Drug-drug interactions in atrial fibrillation patients receiving direct oral anticoagulants

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Polypharmacy is common in patients with atrial fibrillation (AF), making these patients vulnerable to the occurrence of potential drug-drug interactions (DDIs). We assessed the risk of ischemic stroke and major bleeding in the context of concomitant treatment with potential DDIs in patients with AF prescribed direct oral anticoagulants (DOACs). Using the common data model (CDM) based on an electronic health record (EHR) database, we included new users of DOACs from among patients treated for AF between January 2014 and December 2017 (n = 1938). The median age was 72 years, and 61.8% of the patients were males, with 28.2% of the patients having a CHA2DS2-VASc score in category 0–1, 49.4% in category 2–3, and 22.4% in category ≥ 4. The CHA2DS2-VASc score was significantly associated with ischemic stroke occurrence and hospitalization for major bleeding. Multiple logistic regression analysis showed that increased risk of ischemic stroke and hospitalization for major bleeding was associated with the number of DDIs regardless of comorbidities: ≥ 2 DDIs was associated with ischemic stroke (OR = 18.68; 95% CI, 6.22–55.27, P < 0.001) and hospitalization for major bleeding (OR = 5.01; 95% CI, 1.11–16.62, P < 0.001). DDIs can cause reduced antithrombotic efficacy or increased risk of bleeding in AF patients prescribed DOACs.

Atrial fibrillation (AF) is a major public health burden worldwide, and the prevalence of AF is remarkably increasing according to population aging. AF increases the risk of ischemic stroke by nearly fivefold and accounts for up to 15% of strokes in people of all ages and 30% in people over the age of 80 years. Direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, are being increasingly prescribed in clinical practice as the preferred class of oral anticoagulants for stroke prevention in non-valvular AF. Although DOACs represent an advance in therapeutic safety when compared to warfarin for the prevention of stroke, the appropriateness and accuracy of prescribing medications are important.

Drug–drug interactions (DDIs) are a concern for both patients and providers, as polypharmacy is becoming more common in managing complex diseases or comorbidities. Among AF patients included in recent clinical trials, the prevalence of polypharmacy ranged between 40 and 75% and was linked to increased rates of cardiovascular mortality, bleeding, and thromboembolic complications. Recently, data on DDIs with DOACs and increased risk of bleeding have emerged from large claims database studies. Momo et al. showed that both the pharmacokinetics and the pharmacodynamics of DDIs increased the risk of bleeding in AF patients receiving anticoagulants by about 7-fold. Our group reported an approximately fourfold increase in risk for major bleeding events in DOAC users concomitantly taking ≥ 2 potentially interacting drugs, regardless of comorbidities.

The Observational Health Data Sciences and Informatics (OHDSI) is an international collaborative organization whose goal is to create and apply open-source data analytic solutions to a large network of health databases. OHDSI adopts a distributed research network with the Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM), which allows for the systematic analysis of disparate observational databases for clinical research. Recent studies demonstrated that the use of OMOP-CDM was feasible for pharmacoepidemiologic and pharmacovigilance research.

The purpose of this study was to assess whether potential DDIs affect the safety and efficacy of DOACs in patients with AF using a CDM at a single institution.

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Methods

Data sources. Electronic health records (EHRs) data from Seoul National University Bundang Hospital were transformed into OMOP-CDM version 5.2. Diagnoses were coded according to the 6th Korean Classification of Disease modified classification systems from the International Classification of Disease-10 (ICD-10). Drug names were mapped to the Anatomical Therapeutic Chemical Classification System.

This study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Seoul National University Bundang Hospital. The need for informed consent from each patient was waived because the authors did not have access to identifiable information (IRB No: X-19040/535-901).

