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The Official Journal of the American Academy of Neurology



Neurology Publish Ahead of Print  
DOI:10.1212/WNL.0000000000207422

Association of Alternative Anticoagulation Strategies and Outcomes in Patients With  
Ischemic Stroke While Taking a Direct Oral Anticoagulant

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*Neurology*® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

**Equal Author Contribution:**

Bonaventure Y Ip contributed as the first author. David J Seiffge and Thomas W Leung contributed equally as co-senior authors.

**Contributions:**

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Ho Ko: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

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Alan Yao: Major role in the acquisition of data; Analysis or interpretation of data

Grace Lai-Hung Wong: Major role in the acquisition of data; Analysis or interpretation of data

Terry Cheuk-Fung Yip: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

Xinyi Leng: Study concept or design; Analysis or interpretation of data

Howard Chan: Major role in the acquisition of data; Study concept or design

Helen Chan: Major role in the acquisition of data; Analysis or interpretation of data

Vincent Mok: Study concept or design; Analysis or interpretation of data

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David Seiffge: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Thomas W Leung: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

**Figure Count:**

3

**Table Count:**

2

**Search Terms:**

[ 2 ] All Cerebrovascular disease/Stroke, [ 5 ] Embolism, [ 290 ] Cardiac, [ 6 ] Infarction, [ 322 ] Class II

**Acknowledgment:**

The authors acknowledge the contributions from Dr. Robert Dan (The Chinese University of Hong Kong), Mrs. Sophia Dan (The Chinese University of Hong Kong), Ms. Anki Miu (The Chinese University of Hong Kong), Ms. Trista Hung (The Chinese University of Hong Kong) and Kwok Tak Seng Centre for Stroke Research and Intervention (The Chinese University of Hong Kong). Dr. Robert Dan provided general advice for the study. Mrs. Sophia Dan provided general advice for the study. Ms Anki Miu provided clerical assistance for the study. Ms Trista Hung provided clerical assistance for the study. Kwok Tak Seng Centre for Stroke Research and Intervention provided clerical assistance for the study.

**Study Funding:**

The authors report no targeted funding.

**Disclosure:**

Y.M.B. Ip, H. Ko, L. Lau, A. Yao, G.L.H. Wong, T.C.F. Yip, X. Leng, H. Chan, H. Chan, V. Mok, Y. Soo and T.W. Leung report no disclosures relevant to the manuscript. G. Lau received grants from Croucher Foundation, Research Fund Secretariat of the Food and Health Bureau, Innovation and Technology Bureau, Research Grants Council, Amgen, Boehringer Ingelheim, Eisai and Pfizer; and consultation fees from Amgen, Boehringer Ingelheim, Daiichi Sankyo and Sanofi, all outside the submitted work. D. Seiffge received research funding from the Bangerter Rhyner Foundation and AstraZeneca. He served on advisory boards, consultancy or speaker bureau for AstraZeneca, Bioxodes, VarmX, Javeline and Vifor. All fees were paid to his employer and used for research funding. All outside the submitted work.

**Preprint DOI:****Received Date:**

2022-12-20

**Accepted Date:**

2023-04-03

**Handling Editor Statement:**

Submitted and externally peer reviewed. The handling editor was Editor-in-Chief José Merino, MD, MPhil, FAAN.

**ABSTRACT**

**Background and Objectives:** Ischemic stroke despite direct oral anticoagulant (DOAC) is increasingly common and portends high risk of subsequent ischemic stroke. Efficacy and safety of antithrombotic regimens following the condition are unclear. We aimed to compare the outcomes of patients with ischemic stroke despite DOAC with and without an alternative antithrombotic regimen, and determine the risk factors of recurrent ischemic stroke while on anticoagulation.

