A Common Data Model for Oral Anticoagulants-related Risk of Spontaneous Intracranial Hemorrhage

Noah Hong, Yeh-Hee Ko, Jeong Hyun Park, Eun Jin Ha, Sung Ho Lee, Kang Min Kim, Hyun-Seung Kang, Jeong Eun Kim, Kwangsoo Kim, Won-Sang Cho

Submitted to: Interactive Journal of Medical Research
on: May 01, 2024

Table of Contents

A Common Data Model for Oral Anticoagulants-related Risk of Spontaneous Intracranial Hemorrhage

Noah Hong[1*]; Yeh-Hee Ko[2*] BA; Jeong Hyun Park[3, 4] MS; Eun Jin Ha[5] MD; Sung Ho Lee[1] MD, PhD; Kang Min Kim[1] MD; Hyun-Seung Kang[1] MD, PhD; Jeong Eun Kim[1] MD, PhD; Kwangsoo Kim[6] PhD; Won-Sang Cho[1] MD, PhD

[1]Department of Neurosurgery Seoul National University Hospital Seoul KR
[2]Department of Applied Statistics Yonsei University Seoul KR
[3]Biomedical Research Institute Seoul National University Hospital Seoul KR
[4]Naver Corporation Seongnam KR
[5]Department of Critical Care Medicine Seoul National University Hospital Seoul KR
[6]Transdisciplinary Department of Medicine and Advanced Technology Seoul National University Hospital Seoul KR
[*]these authors contributed equally

Corresponding Author:
Won-Sang Cho MD, PhD
Department of Neurosurgery
Seoul National University Hospital
101, Daehak-ro
Jongno-gu
Seoul
KR

Abstract

Background: Spontaneous intracranial hemorrhage (sICH) is a major complication associated with oral anticoagulation which results in a high mortality rate, and the incidence of anticoagulant-induced sICH has increased markedly, so it is necessary to investigate the risk of anticoagulation-related sICH in a real-world setting.

Objective: We aimed to investigate the incidence and risk factors of oral anticoagulant-related sICH using a common data model (CDM), and to determine whether a clinical study using the CDM would be comparable to conventional studies.

Methods: After converting the various clinical codes of 12,821 patients taking oral anticoagulants, such as warfarin and non-vitamin K antagonist oral anticoagulants (NOACs), into the Observational Medical Outcomes Partnership (OMOP) CDM format, we analyzed the incidence and risk factors of sICH.

Results: sICH occurred in 0.5% of 5,626 patients with warfarin and 0.2% of 7,195 patients with NOAC. The mean duration of warfarin and NOACs before sICH occurrence was 251.4 ± 373.6 and 124.2 ± 135.7 days, respectively. Multivariable analysis showed significant risk factors of the sICH, such as warfarin over NOACs; hypertension; diabetes mellitus; brain tumors; and decreased duration of oral anticoagulation.

Conclusions: NOAC demonstrated a lower risk of sICH than warfarin in a real-world setting using OMOP CDM confined to a single institution. Clinical studies using a CDM for the multicenter datasets may provide more reliable information about the risk of sICH.

(JMIR Preprints 01/05/2024:60091)
DOI: https://doi.org/10.2196/preprints.60091

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users. Only make the preprint title and abstract visible.

No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✔ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**

Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v

Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

Original Manuscript

A Common Data Model for Oral Anticoagulants-related Risk of Spontaneous Intracranial Hemorrhage

Noah Hong[†], MD[1], Yeh-Hee Ko[†], BA[2], Jeong Hyun Park, MS[3 4], Eun Jin Ha, MD[5], Sung Ho Lee, MD, PhD[6], Kang Min Kim, MD[6], Hyun-Seung Kang, MD, PhD[6], Jeong Eun Kim, MD, PhD[6], Kwangsoo Kim[*], PhD[7], Won-Sang Cho[*], MD, PhD[6]

1Department of Neurosurgery, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Republic of Korea

2Department of Applied Statistics, Yonsei University, Seoul, Republic of Korea

3Biomedical Research Institute, Seoul National University Hospital, Seoul, Republic of Korea

4Naver Corporation, Seongnam-si, Republic of Korea

5Department of Critical Care Medicine, Seoul National University Hospital, Seoul, Republic of Korea

6Department of Neurosurgery, Seoul National University Hospital, Seoul, Republic of Korea

7Transdisciplinary Department of Medicine and Advanced Technology, Seoul National University Hospital, Seoul, Republic of Korea

†The authors consider that the first two authors should be regarded as joint First Authors.

*The authors consider that the last two authors should be regarded as joint Corresponding Authors.

***Correspondence:**

Won-Sang Cho, MD, PhD

Department of Neurosurgery, Seoul National University College of Medicine, Seoul National University Hospital; 101 Daehak-Ro, Jongno-Gu, Seoul 03080, Republic of Korea

Tel: +82-2-2072-3775

E-mail: nsdrcho@snu.ac.kr, nsdrcho@gmail.com

Kwangsoo Kim, PhD

Transdisciplinary Department of Medicine and Advanced Technology, Seoul National University Hospital 101 Daehak-Ro, Jongno-Gu, Seoul 03080, Republic of Korea

Tel: +82-2-2072-4489

E-mail: kksoo716@gmail.com

ABSTRACT

Background

Spontaneous intracranial hemorrhage (sICH) is a major complication associated with oral anticoagulation which results in a high mortality rate, and the incidence of anticoagulant-induced sICH has increased markedly, so it is necessary to investigate the risk of anticoagulation-related sICH in a real-world setting.

Objective

We aimed to investigate the incidence and risk factors of oral anticoagulant-related sICH using a common data model (CDM), and to determine whether a clinical study using the CDM would be comparable to conventional studies.

Methods

After converting the various clinical codes of 12,821 patients taking oral anticoagulants, such as warfarin and non-vitamin K antagonist oral anticoagulants (NOACs), into the Observational Medical Outcomes Partnership (OMOP) CDM format, we analyzed the incidence and risk factors of sICH.