Study population. We included patients with diagnostic codes for AF from January 2013 to December 2017 and who received DOAC (rivaroxaban, apixaban, dabigatran, or edoxaban) treatment for 7 days or longer from initial diagnosis (n = 3681). We used several exclusion criteria to maximize data accuracy. First, we excluded AF patients previously prescribed DOAC between January 2013 and December 2013 to analyze only new cases (n = 1188). Second, patients < 20 years of age diagnosed with AF and patients with valvular AF were excluded (n = 2). Third, patients with an alternative indication for DOAC treatment and prophylaxis, including deep vein thrombosis, pulmonary embolism, and joint replacement surgery, were excluded (n = 25). Fourth, patients with end-stage renal disease were excluded (n = 0). Lastly, patients with ischemic stroke (IS), intracranial hemorrhage (ICH), or gastrointestinal (GI) bleeding in the 6 months prior to cohort entry were excluded in the analysis of primary prevention (n = 528). Finally, a total of 1938 patients (diagnosed between January 2014 and December 2017) were selected for this study. The detailed patient enrollment flow is described in Supplementary Figure 1.

DDIs. Forty-five concurrent medications that may have a potential DDI with DOACs were selected as follows: (1) drugs affecting platelet function such as antiplatelet agents, non-steroidal anti-inflammatory drugs (NSAIDs), and serotonergic agents such as selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs); (2) P-glycoprotein inhibitors or CYP3A4 inhibitors such as amiodarone, clarithromycin, cobicistat, fluconazole, itraconazole, and voriconazole; and (3) P-glycoprotein inducers or CYP3A4 inducers such as carbamazepine, phenobarbital, phenytoin, and rifampin22–25 (Supplementary Table 1).

Study outcomes. We identified four clinical outcomes as follows: IS, ICH, hospitalization for GI bleeding, and hospitalization for major bleeding. To assess the outcomes, we followed up the patients for 1 year. Detailed definitions of the clinical outcomes are described in Supplementary Table 2.

DOACs administered within 30 days before the clinical outcomes were examined to assess clinical outcomes associated with DOACs. If DOACs were not administered within 30 days before the events, the event was not counted in our analysis. To identify potential drug interactions causing an increased risk of DOAC-related bleeding or a reduced antithrombotic efficacy, we examined the use of DDI drugs 30 days prior to the events.

Comorbidities. Comorbidities were included in the model as CHA2DS2-VASc scores by assigning 1 point for age between 65 and 74 years, female sex, hypertension, diabetes, congestive heart failure, or vascular disease, and adding 2 points for age 75 years or older, history of stroke, transient ischemic attack, or systemic thromboembolism26. CHA2DS2-VASc scores were divided into three categories: 0–1, 2–3, and ≥4.

Statistical methods. Patient characteristics were summarized using descriptive statistics. The median and interquartile range (IQR) was reported for continuous variables, and categorical variables were expressed as frequencies (percentage). Multiple logistic regression analysis was performed using a forced entry method to examine the associations of the CHA2DS2-VASc score and DDIs with the risk for poor clinical outcomes. For each independent variable, the odds ratio (OR) and 95% confidence interval (CI) were determined. All tests were 2-tailed, with P < 0.05 considered significant. All statistical analysis was performed using R Statistical Software version 3.6.3 (Vienna, Austria; http://www.R-project.org/).

Results

Baseline characteristics. Between 2014 and 2017, a total of 1,938 patients with AF who were newly administered DOACs were included in the study. The clinical baseline characteristics of the study are shown in Table 1. The median age was 72 years, and 61.8% of the patients were males. Among the DOACs, rivaroxaban was the most used (29.4%), followed by apixaban (22.3%) and dabigatran (15.2%). The proportion of subjects in each CHA2DS2-VASc score category was as follows: 28.2% in category 0–1, 49.4% in category 2–3, and 22.4% in category ≥4.