**Methods:** In a population-based, propensity-score weighted, retrospective cohort study, we compared the clinical outcomes of DOAC-to-warfarin switch, DOAC-to-DOAC switch (DOAC<sub>switch</sub>) or addition of antiplatelet agents, with unchanged DOAC regimen (DOAC<sub>same</sub>) among non-valvular atrial fibrillation (NVAF) patients who developed the first ischemic stroke despite DOAC from 1<sup>st</sup> January 2015 to 31<sup>st</sup> December 2020 in

Hong Kong. Primary outcome was recurrent ischemic stroke. Secondary outcomes were intracranial hemorrhage, acute coronary syndrome and death. We performed competing risk regression analyses to compare the clinical endpoints, and determined the predictors of recurrent ischemic stroke in an unweighted multivariable logistic regression model.

**Results:** During the 6-year study period, among 45,946 AF patients on DOAC as stroke prophylaxis, 2,908 patients developed ischemic stroke despite DOAC. 2,337 NVAF patients were included in the final analyses. Compared to DOAC<sub>same</sub>, warfarin (aHR 1.96, 95% CI 1.27-3.02, p=0.002) and DOAC<sub>switch</sub> (aHR 1.62, 95% CI 1.25-2.11, p-value <0.001) were associated with increased risk of recurrent ischemic stroke. In DOAC<sub>same</sub> group, adjunctive antiplatelet agent was not associated with reduced risk of recurrent ischemic stroke. Diabetes mellitus, concurrent cytochrome P450/P-glycoprotein (CYP/P-gp) modulators and large artery atherosclerotic disease (LAD) were predictors of recurrent ischemic stroke.

**Discussion:** In NVAF patients with ischemic stroke despite DOAC, the increased risk of recurrent ischemic stroke with switching to warfarin called for caution against such practice, while the increased ischemic stroke with DOAC-to-DOAC switch demands further studies. Adjunctive antiplatelet agent did not appear to reduce ischemic stroke relapse. As diabetes mellitus, use of CYP/P-gp modulators and LAD were predictors of recurrent ischemic stroke, further investigations should evaluate if strict glycemic control, DOAC level monitoring and routine screening for carotid and intracranial atherosclerosis may reduce ischemic stroke recurrence in these patients.

**Classification of Evidence:** This study provides Class II evidence that in patients with non-valvular atrial fibrillation suffering an ischemic stroke while being treated with a

DOAC, continuing treatment with that DOAC is more effective at preventing recurrent ischemic stroke than switching to a different DOAC or to warfarin.

## **BACKGROUND**

Direct oral anticoagulants (DOAC) effectively prevent ischemic stroke in patients with non-valvular atrial fibrillation (NVAF) [1]. Yet, ischemic stroke despite DOAC still occurred in 1-2% of AF patients in pivotal randomized controlled trials; and up to 30% of AF patients who developed ischemic stroke were on oral anticoagulants at stroke onset [2-6]. As the condition often precluded intravenous thrombolytic therapy and predicted high risk of recurrence [7], it is critical to improve secondary stroke prevention for patients with ischemic stroke despite DOAC.

In practice, there are broadly 3 alternative antithrombotic regimens following ischemic stroke despite DOAC: 1) switching between the four DOACs (apixaban, dabigatran, edoxaban and rivaroxaban); 2) switching to warfarin; and 3) addition of antiplatelet agents. These therapeutic options were highly variable across different regions. For instance, while the majority of German stroke neurologists favored switching between DOACs [8], in an Irish study, thrombotic events during DOAC usage commonly prompted switching to warfarin treatment [9]. Nonetheless, in an epidemiological study, adjustment of oral anticoagulant therapy collectively did not reduce subsequent ischemic stroke risk [7]. As ischemic stroke despite DOAC is increasingly common due to surging DOAC prescriptions [10-12], investigating the outcomes of patients on alternative

antithrombotic regimens following an episode of ischemic stroke despite DOAC may inform treatment decisions.

In this population-based analysis, we compared the clinical outcomes of NVAF patients with ischemic stroke despite DOAC who were kept on the same DOAC regimen, with those given alternative DOAC, warfarin or adjunctive antiplatelet agent, with a primary research question of whether switching the original DOAC to another DOAC or warfarin was associated with reduced risk of recurrent ischemic stroke.