Results

sICH occurred in 0.5% of 5,626 patients with warfarin and 0.2% of 7,195 patients with NOAC. The mean duration of warfarin and NOACs before sICH occurrence was 251.4 ± 373.6 and 124.2 ± 135.7 days, respectively. Multivariable analysis showed significant risk factors of the sICH, such as warfarin over NOACs; hypertension; diabetes mellitus; brain tumors; and decreased duration of oral anticoagulation.

Conclusions

NOAC demonstrated a lower risk of sICH than warfarin in a real-world setting using OMOP

CDM confined to a single institution. Clinical studies using a CDM for the multicenter datasets may provide more reliable information about the risk of sICH.

Keywords: Warfarin; Non-vitamin K antagonist oral anticoagulants; Risk factors; Spontaneous intracranial hemorrhage; Common data model

INTRODUCTION

Spontaneous intracranial hemorrhage (sICH) is a significant causes of morbidity and mortality, [1] with an overall incidence of 24.6 per 100,000 person-years. [2] The fatality rate of sICH is approximately 40% in one month and 54% in one year, and only 12-39% of the patients have favorable functional outcomes. [3] Well-known risk factors for sICH include hypertension, old age, male gender, cigarette smoking, diabetes mellitus, cerebral amyloid angiopathy, and anticoagulation medications. [3,4,5,6,7,8,9] Among them, oral anticoagulation is thought to increase the risk of sICH by up to 11 times, [10] and the annual incidence of anticoagulant-related sICH has shown tremendous growth in the United States population from 0.8 to 4.4 per 100,000 persons during the 1990s. [11]

Oral anticoagulants are an important therapeutic option to prevent and treat venous thromboembolism, stroke related to atrial fibrillation, and valvular heart disease. [12,13] In addition to warfarin, conventional oral anticoagulants and non-vitamin K antagonist oral anticoagulants (NOACs) have been widely used, with concrete evidence of non-inferior effects and lower complication rates than warfarin. [12,14,15] The annual risk of sICH in patients taking warfarin ranges from 0.3% to 3.7%. [10] Furthermore, NOACs show an incidence of approximately 0.7% for sICH combined with reduction in the risk of sICH compared with warfarin (relative risk 0.48) in a meta-analysis of randomized trials. [14] In the Korean population, the proportion of sICH among all strokes cases remained fairly stable, between 23.9% and 25.3%, in the late 2000s. [16] Studies using the Korean Health Insurance Review and Assessment database mentioned that the incidence of sICH in patients receiving warfarin is 1.3% per year and in those receiving NOACs is 0.7%. NOAC use is also associated with a 34% lower risk of sICH than warfarin use. [17,18]

The best way to obtaining strong medical evidence is through randomized controlled trials (RCT) or meta-analysis of RCTs; however, this method may have practical constraints, such as cost, time, and difficulties in patient enrollment. Compared to conventional research methods, the Common Data Model (CDM) can provide real-world data that standardizes, structures, and reflects clinical information of patients. [19] However, the CDM has the potential for information loss and risk of bias due to data quality, selection bias and residual confounding factors. [20] Also, data interoperability among institutions is the main benefit of CDMs, but cannot work in the presence of barriers, such as Korean Health Insurance Portability and Accountability Act (HIPAA). To the best of our knowledge, no studies assessing the real-world risk of sICH related to oral anticoagulants use in a CDM. We aimed to investigate the incidence and risk factors of oral anticoagulant-related sICH in our institution using a CDM, and to determine whether a clinical study using a CDM would be comparable to well-designed conventional studies.

METHODS

Data source

We used the dataset based on the clinical data warehouse (CDW) from our institution by retrospective searching the period from 15 October 2004 to 28 February 2019, for codes related to diagnoses, prescriptions, and laboratory tests. These data were encoded using the Observational Medical Outcomes Partnership (OMOP) CDM version 5. This study was approved by the institutional review board of Seoul National University Hospital, and informed consent was waived due to de-identification of data source during transformation processing into the

CDM data (IRB No. E-2002-090-1102). All data and methods were handled in accordance with relevant guidelines and regulations, including the Declaration of Helsinki.

Study population

We searched for patients with diagnostic codes for sICH and prescription codes for warfarin or NOAC in dataset as described above. According to the operational definitions, the total number of patients was 14,199 for warfarin and 7,195 on NOAC, excluding those who received a combination of both. The total number of patients with sICH was 5,042. For a significant comparison, the starting point of data evaluation was adjusted to February 2011, when the prescription codes of NOAC appeared for the first time in our dataset. So, final number of the patients taking warfarin or NOAC was 5,626 and 7,195, respectively, and the number of patients who presented with sICH was 3,483. Details of patient selection process are shown in **Figure 1.**

Common data model

Multiple disparate healthcare dataset have a wide variety of its system, recording formats, and terminologies; therefore, the use of the CDM has led to the development of a consistent and standardized way to accommodate these databases. Using longitudinal electronic health record (EHR) data, a vocabulary-driven extract-transform-load (ETL) process was developed to convert the dataset from the CDW of our institution into an OMOP CDM integrated into standardized vocabularies. In these processes, various domains, such as the basal characteristics (de-identified) of patients, diseases, prescription of drugs, diagnosis, and procedures, are encoded with standard vocabularies. These standardized datasets in OMOP CDM format can be reviewed and analyzed using statistical tools such as R packages. [21] We performed the conversion

process of raw data source into the OMOP CDM, including concept code mapping, via categorization and standardization of local codes according to commercially available mapping table.

Operational definitions

To define ambiguous meaning of the variables, they were imported into the CDM, which yielded dichotomous results concerning the variable, such as whether it existed, after which we established the operational definition and queries. sICH was defined as the relevant diagnostic code, including supratentorial intracerebral, cerebellar, subdural and epidural, and subarachnoid hemorrhage. To distinguish secondary or traumatic intracranial hemorrhage, the codes indicating trauma and ruptured intracranial vascular abnormalities, such as ‘ruptured’ intracranial aneurysms, ‘ruptured’ arteriovenous malformations, ‘ruptured’ arteriovenous fistulas, and ‘ruptured’ dissections were excluded.