Ischemic stroke. IS events associated with DOACs occurred in 29 patients (1.5%) during the observation period (Table 2). Although not statistically significant, the median age was higher in the IS group than in the group without IS (76 vs. 71 years, P = 0.062). The CHA2DS2-VASc score was significantly associated with IS occurrence; as the score increased, so did the risk of IS. In addition, IS events were more common in patients who simultaneously took drugs with potential DDIs and DOACs, with risk increasing alongside the number of DDIs: 1 (OR = 6.22; 95% CI, 2.65–15.67, P < 0.0001) and ≥2 (OR = 12.22; 95% CI, 4.21–34.72, P < 0.001). The use of P-glycoprotein inducers or CYP3A4 inducers was not observed in patients with IS (Supplementary Table 3). Most of the potential drugs used in patients with IS were identified as pharmacodynamic drugs: antiplatelet agents such as aspirin (n = 15) and clopidogrel (n = 5) (Supplementary Table 3).
Table 1. Baseline characteristics of the study population. IQR, interquartile range; DOAC, direct oral anticoagulant. CHA2DS2-VASc scores indicate congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65 to 74 years, and female sex. *Mixed signifies the patient switched DOACs.

| Age, years | N   | %   |
|------------|-----|-----|
| Median (IQR) | 72 (62–78) |  |
| < 65    | 571 | 29.5 |
| 65–74  | 621 | 32.0 |
| ≥ 75   | 746 | 38.5 |
| Sex |  |  |
| Male | 1,198 | 61.8 |
| Female | 740 | 38.2 |
| DOAC |  |  |
| Rivaroxaban | 569 | 29.4 |
| Apixaban | 433 | 22.3 |
| Dabigatran | 295 | 15.2 |
| Edoxaban | 159 | 8.2 |
| Mixed* | 482 | 24.9 |

| CHA2DS2-VASc score | N   | %   |
|---------------------|-----|-----|
| 0–1                | 546 | 28.2 |
| 2–3                | 957 | 49.4 |
| ≥ 4                | 435 | 22.4 |

Table 2. Comparisons between patients with and without ischemic stroke. IQR, interquartile range; DOAC, direct oral anticoagulant; DDI, drug-drug interaction; REF, reference. CHA2DS2-VASc score indicates congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65 to 74 years, and female sex. *Mixed signifies the patient switched DOACs.

| Ischemic stroke (N=29) | No ischemic stroke (N=1,909) | Odds ratio (95% CI) | P-value |
|-------------------------|-------------------------------|---------------------|---------|
| Age, median (IQR)       | 76 (71–80)                    | 71 (62–78)          | 1.04 (1.00–1.08) | 0.062 |
| Sex                     |                               |                     |         |
| Male                    | 18                            | 1,180               | 61.8   | REF |
| Female                  | 11                            | 729                 | 38.2   | 0.99 (0.45–2.08) | 0.977 |
| CHA2DS2-VASc            |                               |                     |         |
| 0–1                     | 4                             | 542                 | 28.4   | REF |
| 2–3                     | 10                            | 947                 | 49.6   | 1.43 (0.48–5.24) | 0.546 |
| ≥ 4                     | 15                            | 420                 | 22.0   | 4.84 (1.74–17.07) | 0.005 |
| DOAC                    |                               |                     |         |
| Rivaroxaban             | 9                             | 560                 | 29.3   | REF |
| Apixaban                | 1                             | 432                 | 22.6   | 0.14 (0.01–0.77) | 0.067 |
| Dabigatran              | 1                             | 294                 | 15.4   | 0.21 (0.11–1.13) | 0.142 |
| Edoxaban                | 1                             | 158                 | 8.3    | 0.39 (0.02–2.12) | 0.378 |
| Mixed*                  | 17                            | 465                 | 24.4   | 2.28 (1.03–5.36) | 0.049 |
| DDI                     |                               |                     |         |
| No                      | 8                             | 1,411               | 73.9   | REF |
| Yes                     | 21                            | 498                 | 26.1   | 7.44 (3.40–17.97) | <0.001 |
| Number of DDIs          |                               |                     |         |
| 0                       | 8                             | 1,411               | 73.9   | REF |
| 1                       | 14                            | 483                 | 20.8   | 6.22 (2.65–15.67) | <0.001 |
| ≥ 2                     | 7                             | 101                 | 5.3    | 12.22 (4.21–34.72) | <0.001 |
Hospitalization for major bleeding. Hospitalization for major bleeding associated with the use of DOACs occurred in 22 patients (1.1%) during the observation period (Table 3). The median age was significantly higher in the hospitalization for major bleeding group than in the group without hospitalization for major bleeding (81 vs. 71 years, \( P < 0.001 \)). When analyzed against the CHA\(_2\)DS\(_2\)-VASc score, events of hospitalization for major bleeding were significantly more likely patients with \( \geq 4 \) points or more compared to patients with \( 0–1 \) points (OR = 11.51; 95% CI, 2.15–212.75, \( P = 0.021 \)). There was no association between DOAC type and hospitalization for major bleeding events. Hospitalization for major bleeding events had a statistically significant relationship with potential DDIs (OR = 2.81; 95% CI, 1.20–6.60, \( P = 0.016 \)), and the risk tended to increase as the number of DDIs increased. Most of the potential drugs used in patients with hospitalization for major bleeding were antiplatelet agents (n = 4) or NSAIDs (n = 3) (Supplementary Table 4). The relationship between ICH and hospitalization for GI bleeding and DDI is described in Supplementary Tables 5 and 6, respectively. GI bleeding showed a statistically significant relationship with DDI, whereas ICH did not.