## **METHODOLOGY**

### **Study Design and data source**

We performed a population-based retrospective cohort study and recruited all patients with ischemic stroke despite DOAC admitted to public hospitals in Hong Kong from 1<sup>st</sup> January 2015 to 31<sup>st</sup> December 2020. Clinical parameters were retrieved via the Clinical Data Analysis and Reporting System (CDARS), a territory-wide database that contains clinical information of more than 90% of the 7.5-million population in Hong Kong. CDARS had a coding accuracy of 85-100% according to previous studies [13]. We followed the STROBE reporting guidelines.

### **Study Subjects**

We enrolled NVAF patients who developed ischemic stroke while on apixaban, dabigatran, edoxaban, or rivaroxaban during the 6-year study period. We recorded the baseline clinical and laboratory parameters (see *Covariates* section). Based on

*International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM)*, diagnoses of AF, ischemic stroke, intracranial hemorrhage, congestive heart failure, hypertension, diabetes mellitus (DM), peripheral vascular disease, acute coronary syndrome (ACS), hyperlipidaemia, arterial and venous thromboembolism, were retrieved. We collected any documented history of small vessel disease and large intra- or extracranial artery atherosclerotic disease (LAD). We recorded use of antiplatelet agents (clopidogrel, aspirin, cilostazol, ticagrelor), intensity of statins (none, low, moderate, high [14]), cytochrome P450 or P-glycoprotein (CYP/P-gp) modulators (phenytoin, valproate, carbamazepine, amiodarone, dronedarone, rifampicin, cyclosporin and verapamil), non-steroidal anti-inflammatory drugs (NSAIDs). CHADS2-Vasc and HAS-BLED scores after the first ischemic stroke despite DOAC were calculated [15]. We excluded patients with active malignancy, mitral stenosis, left ventricular thrombus, valvular replacement, left atrial appendage occlusion, atrial septal defect, polycythemia rubra vera, essential thrombocytosis and thrombophilia. We also excluded patients who had anticoagulation discontinued after the stroke episode, or with inappropriate DOAC dosage with respect to body weight, renal function and age at stroke onset. eTable 1 in the Supplement listed the ICD9-CM codes used in the study.

### **Ischemic stroke despite DOAC**

Ischemic stroke despite DOAC was defined as an episode of acute ischemic stroke during DOAC usage. Anticoagulation type and dosage immediately before and after the first ischemic stroke despite DOAC were retrieved. Anticoagulation therapy after the first episode of ischemic stroke despite DOAC was classified into 1) unchanged group

(DOAC<sub>same</sub>); 2) DOAC-to-warfarin group; or 3) DOAC-to-another DOAC group (DOAC<sub>switch</sub>) i.e., switching to another DOAC. We also retrieved antiplatelet use before and within 8 weeks of the index ischemic stroke event during DOAC usage.

### **Outcome definitions**

Primary outcome was recurrent ischemic stroke following the first episode of ischemic stroke despite DOAC. Secondary outcomes were intracranial hemorrhage, ACS and all-cause death.

### **Covariates**

We included 5 demographic variables (age, gender, history of smoking or drinking and modified Rankin Scale after the first ischemic stroke despite DOAC), 12 medical comorbidities (intracranial haemorrhage, congestive heart failure, hypertension, DM, ischemic heart disease, arterial and venous thromboembolism, peripheral vascular disease, chronic kidney and liver disease, small vessel disease, LAD), 9 baseline laboratory parameters (total cholesterol, low- and high-density lipoprotein cholesterol, triglycerides, glycated haemoglobin A1c, creatinine, alanine transaminase, haemoglobin and platelet count), and 5 classes of medications (CYP or P-gp modulators, NSAIDs, antiplatelet agents and statins) in our propensity score (PS) weighting model and secondary unweighted analyses.



## **Standard Protocol Approvals, Registrations, and Patient Consents**

The institutional review board approved the study (Joint CUHK-NTEC Clinical Research Ethics Committee Reference No. 2021.349). The need for written informed consent was waived due to the de-identified data.