Patient age was defined as that at the start of warfarin or NOAC therapy. Underlying diseases such as hypertension and diabetes were defined as having a diagnostic code at least once during the study period. Intracranial conditions related to sICH included brain tumors, cerebral infarction, cerebral vasculitis, cerebral aneurysms, and other cerebrovascular diseases. Such conditions related to sICH were considered to exist if the diagnostic codes corresponding to these diseases were entered once before the sICH occurred. The presence of indicated diseases for which warfarin or NOAC were administered was defined as the entry of diagnostic code related to those diseases at least once before the start of warfarin or NOAC. Heart diseases included coronary artery disease and atrial fibrillation. Thromboembolic diseases included pulmonary embolism and other venous thromboembolisms, except for pulmonary artery embolism. Diseases

requiring total hip or knee arthroplasty meant any condition, including degenerative or traumatic disease, for which hip or knee arthroplasty should be performed.

Considering the action duration and half-life of warfarin and NOACs, the dose duration was defined as the day from the start to five days after the end of warfarin and from day of start to one day after the end of NOAC. Antiplatelet medications were divided into two categories: (1) in cases in which sICH did not occur, the period of prescription coincided with the prescription period of warfarin or NOAC by > 90%; or (2) in cases of sICH, the period of prescription matched the prescription period of warfarin or NOAC by > 90% from the time of the start of warfarin or NOAC to the point of occurrence of sICH.

In patients detected using diagnostic codes referring to sICH, the divisions of the hospital in which the diagnostic codes were inputted could be segregated. If the diagnostic codes were entered at the outpatient clinic only and did not pass through the emergency center, patients corresponding to these situations were excluded because we were not convinced that patients with sICH presented their hemorrhagic event acutely or that were previously events remaining in the CDM.

The international normalized ratio (INR) was excluded if it existed only at the time of more than one day after the occurrence of sICH event but not on the date of event except for the patients with no INR data in the CDM. The 23 individuals (79.3% of patients with sICH treated with warfarin) and 13 (76.5% of patients with sICH treated with NOAC) were selected to explore INR distribution.

Statistical analysis

Categorical variables were presented as the numbers and percentages of total cases.

Continuous variables were expressed as means ± standard deviations (SD) and range. The relationship between intracranial hemorrhage (spontaneous and traumatic) and anticoagulant groups were analyzed using Chi-squared and Fisher's exact tests. For the event of sICH, Kaplan–Meier survival analyses for each variable were performed first, followed by risk factor analysis using Cox proportional hazards regression to produce hazard ratios (HRs) with 95% confidence intervals (CIs) for the predisposing variables of sICH. Univariable analyses were performed first, and the variables with $P<.3$ were selected for multivariable analysis by stepwise elimination. For all statistical analyses, a $P<.05$ was regarded to be significant, and $.1>P\geq.05$ was considered borderline significance. All statistical analyses were conducted using R version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Incidence of sICH

The baseline characteristics of all patients taking oral anticoagulants are shown in **Table 1**. The total intracranial hemorrhage rates were 0.7% and 0.4% in the warfarin and NOAC groups, respectively. Traumatic intracranial hemorrhage rates in the warfarin and NOAC groups were 0.5% and 0.2%, respectively. The incidences of sICH were 0.5% and 0.2% for warfarin and NOAC, respectively. Warfarin showed a significantly higher rate for all types of intracranial hemorrhage than NOAC (total intracranial hemorrhage: OR: 1.95, 95% CI: 1.19–3.17, P=.01, by Chi-square test; sICH: OR: 2.18, 95% CI: 1.20–3.99, P=.01, by Chi-square test; traumatic intracranial hemorrhage: OR: 5.12, 95% CI: 1.09–24.13, P=.03, by Fisher's exact test). The most common underlying disease was hypertension (31.4% of total patients), and the second most

common condition was diabetes mellitus (20.9%). The most common indications for oral anticoagulation therapy were atrial fibrillation, coronary artery disease, and orthopedic surgery. Atrial fibrillation and coronary artery disease were the main cause for anticoagulation in the warfarin group, whereas atrial fibrillation, orthopedic surgery, and coronary artery disease were the main indications for initiating anticoagulation in the NOAC group.

In the patients with sICH during anticoagulation therapy, no significant differences in age, gender, underlying disease, rate for concomitant administration of antiplatelet medication, or indications for anticoagulation between the warfarin and NOAC groups, were found. Also, no significant difference in duration of anticoagulation before sICH occurrence was found (mean 251.4 ± 272.6 days in the warfarin group versus 124.2 ± 135.7 days in the NOAC group). The baseline characteristics of the patients who experienced sICH during the administration of oral anticoagulants are summarized in **Table 2**.

The distribution of INR at the time of sICH occurrence is shown in **Table 3**. Although some missing data are missing, the mean INR was 2.41 in the warfarin group and 1.27 in the NOAC group. Most patients (92.3%) in NOAC group had INR < 2 (69.2% patients' INR ≤ 1.2), and, even in patient with sICH, the majority of individuals (47.8%) in the warfarin group had INR values < 2 (13.0% patients' INR ≤ 1.2), with same distribution of INR range 2–3 and INR value > 3 (26.1% each, respectively).

Risk factors of sICH

Figure 2 shows the cumulative incidence of sICH based on follow-up duration using the Kaplan–Meier curve. In the multivariable Cox proportional hazards regression (**Table 4**), several risk factors were found to be significant: warfarin over NOAC (adjusted HR: 2.56, 95% CI:

1.35–4.86; *P*=.004); hypertension (adjusted HR: 1.91, 95% CI: 1.03–3.54; *P*=.04); diabetes mellitus (adjusted HR: 1.87, 95% CI: 1.03–3.38; *P*=.04); brain tumors (adjusted HR: 5.66, 95% CI: 1.84–17.40; *P*=.003); and decreased duration of oral anticoagulation (adjusted HR: 0.99, 95% CI: 0.998–0.999; *P*=.003). Age showed borderline significance (adjusted HR: 1.03, 95% CI: 1.00–1.06; *P*=.09). **Figure 3** shows the results of the subgroup analysis of sICH caused by oral anticoagulants. The risk of sICH was increased with males taking warfarin (adjusted HR: 2.8, 95% CI: 1.2-6.5) compared to females, in those with hypertension (adjusted HR: 3.4, 95% CI: 1.5–7.5), without diabetes (adjusted HR: 2.9, 95% CI: 1.3–4.8), without brain tumors (adjusted HR: 2.4, 95% CI: 1.3-4.8), and in those with other intracranial diseases except brain tumors (adjusted HR: 4.1, 95% CI: 1.2–14.4).