Multiple logistic regression analysis for clinical outcomes. Multiple logistic regression analysis showed that increased risk of IS and hospitalization for major bleeding was associated with the number of DDIs regardless of comorbidities: \( \geq 2 \) DDIs was associated with IS (OR = 18.68; 95% CI, 6.22–55.27, \( P < 0.001 \)) and hospitalization for major bleeding (OR = 5.01; 95% CI, 1.11–16.62, \( P < 0.001 \)) (Table 4).

Discussion

Management of oral anticoagulant drug interaction is essential to ensure safe and effective use. Warfarin has over 200 identified drug interactions that must be considered before use\(^{25}\). Wang et al. conducted meta-analysis based on low- to moderate-strength evidence supporting interaction between warfarin and a small group of medications leading to bleeding risk or thromboembolic outcomes\(^{26}\). Although DOACs have comparable efficacy and enhanced safety compared to warfarin, the appropriateness and accuracy of prescribing medications are important to prevent increased risk of bleeding or reduced antithrombotic efficacy. In the current study, we found that potential DDIs were associated with a substantially high risk for both ischemic stroke and hospitalization for major bleeding regardless of comorbidities.

Drug interactions have been previously associated with decreased potency of DOACs\(^{25}\). Based on pharmacokinetic data and published case reports, there is a significant decrease in DOAC drug concentration and an increased risk of adverse thrombotic events in patients receiving concomitant P-glycoprotein inducers or CYP3A4 inducers\(^{26–32}\). DDIs were associated with a significantly higher risk for IS, in particular for DDIs with \( \geq 2 \)
prescribed drugs (OR, 18.68; 95% CI, 6.22–55.27). Most of the DDIs related to IS were pharmacodynamic drugs such as antiplatelet agents or NSAIDs and were not related to P-glycoprotein inducers or CYP3A4 inducers. The ARISTOTLE trial reported that participants on aspirin were at higher risk for ischemic events, with higher CHADS2 scores, than were participants not receiving aspirin33. In the current study, concomitant use of antiplatelet agents was observed in patients with IS, which could explain the higher CHADS2-VASc scores of those on antiplatelet agents. Previous studies demonstrated a thrombotic risk associated with NSAIDs34–36. Kent et al. demonstrated that the use of NSAIDs was associated with an increased risk for ischemic stroke as well as major bleeding37. It is difficult to assess the clinical relevance of DOAC drug interactions because the available data are frequently limited to pharmacokinetic studies in a small number of healthy volunteers or retrospective case–control or cohort studies.