## **Statistical Analyses**

In order to minimize the effects of confounding variables, we developed a PS weighting model for comparisons between the average treatment effect of each oral anticoagulant strategy (warfarin, DOAC<sub>switch</sub>) with the reference group (DOAC<sub>same</sub>) by inverse probability of treatment weighting. We estimated the PS of each patient by generalized boosted models (GBM) that included the covariates mentioned above. The optimal iteration of GBM was determined by four stopping rules described previously [16], the stopping rule with the best covariate balance and effective sample size was selected. We adjusted covariates that failed to achieve an absolute standardized mean difference of <0.1 in a doubly robust model. Time-to-event was determined as the time lapse (in months) between the date of first ischemic stroke despite DOAC and the date of the outcome events, while that for patients without outcome occurrence was defined as the time lapse between the date of first ischemic stroke despite DOAC and the earliest date among 1) study-end, 2) death, and 3) DOAC discontinuation. Fine-Gray regression model was used to analyze the primary and secondary endpoints with death as a competing risk while Cox regression was used to analyze all-cause death. We used the Gray's method to estimate the cumulative incidence of the primary and secondary endpoints and the Kaplan Meier method to estimate the cumulative incidence of death. The Bonferroni method was

used to correct for multiple testing. A two-sided test with p-value <0.05 was considered statistically significant.

## **Secondary analyses**

We performed three planned secondary analyses:

### **I) Antiplatelet therapy**

To evaluate the safety and efficacy of antiplatelet therapy, we performed a PS weighted analysis for patients with new adjunctive antiplatelet therapy within 8 weeks of the index ischemic stroke despite DOAC, versus patients with no antiplatelet therapy before and after the event. We confined the analysis to the DOAC<sub>same</sub> group.

### **II) DOAC regimen after the index ischemic stroke during DOAC**

In an exploratory analysis, we compared the outcomes of patients who received apixaban 5mg twice daily (API10), dabigatran 110mg twice daily (DAB220), dabigatran 150mg twice daily (DAB300), edoxaban 60mg daily (EDO60) or rivaroxaban 20mg (RIV20) daily after the first ischemic stroke despite DOAC, regardless of the initial DOAC regimen in a PS weighted analysis. We excluded patients who took apixaban 2.5mg twice daily, edoxaban 30mg daily, or rivaroxaban 15mg daily in this analysis owing to the higher intrinsic risk of cerebrovascular events from the advanced age, renal impairment and low body weight that could bias the comparison [4, 17]. We included dabigatran 110mg twice daily in this comparison as the regimen was considered a standard dosage locally, i.e. dabigatran recipients who received DAB220 may otherwise be eligible for DAB300, in contrast to European summary of product characteristics (SmPC) on dabigatran dosage [18].

### **III) Risk factors associated with recurrent ischemic stroke**

To identify risk factors of recurrent ischemic stroke, we compared the demographics, medical co-morbidities, laboratory parameters, and medications among patients with and without recurrent ischemic stroke in an unweighted logistic regression analysis. We limited this analysis to the DOAC<sub>same</sub> group. Covariates that were clinically relevant; or reached a p-value  $\leq 0.25$  in the univariate logistic regression model were subjected to a final multivariate logistic regression model. Schoenfeld residual plots was used to determine the variability of the computed hazard ratios with time.

Normally distributed continuous variables, non-normally distributed continuous variables and categorical variables were expressed as mean $\pm$ SD, median (interquartile range) and number (percentage) respectively. Assuming missing baseline data to be missing at random, we substituted missing data with values computed by multiple imputation with chained equations that created 20 complete data sets after the first 20 iterations. In descending order of missingness, missing data on HbA1c (17.9%), lipid profile (13.8%), alkaline phosphatase (0.1%), alanine transferase (0.04%), hemoglobin (0.04%), platelet (0.04%) were imputed and kept within reasonable ranges. We performed sensitivity analyses using patients with complete data. All statistical analyses were performed with RStudio V.1.4.1717.