DISCUSSION

In this study using the OMOP CDM in a single institution, the incidence of sICH was 0.5% with warfarin and 0.2% with NOAC administration. During the course of oral anticoagulation, warfarin over NOAC, hypertension, diabetes, brain tumors and decreased duration of oral anticoagulation were significant risk factors for sICH. Several pivotal multicenter RCTs addressing NOAC [22,23,24,25,26,27,28,29] indicated their efficacy with fewer hemorrhagic complications compared to warfarin. However, except for a few studies conducted with Korean health insurance claim data, few studies concerning sICH-related oral anticoagulation therapy based on real-world data in Asian population are available. Therefore, the results from this study seem meaningful in terms of comparable results of the incidence and risk factors of oral anticoagulation-related sICH using the CDM for the first time.

The representative RCTs investigating beneficial evidences of NOAC showed non-yearly rates of hemorrhagic stroke for NOAC, which ranged 0.43% to 0.9%, whereas that for warfarin was 0.86% to 1.28%, and a significant risk reduction of hemorrhagic stroke related to NOAC over warfarin was indicated. [23,25,27,29] Compared to those studies, our results (incidence rate of sICH: 0.5% with warfarin and 0.2% with NOAC) of a significantly higher incidence of sICH in the warfarin group (OR: 2.18, 95% CI: 1.20–3.99, *P*=.01, by Chi-square test) had slightly lower values but showed a similar trend. The uncontrolled and heterogeneous patient population may have contributed to this small difference.

A considerable number of studies presented the risk factors for sICH, [3,4,5,6,7,8,9] and similar results for risk factors predisposing an individual to sICH have been derived. Among these risk factors, the duration of oral anticoagulation can be defined as exposure to oral anticoagulation for longer than the duration itself. The finding of the protective effect of oral anticoagulant duration on sICH may be explained by the fact that the proportion of patients who remained on oral anticoagulation for a longer period and at follow-up was significantly higher than that of patients who had sICH. Brain tumors presented the highest HR with statistical significance; however, it seems unreasonable to consider this as valid. First, sample numbers that were too small corresponded to only two persons in the warfarin group and one individual in the NOAC group (6.9% and 5.9%, respectively), and second, the 95% CIs was overestimated (1.84–17.40); thus, it was assumed that this interval had an association with other variables. Due to the characteristics of CDM dataset, in which patient personal information was masked and de-individualized, it was not possible to determine the characteristics of individual patients with brain tumors. We cautiously suggest that the CDM is a convincing tool. In particular, if temporal, spatial, and/or cost are limited, or if cost limitations limited the ability of researchers to conduct

RCT, research using the CDM could be a reasonable alternative.

The INR is a common laboratory tests used to estimate the anticoagulation effects of warfarin. [30] The risk of fatal sICH was more than double when INR values were > 3.5 at presentation. [31] However, approximately two-thirds of sICH related to warfarin occurred even though INR range was within the therapeutic window. [32] In addition, even in the subtherapeutic INR range, warfarin-related sICH showed an increased risk for hematoma expansion. [33] In our results, nearly half of the patients with sICH in the warfarin group had INR values < 2 (47.8%). This finding agrees with those of previous studies, in which elevated INR during warfarin administration was an important risk factor for the occurrence of sICH; however, it is not safe to assume that the INR value is at a subtherapeutic level. Even in patients with low INR values while taking warfarin, caution must be exercised regarding the possibility of sICH. As is well known, INR does not provide reliable check of NOAC's efficacy. [30,34,35] Almost patients presenting with sICH in the NOAC group (92.3%) had INR value < 2, and this result showed the drawback of NOAC, which do not yet have an appropriate therapeutic monitoring tool.

This study has several limitations. First, the key limitation is the problem with the CDM methodology. This is not only limited to the CDM but is also a fundamental problem of standardized datasets. Various clinical circumstances were simplified, standardized, and expressed using codes. Of course, an operational definition is most important to determine the identities of the variables. However, it is impossible to accurately specify complex and varied clinical circumstances using only operational definitions. Furthermore, the possibility of an error in the step during which researchers input the diagnostic code into the electric medical records always exists. In fact, when the authors examined raw data, quite a few cases in which the medical records were described or diagnosed differently from actual situations were found. One

solution for these discrepancies could be the reflection of formal readings of image studies by the radiologists into the CDM dataset; however, importing free text into the CDM is not yet possible. Drug compliance is also poorly embedded in CDM-based analyses, which means that only prescription codes, even with delicate operational definitions, cannot provide information on whether patients take drugs according to their medication schedule. Second, the evaluation of quantifiable scales that describe the patient neurological status or clinical outcomes (such as modified Rankin scale or Glasgow outcome scale) could not be coded and represented within the CDM. This drawback led to the failure of demonstrate the severity and clinical outcomes of sICH related to anticoagulation apart from our initial intention. Third, selection bias occured because the study was not randomized. To solve this problem, we considered propensity score matching; however, it was impossible because the sICH event rate was low and, therefore, not a satisfactory statistical process to correct for selection bias. Fourth, this study is based on a CDM dataset from a single institution. Regarding the original reason for the development of the CDM, in which multicenter research can be facilitated by sharing discrete forms of database from each institution, we did not thoroughly utilize the CDM and its advantages. We initially planned to merge the clinical data from not only our facility but also branched or connected hospitals, and to establish a large multicentered dataset by matching codes corresponding to the vocabulary of each components. Unfortunately, is is impossible to share communication network and data frames with branched facilities because of the Korean HIPAA rules. Therefore, only one dataset from our institution was available. Finally, the CDM dataset was updated as time went on during the revision process and the number in each subgroup of patients excluded from the ‘Patient with intracranial hemorrhage’ shown in Figure 1 differs from the initial number. Therefore, the exact number of patients required for each exclusion criterion could not be determined.