Romoli et al. showed that switching between DOACs is frequent, occurring in up to 11% of patients prescribed with DOAC for AF. In this study, one in 4 patients had to switch between DOACs within 30 days before ischemic stroke or bleeding events. Due to the anonymization of CDM data, the cause of switching between DOACs was not known, but other studies reported that minor bleeding and non-CV adverse events had been reported as one of the most common causes to justify switching between DOACs38,39. IS was more common in those on antiplatelet agents. Previous studies reported increased risk for both IS and hospitalization for major bleeding regardless of comorbidities.

| Variables | Ischemic stroke | Hospitalization for major bleeding |
|-----------|----------------|-----------------------------------|
| CHA2DS2-VASc | Odds ratio (95% CI) | P value | Odds ratio (95% CI) | P value |
| 0–1 | REF | REF | 4.82 | 0.002 |
| 2–3 | 2.35 (0.77–8.71) | 0.157 | 9.42 (1.82–17.29) | 0.032 |
| ≥ 4 | 8.27 (2.87–30.03) | <0.001 | 15.09 (2.78–80.42) | 0.011 |
| Number of DDIs | | | | |
| 0 | REF | REF | 6.92 (2.91–17.61) | <0.001 |
| 1 | 6.92 (2.91–17.61) | <0.001 | 3.27 (1.25–8.21) | 0.012 |
| ≥ 2 | 18.68 (6.22–55.27) | <0.001 | 5.01 (1.11–16.62) | 0.016 |

Table 4. Multiple logistic regression analysis for clinical outcomes. DDI, drug-drug interaction; REF, reference. CHA2DS2-VASc indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65 to 74 years, and female sex.
References

1. Rahman, F., Kwan, G. F. & Benjamin, E. J. Global epidemiology of atrial fibrillation. *Nat. Rev. Cardiol.* **11**, 639–654. https://doi.org/10.1038/s41591-014-0118 (2014).

2. Schnabel, R. B. et al. 50-year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* **386**, 154–162. https://doi.org/10.1016/S0140-6736(14)67748-5 (2015).

3. Wolf, P. A., Abbott, R. D. & Kannel, W. B. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* **22**, 983–988. https://doi.org/10.1161/01.str.22.8.983 (1991).

4. Wolf, P. A., Abbott, R. D. & Kannel, W. B. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch. Intern. Med.* **147**, 1561–1564 (1987).

5. Connolly, S. J.

6. Patel, M. R. et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N. Engl. J. Med.* **365**, 883–891. https://doi.org/10.1056/NEJMoa1009638 (2011).

7. Granger, C. B.

8. Tellor, K. B., Patel, S., Armbruster, A. L. & Daly, M. W. Evaluation of dabigatran for appropriateness of use and bleeding events in a community hospital setting. *Am. Health Drug Benefits* **7**, 376–384 (2014).

9. Spinewine, A. et al. Appropriate prescribing in elderly people: how well can it be measured and optimised?. *Lancet* **370**, 173–184. https://doi.org/10.1016/S0140-6736(07)61091-5 (2007).

10. Proietti, M., Raparelli, V., Olshansky, B. & Lip, G. Y. Polypharmacy and major adverse events in atrial fibrillation: observations from the AFFIRM trial. *Clin. Res. Cardiol.* **105**, 410–422. https://doi.org/10.1007/s00392-013-0936-y (2016).

11. Piccini, J. P. et al. Polypharmacy and the efficacy and safety of rivaroxaban in the prevention of stroke in patients with nonvalvular atrial fibrillation. *Circulation* **133**, 352–360. https://doi.org/10.1161/CIRCULATIONAHA.115.018544 (2016).

12. Jaspers Focks, J. et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **369**, 2093–2104. https://doi.org/10.1056/NEJMoa1310907 (2013).

13. Kirchhof, P. et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. * Eur. Heart J.* **37**, 2893–2962. https://doi.org/10.1093/eurheartj/ehw210 (2016).

14. Toller, K. B., Patel, S., Armbruster, A. L. & Daly, M. W. Evaluation of the appropriateness of dosing, indication and safety of rivaroxaban in a community hospital. *J. Clin. Pharm. Ther.* **40**, 447–451. https://doi.org/10.1111/jcpt.12288 (2015).

15. Armbruster, A. L., Buehler, K. S., Min, S. H., Riley, M. & Daly, M. W. Evaluation of dabigatran for appropriateness of use and bleeding events in a community hospital setting. *Am. Health Drug Benefits* **7**, 376–384 (2014).