#### **Data Availability Statement**

Anonymized data not published within this article will be made available by request from any qualified investigator.

## **RESULTS**

From 1<sup>st</sup> January 2015 to 31<sup>st</sup> December 2020, 2,908 out of 45,496 AF patients developed ischemic stroke despite DOAC. We excluded 571 patients with valvular AF, thrombophilia, underdosed DOAC or discontinuation of anticoagulation after the first ischemic stroke despite DOAC (Figure 1). Among 2,337 patients who were included in the final analyses, 1,652(70.7%) patients remained on the same DOAC regimen (DOAC<sub>same</sub>); 477(20.4%) patients received an alternative DOAC (DOAC<sub>switch</sub>); 122(5.2%) patients were prescribed warfarin, 86(3.7%) patients stepped up from dabigatran 110mg twice daily to 150mg twice daily. We excluded patients with increased dabigatran dosage from the primary analysis due to the small sample size. Over a median follow-up period of 16.5 months, 315(13.4%) patients experienced another episode of ischemic stroke.

### **Primary analysis**

Compared to DOAC<sub>same</sub>, warfarin (adjusted hazard ratio [aHR] 1.96, 95% confidence interval [CI] 1.29-3.02, p=0.002) and DOAC<sub>switch</sub> (aHR 1.62, 95%CI 1.25-2.11, p<0.001) were associated with an increased risk of recurrent ischemic stroke (Figure 1A). DOAC<sub>switch</sub> was also associated with an increased risk of ACS (aHR 2.18, 95%CI 1.29-6.67 p=0.003, Figure 1C). DOAC<sub>switch</sub> and warfarin groups were not associated with intracranial hemorrhage or death (Tables 1–2, Figure 2, A–D).

### **Secondary analyses**

#### **Adjunctive antiplatelet therapy**

Among 1,652 patients in the DOAC<sub>same</sub> group, 249(15.1%) patients were started on antiplatelet agents within 8 weeks of the first ischemic stroke despite DOAC (eTable 2 in the Supplement), 1,166 (70.6%) patients did not receive any antiplatelet therapy. Adjunctive antiplatelet treatment did not reduce risk of recurrent ischemic stroke (aHR 1.28, 95%CI 0.88-1.84, p=0.188), intracranial hemorrhage (aHR 1.20, 95%CI 0.54-2.68, p=0.654), ACS (aHR 1.71, 95%CI 0.80-3.66, p=0.167) or death (aHR 1.09, 95%CI 0.84-1.41, p=0.512) (Table 2, Figure 3, A–D).

### **Associated factors of recurrent ischemic stroke**

After adjusting covariates that were clinically relevant or reached a p-value of  $\leq 0.25$  in the univariate logistic regression analyses (eTable 3 in the Supplement), our multivariable logistic regression analysis within the DOAC<sub>same</sub> group revealed that advanced age (aHR 1.02, 95%CI 1.00-1.03, p=0.029), history of DM (aHR 1.49 95%CI 0.73-1.20, p=0.002), use of CYP/P-gp modulators (aHR 1.39, 95%CI 1.05-1.84, p=0.021) and LAD (aHR 2.84, 95%CI 1.16-6.91, p=0.021) were associated with recurrent ischemic stroke (eTable 4). Schoenfeld residual plots suggested that these risk factors did not vary significantly with time (p=0.131) (eFigure 1).

### **Between-DOAC comparison**

After the first ischemic stroke despite DOAC, 371(16.4%) patients received API10; 516(22.9%) received DAB220; 261(11.5%) received DAB300; and 297(13.2%) received RIV20. Edoxaban was excluded due to the small sample size (n=47). Covariate balance was listed in eTable 5 with API10 as the reference group. The risks of recurrent ischemic

stroke were comparable among the four DOAC regimens. Compared to API10, DAB220 was associated with lower risk of intracranial hemorrhage (aHR 0.27, 95%CI 0.15-0.99,  $p=0.019$ ), RIV20 was associated with higher risk of ACS (aHR 6.20, 95%CI 1.41-27.30,  $p=0.016$ ). DAB300 was associated with a lower risk of all-cause death (aHR 0.42, 95%CI 0.24-0.73,  $p=0.003$ ) (eTable 6, eFigure 2, A–D).