Despite these limitations, this study is the first to demonstrate the risk of sICH with oral anticoagulation using the CDM. The application of real-world data using the CDM in this manner will be useful and valuable in other fields of medicine, especially in situations with practical constraints such as cost and time limitations.

In this real-world study using the OMOP CDM confined to our institution, NOAC demonstrated a lower incidence of sICH than warfarin. Other predisposing factors that increased the risk of sICH related to oral anticoagulants were hypertension, diabetes mellitus, brain tumors, and decreased duration of oral anticoagulation. Further investigations with sophisticated study designs, including multicenter disparate databases using CDM and delicate operational definitions, are needed to provide more reliable results.

Acknowledgments

There is no acknowledgment.

Source of Funding

This work was supported by the Bio Industrial Strategic Technology Development Program (20003883), funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea).

Conflicts of Interest

The Authors declare no conflicts of interest.

REFERENCES

1. Hemphill, J.C., 3rd, *et al.* Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* **46**, 2032-2060 (2015). PMID:20651276.
2. van Asch, C.J., *et al.* Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol* **9**, 167-176 (2010). PMID:20056489.
3. An, S.J., Kim, T.J. & Yoon, B.W. Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update. *J Stroke* **19**, 3-10 (2017). PMID:28178408.
4. Sturgeon, J.D., *et al.* Risk factors for intracerebral hemorrhage in a pooled prospective study. *Stroke* **38**, 2718-2725 (2007). PMID:17761915.
5. Ariesen, M.J., Claus, S.P., Rinkel, G.J. & Algra, A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke* **34**, 2060-2065 (2003). PMID:12843354.
6. Morawo, A.O. & Gilmore, E.J. Critical Care Management of Intracerebral Hemorrhage. *Semin Neurol* **36**, 225-232 (2016). PMID:27214697.
7. Giray, S., *et al.* Spontaneous primary intraventricular hemorrhage in adults: clinical data, etiology and outcome. *Turk Neurosurg* **19**, 338-344 (2009). PMID:19847752.
8. Qureshi, A.I., *et al.* Spontaneous intracerebral hemorrhage. *N Engl J Med* **344**, 1450-1460 (2001). PMID:11346811.
9. Juvela, S., Hillbom, M. & Palomäki, H. Risk factors for spontaneous intracerebral

hemorrhage. *Stroke* **26**, 1558-1564 (1995). PMID:7660398.

10. Steiner, T., *et al.* Recommendations for the management of intracranial haemorrhage - part I: spontaneous intracerebral haemorrhage. The European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee. *Cerebrovasc Dis* **22**, 294-316 (2006). PMID:16926557.
11. Flaherty, M.L., *et al.* The increasing incidence of anticoagulant-associated intracerebral hemorrhage. *Neurology* **68**, 116-121 (2007). PMID:17210891.
12. Caldeira, D., Barra, M., Pinto, F.J., Ferreira, J.J. & Costa, J. Intracranial hemorrhage risk with the new oral anticoagulants: a systematic review and meta-analysis. *J Neurol* **262**, 516-522 (2015). PMID:25119841.
13. Fanaroff, A.C., Vora, A.N. & Lopes, R.D. Non-vitamin K antagonist oral anticoagulants in patients with valvular heart disease. *Eur Heart J Suppl* **24**, A19-a31 (2022). PMID:35185406.
14. Ruff, C.T., *et al.* 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**, 955-962 (2014). PMID:24315724.
15. Kundu, A., *et al.* Intracranial hemorrhage with target specific oral anticoagulants in patients with atrial fibrillation: An updated meta-analysis of randomized controlled trials. *Int J Cardiol* **203**, 1000-1002 (2016). PMID:26630621.
16. Hong, K.S., *et al.* Stroke statistics in Korea: part I. Epidemiology and risk factors: a report from the korean stroke society and clinical research center for stroke. *J Stroke* **15**, 2-20 (2013). PMID:24324935.
17. Cha, M.J., *et al.* Effectiveness and Safety of Non-Vitamin K Antagonist Oral

Anticoagulants in Asian Patients With Atrial Fibrillation. *Stroke* **48**, 3040-3048 (2017). PMID:28974629.

18. Lee, S.R., *et al.* Oral Anticoagulation in Asian Patients With Atrial Fibrillation and a History of Intracranial Hemorrhage. *Stroke* **51**, 416-423 (2020). PMID:31813363.
19. Jeon, Y., Choi, Y., Kim, E.H., Oh, S. & Lee, H. Common data model-based real-world data for practical clinical practice guidelines: clinical pharmacology perspectives. *Transl Clin Pharmacol* **28**, 67-72 (2020). PMID:32656157.
20. Kent, S., *et al.* Common Problems, Common Data Model Solutions: Evidence Generation for Health Technology Assessment. *Pharmacoeconomics* **39**, 275-285 (2021). PMID:33336320.
21. Hripcsak, G., *et al.* Observational Health Data Sciences and Informatics (OHDSI): Opportunities for Observational Researchers. *Stud Health Technol Inform* **216**, 574-578 (2015). PMID:26262116.
22. Ezekowitz, M.D., *et al.* Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J* **157**, 805-810, 810.e801-802 (2009). PMID:19376304.
23. Connolly, S.J., *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* **361**, 1139-1151 (2009). PMID:19717844.
24. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. *Am Heart J* **159**, 340-347.e341 (2010). PMID:20211293.
25. Patel, M.R., *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J*

Med **365**, 883-891 (2011). PMID:21830957.

26. Lopes, R.D., *et al.* Apixaban for reduction in stroke and other ThromboembоLic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. *Am Heart J* **159**, 331-339 (2010). PMID:20211292.

27. Granger, C.B., *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* **365**, 981-992 (2011). PMID:21870978.

28. Ruff, C.T., *et al.* Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). *Am Heart J* **160**, 635-641 (2010). PMID:20934556.

29. Giugliano, R.P., *et al.* Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* **369**, 2093-2104 (2013). PMID:24251359.

30. Nutescu, E.A., Dager, W.E., Kalus, J.S., Lewin, J.J., 3rd & Cipolle, M.D. Management of bleeding and reversal strategies for oral anticoagulants: clinical practice considerations. *Am J Health Syst Pharm* **70**, 1914-1929 (2013). PMID:24128967.