16. Lee, J. Y. et al. The increased risk of bleeding due to drug-drug interactions in patients administered direct oral anticoagulants. *Thromb. Res.* **195**, 243–249. https://doi.org/10.1016/j.thromres.2020.07.054 (2020).

17. Hripcsak, G. et al. Observational health sciences and informatics (OHDSI): opportunities for observational researchers. *Stud. Health Technol. Inform.* **216**, 574–578 (2015).

18. Overhage, J. M., Ryan, P. B., Reich, C. G., Hartzema, A. G. & Stang, P. E. Validation of a common data model for active safety surveillance research. *J. Am. Med. Inform. Assoc.* **19**, 54–60. https://doi.org/10.1136/amiajnl-2011-000376 (2012).

19. Kim, H. et al. Characterization of anti-seizure medication treatment pathways in pediatric epilepsy using the electronic health record-based common data model. *Front. Neurol.* **11**, 409. https://doi.org/10.3389/fneur.2020.00409 (2020).

20. Choi, S. A. et al. Analysis of antiseizure drug-related adverse reactions from the electronic health record using the common data model. *Epilepsia* **61**, 610–616. https://doi.org/10.1111/epi.16472 (2020).

21. Heidbuchel, H. et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur. Heart J.* **34**, 2094–2106. https://doi.org/10.1093/eurheartj/ehu134 (2013).

22. Heidbuchel, H. et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anti-coagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur. Heart J.* **38**, 2137–2149. https://doi.org/10.1093/eurheartj/ehw058 (2017).

23. Stöllberger, C. Drug interactions with new oral anticoagulants in elderly patients. *Exp. Rev. Clin. Pharmacol.* **10**, 1191–1202. https://doi.org/10.1080/17512433.2017.1370369 (2017).

24. Vazquez, S. R. Drug-drug interactions in an era of multiple anticoagulants: a focus on clinically relevant drug interactions. *Blood* **132**, 2230–2239. https://doi.org/10.1182/blood-2018-06-848747 (2018).

25. Lip, G. Y., Nieuwlaat, R., Pisters, R., Lane, D. A. & Crijns, H. J. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* **137**, 263–272. https://doi.org/10.1378/chest.09-1584 (2010).

26. Nutescu, E., Chuatrisorn, I. & Hellenbart, E. Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. *J. Thromb Thrombolysis* **31**, 326–343. https://doi.org/10.1007/s11239-011-0561-1 (2011).

27. Wang, M. et al. Drug-drug interactions with Warfarin: a systematic review and meta-analysis. *Br. J. Clin. Pharmacol.* https://doi.org/10.1111/bcp.13433 (2021).

28. Burnett, A. E. et al. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J. Thromb Thrombolysis* **41**, 206–232. https://doi.org/10.1007/s11239-015-1310-7 (2016).

29. Steffen, J. et al. The 2018 European heart rhythm association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *Europace* **20**, 1231–1242. https://doi.org/10.1093/europace/euy054 (2018).

30. Wiggins, B. S., Northup, A., Johnson, D. & Senfield, J. Reduced anticoagulant effect of dabigatran in a patient receiving concomitant phenytoin. *Pharmacotherapy* **36**, e5–7. https://doi.org/10.1002/phar.1698 (2016).

31. Stöllberger, C. & Finsterer, J. Recurrent venous thrombosis under rivaroxaban and carbamazepine for symptomatic epilepsy. *Neurolo. Neurochir. Pol.* **51**, 194–196. https://doi.org/10.5604/17395598.100103 (2017).

32. Kumar, S. et al. Non-vitamin K antagonist oral anticoagulants and antipate therapy for stroke prevention in patients with atrial fibrillation: a meta-analysis of randomized controlled trials. *Cardiol. Res. Stud.* **24**, 218–223. https://doi.org/10.1007/s12479-015-000088 (2016).

33. Chang, C. H., Shau, W. Y., Kuo, C. W., Chen, S. T. & Lai, M. S. Increased risk of stroke associated with nonsteroidal anti-inflammatory drugs: a nationwide case–crossover study. *Stroke* **41**, 1884–1890. https://doi.org/10.1161/STROKEAHA.110.585828 (2010).