### **Sensitivity analyses**

Sensitivity analyses of 1,848 patients without any missing data yielded similar findings: warfarin and DOAC<sub>switch</sub> were associated with increased risk of recurrent ischemic stroke. Addition of antiplatelet after the first ischemic stroke despite DOAC was not associated with a lower risk of subsequent ischemic stroke. eTables 7–12 in the Supplement listed the details of sensitivity analyses.

### **Classification of Evidence**

This study provides Class II evidence that in patients with non-valvular atrial fibrillation suffering an ischemic stroke while being treated with a DOAC, continuing treatment with that DOAC is more effective at preventing recurrent ischemic stroke than switching to a different DOAC or to warfarin.

## **DISCUSSION**

In this population-based study of NVAF patients with an episode of ischemic stroke despite DOAC, we found: 1) Switching from the original DOAC to warfarin or another DOAC was associated with an increased risk of recurrent ischemic stroke. 2) Addition of

antiplatelet agents did not reduce the risk of recurrent ischemic stroke. 3) Recurrent ischemic stroke while on oral anticoagulation was associated with advanced age, DM, concurrent use of CYP/P-gp inducers and large artery atherosclerosis.

To our knowledge, this is the first population-based study that assessed the impact of antithrombotic strategies after the first episode of ischemic stroke while on DOAC. A key finding of our study is that switching from DOAC to warfarin in NVAF patients may increase the risk of ischemic stroke. Although the longer half-life, ease of therapeutic drug monitoring and data availability for intracranial atherosclerotic disease might favor switching to warfarin [19], real-world studies consistently revealed a higher thromboembolic risk with warfarin compared to DOAC [20]. The lower time-within-therapeutic-range in warfarin recipients might play a role in the increased recurrent ischemic stroke risk observed [21]. Since switching to warfarin following a recurrent thrombotic episode with DOAC is popular [9, 22], our study results caution against such practice unless strong indications such as renal insufficiency [18], antiphospholipid syndrome [23], or valvular AF are present [18].

Interestingly, DOAC-to-DOAC switch was associated with an increased risk of recurrent ischemic stroke compared to an unchanged DOAC regimen with well-balanced covariates. The underlying mechanism was unclear. Selection bias may result from unmeasured covariates. We postulate that DOAC adjustment could have been more frequent among patients with ischemic stroke risk unexplained by conventional cardiovascular risk factors. For example, the presence of left atrial appendage thrombus

[24], cardiomyopathies [25], or pharmacogenomic susceptibility such as *ABCB1* and *CES1* single nucleotide polymorphisms may predispose to cardioembolic ischemic strokes [26, 27]. The resultant cortical or wedge-shaped infarct topography may prompt DOAC switching following a verdict of ‘DOAC failure’ [28]. Of note, the higher risk of ACS with DOAC switching might reflect the unmeasured thromboembolic risk and subsequent coronary embolism. Future prospective studies on heart-brain axis and pharmacogenomic assessment should evaluate if these factors would have influenced the decision on DOAC switching.

Adjunctive antiplatelet therapy to DOAC did not appear to reduce risk of ischemic stroke. Although recent studies showed the efficacy of aspirin in combination with rivaroxaban for cardiovascular protection in atherosclerotic diseases [29, 30], our study suggested that this ‘dual-pathway inhibition’ strategy might not be similarly effective in a population purely consisted of NVAf patients. Some studies even found a higher risk of major cardiovascular events in AF patients with dual antithrombotic therapy [31, 32]. However, these comparisons were confounded by the higher prevalence of cardiovascular risk factors in patients who received dual antithrombotic therapy [31], as compared to our cohort with a low incidence of ischemic heart disease of less than 4% in both groups. Overall, our study did not find a clinical benefit of adjunctive antiplatelet therapy in NVAf patients who developed ischemic stroke despite DOAC.