31. Witt, D.M., *et al.* Effect of warfarin on intracranial hemorrhage incidence and fatal outcomes. *Thromb Res* **132**, 770-775 (2013). PMID:24521790.

32. Horstmann, S., *et al.* Intracerebral hemorrhage during anticoagulation with vitamin K antagonists: a consecutive observational study. *J Neurol* **260**, 2046-2051 (2013). PMID:23645221.

33. Zemrak, W.R., *et al.* Low-dose Prothrombin Complex Concentrate for Warfarin-Associated Intracranial Hemorrhage with INR Less Than 2.0. *Neurocrit Care* **27**, 334-

340 (2017). PMID:28660341.

34. Purrucker, J.C., *et al.* Coagulation Testing in Acute Ischemic Stroke Patients Taking Non-Vitamin K Antagonist Oral Anticoagulants. *Stroke* **48**, 152-158 (2017). PMID:27899756.

35. Purrucker, J.C., *et al.* Coagulation Testing in Intracerebral Hemorrhage Related to Non-vitamin K Antagonist Oral Anticoagulants. *Neurocrit Care* **27**, 208-213 (2017). PMID:28477151

FIGURE LEGENDS

Figure 1. Eligibility and exclusion criteria flow. OAC, oral anticoagulant; n, number; ICH, intracranial hemorrhage; NOAC, non-vitamin K antagonist oral anticoagulant

Figure 2. Kaplan–Meier plots with 95% confidence interval for spontaneous intracranial hemorrhage-free survival. **a–j.** Cumulative incidence of spontaneous intracranial hemorrhage by each variable. **f.** Intracranial diseases except brain tumors included cerebral infarction, cerebral vasculitis, cerebral aneurysms, and other intracranial vascular abnormalities such as unruptured vascular malformations. **g.** Heart disease included coronary artery disease and atrial fibrillation. **h.** Thromboembolic disease contained pulmonary embolism and other venous thromboembolisms. **i.** Diseases requiring total hip or knee arthroplasties covered the conditions for which arthroplasty procedures should be performed. NOAC, non-vitamin K antagonist oral anticoagulants.

Figure 3. Forest plot from subgroup analysis by oral anticoagulants. *Intracranial diseases, except brain tumors, included cerebral infarction, cerebral vasculitis, cerebral aneurysms, and other intracranial vascular abnormalities such as unruptured vascular malformations. ref., reference; HR, hazard ratio; CI, confidence interval.

Table 1. Basal characteristics of total patients taking oral anticoagulants

Variables	Total	Drugs		
		Warfarin	NOAC	*P*
Patients, n (%)	12,821 (100)	5,626 (43.6)	7,195 (56.4)	
Age in year, mean ± SD	65.2 ± 15.7	60.5 ± 18.3	68.9 ± 12.0	<.001*
Gender, n (%)				

Male	6,814 (53.1)	3,353 (59.6)	3,461 (48.1)	<.001†
Female	6,007 (46.9)	2,273 (40.4)	3,734 (51.9)	
Underlying diseases, n (%)				
Hypertension	4,022 (31.4)	1,285 (22.8)	2,737 (38.0)	<.001†
Diabetes mellitus	2,679 (20.9)	1,040 (18.5)	1,639 (22.8)	<.001†
Intracranial diseases				
Brain tumors	204 (1.6)	59 (1.0)	145 (2.0)	<.001†
Cerebrovascular diseases				
Cerebral infarction	2,041 (15.9)	821 (14.6)	1,220 (17.0)	<.001†
Cerebral vasculitis	302 (2.4)	170 (3.0)	132 (1.8)	<.001†
Cerebral aneurysms	358 (2.8)	127 (2.3)	231 (3.2)	<.001†
Others	20 (0.2)	11 (0.2)	9 (0.1)	.32†
Simultaneous antiplatelet medication, n (%)	603 (4.7)	352 (6.3)	251 (3.5)	<.001†
Indications of anticoagulant medication, n (%)				
Coronary artery disease	1212 (9.5)	660 (11.7)	552 (7.7)	<.001†
Atrial fibrillation	2,820 (21.9)	1,047 (18.6)	1,773 (24.6)	<.001†
Venous thromboembolism	458 (3.6)	199 (3.5)	259 (3.6)	.85†
Pulmonary embolism	429 (3.3)	116 (2.1)	313 (4.4)	<.001†
Diseases required total hip or knee arthroplasties	1,406 (10.9)	99 (1.8)	1,307 (18.2)	<.001†
Total duration of oral anticoagulation (days), mean ± SD	406.1 ± 556.4	536.7 ± 704.3	303.9 ± 374.2	<.001§
Total intracranial hemorrhage, n (%)	68 (0.5)	41 (0.7)	27 (0.4)	.01†
Spontaneous intracranial hemorrhage, n (%)	46 (0.4)	29 (0.5)	17 (0.2)	.01†
Traumatic intracranial hemorrhage, n (%)	10 (0.1)	8 (0.1)	2 (0.02)	.03‡

NOAC, non-vitamin K antagonist oral anticoagulant; n, number; SD, standard deviation.
*P for Wilcoxon rank-sum test.
†P for Chi-square test.
‡P for Fisher's exact test.
§P for Mann-Whitney test.