34. Isbel, E. L. et al. Use of nonsteroidal anti-inflammatory drugs among healthy people and specific cerebrovascular safety. *Int. J. Stroke* **9**, 943–945. https://doi.org/10.1111/1747-4949.120866 (2014).
36. Lamberts, M. et al. Relation of nonsteroidal anti-inflammatory drugs to serious bleeding and thromboembolism risk in patients with atrial fibrillation receiving antithrombotic therapy: a nationwide cohort study. *Ann. Intern. Med.* **161**, 690–698. [https://doi.org/10.7326/m13-1581] (2014).
37. Kent, A. P. et al. Concomitant oral anticoagulant and nonsteroidal anti-inflammatory drug therapy in patients with atrial fibrillation. *J. Am. Coll. Cardiol.* **72**, 255–267. [https://doi.org/10.1016/j.jacc.2018.04.063] (2018).
38. Hellfritzsch, M. et al. Clinical events preceding switching and discontinuation of oral anticoagulant treatment in patients with atrial fibrillation. *Eurosurprice* **19**, 1091–1095. [https://doi.org/10.1093/eurosurpriceevw241] (2017).
39. Marchetti, G., Bernardini, F., Romoli, M. & Urbinati, S. Switching across direct oral anticoagulants: a real-life-setting pilot prospective study. *J. Cardiovasc. Med. (Hagerstown)* [https://doi.org/10.2459/jcm.0000000000001118] (2020).
40. Borne, R. T. et al. Adherence and outcomes to direct oral anticoagulants among patients with atrial fibrillation: findings from the veterans health administration. *BMC Cardiovasc. Disord.* **17**, 236. [https://doi.org/10.1186/s12872-017-0671-6] (2017).
41. Yao, X. et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. *J. Am. Heart Assoc.* **5**, doi: [https://doi.org/10.1161/jaha.115.003074] (2016).
42. Battistella, M., Mamdami, M. M., Juurlink, D. N., 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. [https://doi.org/10.1001/archinte.165.2.189] (2005).
43. Davidson, B. L. et al. Bleeding risk of patients with acute venous thromboembolism taking nonsteroidal anti-inflammatory drugs or aspirin. *JAMA Intern. Med.* **174**, 947–953. [https://doi.org/10.1001/jamainternmed.2014.946] (2014).
44. Schafer, A. I. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. *J. Clin. Pharmacol.* **35**, 209–219. [https://doi.org/10.1002/j.1552-4604.1995.tb04050.x] (1995).
45. Wallace, J. L. How do NSAIDs cause ulcer disease?. *Baillieres Best Pract. Res. Clin. Gastroenterol.* **14**, 147–159. [https://doi.org/10.1016/S1053-8194(99)00065-0] (2000).
46. Harirforoosh, S. & Jamali, F. Renal adverse effects of nonsteroidal anti-inflammatory drugs. *Exp. Opin. Drug Saf.* **8**, 669–681. [https://doi.org/10.1517/14740330903311023] (2009).
47. Lee, S. R. et al. Oral anticoagulation in asian patients with atrial fibrillation and a history of intracranial hemorrhage. *Stroke* **51**, 416–423. [https://doi.org/10.1161/strokeaha.119.028030] (2020).

**Author contributions**

J.Y.L. and S.M.B. conceived of the study. I.Y.O., J.H.L., S.K., J.C., C.H.P., and S.Y. conducted the experiments, data analysis, and critical discussions of the results. All authors contributed to the writing and editing of the manuscript and approved the final draft of the manuscript.

**Funding**

This research was supported by the Seoul National University Bundang Hospital Research Fund (14-2020-039), and the Technology Innovation Program (20004927, ‘Upgrade of CDM based Distributed Biohealth Data Platform and Development of Verification Technology’) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea).

**Competing interests**

The authors declare no competing interests.

**Additional information**

**Supplementary Information** The online version contains supplementary material available at [https://doi.org/10.1038/s41598-021-01786-2](https://doi.org/10.1038/s41598-021-01786-2).

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