a systematic review and meta-analysis. J. Thromb. Haemost., 12, 595–605 (2014).