Table 2. Basal characteristics of the patients with spontaneous intracranial hemorrhage

Variables	Total	Drugs		
		Warfarin	NOAC	*P*
Patients, n (%)	46 (100)	29 (63.0)	17 (37.0)	
Age in year, mean ± SD	69.2 ± 14.2	67.6 ± 15.2	71.8 ± 12.5	.41*
Gender, n (%)				
Male	31 (67.4)	21 (72.4)	10 (58.8)	.34†
Female	15 (32.6)	8 (27.6)	7 (41.2)	
Underlying diseases, n (%)				
Hypertension	26 (56.5)	16 (55.2)	10 (58.8)	.81†
Diabetes mellitus	19 (41.3)	10 (34.5)	9 (52.9)	.22†

Intracranial diseases				
Brain tumors	3 (6.5)	2 (6.9)	1 (5.9)	1.00‡
Cerebrovascular diseases				
Cerebral infarction	14 (30.4)	10 (34.5)	4 (23.5)	.44†
Cerebral vasculitis	1 (2.2)	1 (3.4)	0 (0)	1.00‡
Cerebral aneurysms	2 (4.3)	2 (6.9)	0 (0)	.52‡
Others	0 (0)	0 (0)	0 (0)	1.00‡
Simultaneous antiplatelet medication, n (%)	2 (4.3)	1 (3.4)	1 (5.9)	1.00‡
Indications of anticoagulant medication, n (%)				
Coronary artery disease	6 (13.0)	5 (17.2)	1 (5.9)	.39‡
Atrial fibrillation	11 (23.9)	6 (20.7)	5 (29.4)	.72‡
Venous thromboembolism	0 (0)	0 (0)	0 (0)	1.00‡
Pulmonary embolism	1 (2.2)	1 (3.4)	0 (0)	1.00‡
Diseases required total hip or knee arthroplasties	2 (4.3)	1 (3.4)	1 (5.9)	1.00‡
Duration of oral anticoagulation before event (days), mean ± SD	204.4 ± 311.9	251.4 ± 373.6	124.2 ± 135.7	.12§

NOAC, non-vitamin K antagonist oral anticoagulant; n, number; SD, standard deviation.
*P for Wilcoxon rank-sum test.
†P for Chi-square test.
‡P for Fisher's exact test.
§P for Mann-Whitney test.

Table 3. INR in patients with spontaneous intracranial hemorrhage

	Drugs	
	Warfarin	**NOAC**
Number of patients		
Available coagulation panel	23	13
(Missing)	(6)	(4)
Mean INR ± SD	2.41 ± 1.3	1.27 ± 0.4
INR count, n (%)		
< 2	11 (47.8)	12 (92.3)
2 – 3	6 (26.1)	1 (7.7)
> 3	6 (26.1)	0 (0.0)

INR, international normalized ratio; n, number; NOAC, non-vitamin K antagonist oral anticoagulants.

Table 4. Risk factor analysis of spontaneous intracranial hemorrhage in patients taking oral anticoagulants

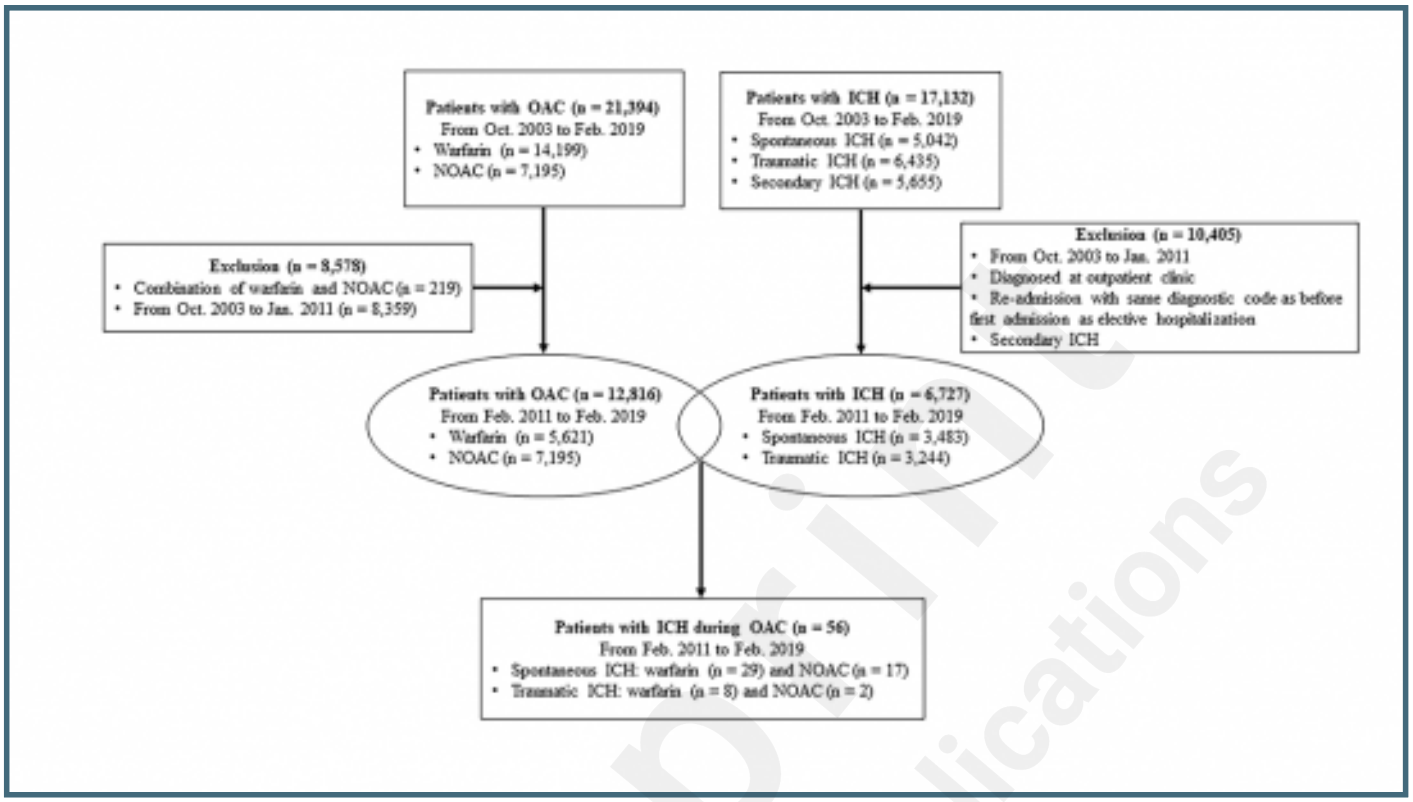
Variables	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Warfarin over NOACs	1.44 (0.90 – 2.62)	.23	2.56 (1.35 – 4.86)	.004
Age	1.03 (1.003 – 1.06)	.02	1.03 (1.00 – 1.06)	.09
Male over female	1.54 (0.84 – 2.85)	.17	1.53 (0.83 – 2.81)	.17
Hypertension	2.22 (1.25 – 3.95)	.01	1.91 (1.03 – 3.54)	.04
Diabetes mellitus	2.44 (1.36 – 4.37)	.003	1.87 (1.03 – 3.38)	.04
Brain tumors	5.93 (1.82 – 19.32)	.003	5.66 (1.84 – 17.40)	.003
Intracranial diseases except brain tumors	1.86 (1.00 – 3.45)	.05	1.52 (0.79 – 2.92)	.21
Simultaneous antiplatelet medication	0.98 (0.24 – 4.01)	.97		
Indications of oral anticoagulants				
Heart diseases	0.93 (0.51 – 1.68)	.81		
Thromboembolic diseases	0.39 (0.05 – 2.92)	.36		
Diseases required total hip or knee arthroplasties	1.00 (0.23 – 4.37)	.99		
Duration of oral anticoagulation	0.99 (0.998 – 0.999)	.007	0.99 (0.998 – 0.999)	.003