In the unweighted multivariable regression analysis, DM was associated with an increased risk of recurrent ischemic stroke. Although DM is modifiable and predicted



ischemic stroke in AF patients [15], the mean glycosylated hemoglobin A1c were not significantly different among DOAC patients with and without recurrent cerebral ischemia in our cohort. Another study also found that the majority of patients with ischemic stroke despite DOAC had satisfactory glycemic control at stroke onset [33]. Further longitudinal studies should determine whether a stringent long-term glycemic control may lower the risk of recurrent ischemic stroke among DOAC recipients. Apart from DM, the use of CYP/P-gp modulators also independently predicted the risk of recurrent ischemic stroke. Due to the small sample size (n=157), we were unable to stratify individual drugs for further analysis. Nevertheless, DOAC level monitoring maybe necessary in these patients to detect under-anticoagulation from drug-drug interactions between DOAC and CYP/P-gp modulators [16, 34].

In our exploratory comparison of different DOAC regimens, all four drug regimens had comparable risk of recurrent ischemic stroke. The lower risk of intracranial hemorrhage with dabigatran 110mg twice daily was similar to population-based studies that included patients without ischemic stroke despite DOAC [35]. This observation may be related to the preservation of blood-brain barrier function through direct thrombin inhibition [36]. On the other hand, the reason behind the lower risk of ischemic heart disease with apixaban 5mg twice daily compared to rivaroxaban 20mg daily is unclear, as previous studies only reported a lower risk of major cardiovascular events with DOAC compared to warfarin without robust comparisons among DOACs [37, 38]. Although the pharmacological mechanisms behind these observations are yet to be confirmed, our findings hinted the importance of personalized DOAC therapy based on individual risk

profile. The lower all-cause death with dabigatran 150mg twice daily, however, could be biased by the younger age, better functional status and renal function. It should also be noted that there were no pre-specified dosage adjustment criteria for dabigatran in patients with normal renal function during the study period. Patients on dabigatran 110mg twice daily might otherwise be eligible for the 150mg twice daily regimen. In comparison to the European SmPC recommendation on dabigatran 110mg twice daily in patients older than 80 years old, on concomitant verapamil or with high bleeding risks [18], patients who received dabigatran 110mg twice daily in our cohort may be younger with lower bleeding propensities. Therefore, caution should be exercised in extrapolating our study findings on dabigatran recipients under the European dosing guidelines.

Lastly, to put our findings into perspective, antithrombotic regimen is only part of the secondary stroke prophylaxis. A comprehensive cardiovascular workup and stringent cardiovascular risk factor control may be equally important in patients with ischemic stroke despite DOAC, as reflected by the risk of recurrent ischemic stroke in patients with LAD.

Our study had several limitations. First, limited by the retrospective study design, unmeasured confounders maybe present. Factors such as DOAC level, compliance and competing stroke etiologies could have biased the comparisons. Although we attempted to retrieve competing stroke etiologies, 12-14% of ischemic stroke patients received incomplete cardiovascular workup for ischemic stroke according to our previous study [39]. Future prospective studies or clinical trials with specific coagulation assays, drug

adherence measures, heart-brain axis assessment and causative classification of stroke are warranted to evaluate whether these factors might influence the treatment decisions and the subsequent stroke risk following an episode of ischemic stroke despite DOAC [27]. Second, the sample size of warfarin group was relatively small and the time-within-therapeutic-range was not measured. Although the incidence of intracranial hemorrhage was numerically higher in warfarin group than the DOAC<sub>same</sub> group, the sample size may not be powered to detect statistical significance. Third, we did not evaluate the outcomes of patients who underwent left atrial appendage occlusion, which is also a potential intervention for patients with ischemic stroke despite DOAC. Lastly, as 98% of our study population were ethnic Chinese, the study findings remained to be confirmed in other ethnicities given the potential disparities in pharmacogenomics and ischemic stroke etiologies [26, 39].