HR, hazard ratio; CI, confidence interval; NOAC, non-vitamin K antagonist oral anticoagulant.

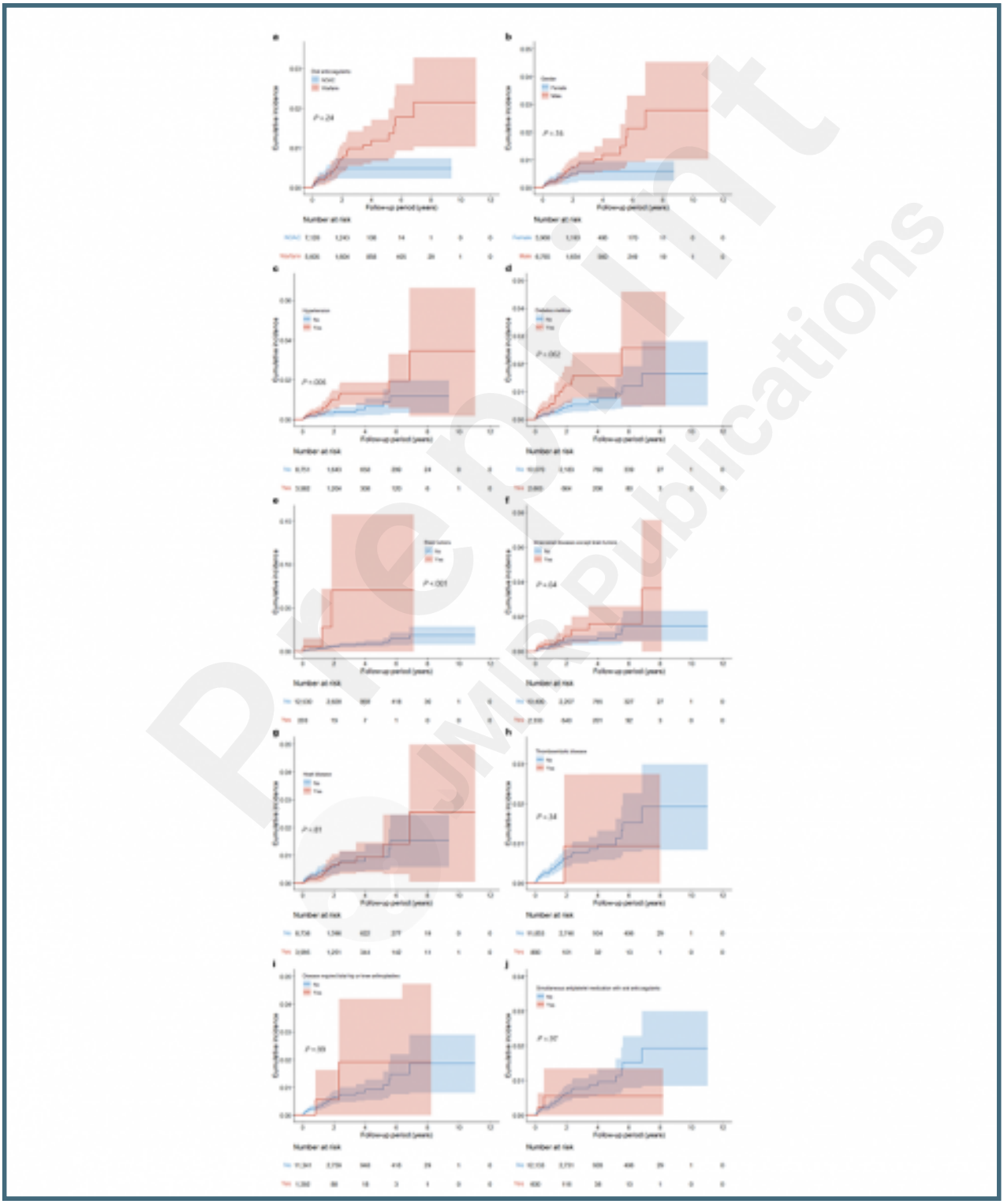
Supplementary Files

Figures

Eligibility and exclusion criteria flow. OAC, oral anticoagulant; n, number; ICH, intracranial hemorrhage; NOAC, non-vitamin K antagonist oral anticoagulant.



Kaplan–Meier plots with 95% confidence interval for spontaneous intracranial hemorrhage-free survival. a–j. Cumulative incidence of spontaneous intracranial hemorrhage by each variable. f. Intracranial diseases except brain tumors included cerebral infarction, cerebral vasculitis, cerebral aneurysms, and other intracranial vascular abnormalities such as unruptured vascular malformations. g. Heart disease included coronary artery disease and atrial fibrillation. h. Thromboembolic disease contained pulmonary embolism and other venous thromboembolisms. i. Diseases requiring total hip or knee arthroplasties covered the conditions for which arthroplasty procedures should be performed. NOAC, non-vitamin K antagonist oral anticoagulants.



Forest plot from subgroup analysis by oral anticoagulants. *Intracranial diseases, except brain tumors, included cerebral infarction, cerebral vasculitis, cerebral aneurysms, and other intracranial vascular abnormalities such as unruptured vascular malformations. ref., reference; HR, hazard ratio; CI, confidence interval.