To conclude, in NVAF patients who developed ischemic stroke despite DOAC, the increased risk of recurrent ischemic stroke with switching to warfarin called for caution against such practice, while the increased ischemic stroke with DOAC-to-DOAC switch demands further studies. Adjunctive antiplatelet agent did not appear to reduce ischemic stroke relapse. As DM, use of CYP/P-gp modulators and LAD were predictors of recurrent ischemic stroke, further investigations should evaluate if strict glycemic control, DOAC level monitoring and routine screening for carotid and intracranial atherosclerosis may reduce ischemic stroke recurrence in these patients.

**WNL-2023-000260 sup --- <http://links.lww.com/WNL/C839>**

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**Table 1. Imputed patient characteristics and covariate balance across different anticoagulation regimens after the first ischemic stroke despite DOAC**

	DOAC <sub>same</sub>	DOAC <sub>switch</sub>	AMSD	Warfarin	AMSD
n	1652	477		122	
<b>Demographics</b>					
Age mean±sd	78.9±9.8	79.1±9.2	0.006	76.4±10.4	0.142
Male n(%)	830(50.2)	215(45.1)	0.034	58(47.5)	0.044
Drinker n(%)	17(1.0)	6(1.3)	0.002	1(0.8)	0.004
Smoker n(%)	12(0.7)	3(0.6)	0.000	2(1.6)	0.007
Baseline mRS median(iqr)	1(3)	1(4)	0.016	1(4)	0.187
Chinese ethnicity n(%)	1622(99.0)	482(99.4)	0.005	119(98.3)	0.002
<b>Medical co-morbidities</b>					
Intracranial hemorrhage n(%)	63(3.8)	26(5.5)	0.015	5(4.1)	0.023
Peripheral vascular disease n(%)	132(8.0)	28(5.9)	0.021	9(7.4)	0.003
Ischemic heart disease n(%)	142(8.6)	38(8.0)	0.015	17(13.9)	0.055
Diabetes Mellitus n(%)	565(34.2)	162(34.0)	0.006	46(37.7)	0.088
Congestive heart failure n(%)	589(35.7)	194(40.7)	0.033	62(50.8)	0.177
Hypertension n(%)	1132(68.5)	336(70.4)	0.020	90(73.8)	0.079
Hyperlipidemia n(%)	546(33.1)	150(31.4)	0.003	45(36.9)	0.039
Chronic liver disease n(%)	13(0.8)	4(0.8)	0.003	1(0.8)	0.001
Chronic kidney disease n(%)	13(0.8)	21(4.4)	0.017	20(16.4)	0.100
Arterial thromboembolism n(%)	42(2.5)	12(2.5)	0.004	5(4.1)	0.008
Venous thromboembolism n(%)	91(5.5)	27(5.7)	0.001	15(12.4)	0.050
Major bleeding n(%)	11(0.7)	3(0.6)	0.002	1(0.8)	0.002
Gastrointestinal bleeding n(%)	114(6.9)	45(9.4)	0.019	14(11.5)	0.050
Non-major bleeding n(%)	88(5.3)	30(6.3)	0.003	12(9.8)	0.062
Small vessel disease n(%)	158(9.6)	34(7.5)	0.029	11(9.1)	0.011
Large artery atherosclerosis n(%)	41(2.5)	10(2.1)	0.002	3(2.4)	0.003
CHADS <sub>2</sub> Vasc mean±sd	4.6±1.7	4.5±1.7	NA	4.6±1.8	NA
HASBLED mean±sd	2.4±0.9	2.3±1.0	NA	2.4±1.1	NA
<b>Concurrent medications</b>					
Antiplatelet n(%)	249(15.1)	128(26.8)	0.028	22(18.0)	0.098
NSAIDs n(%)	119(7.2)	38(8.0)	0.008	8(6.6)	0.004
CYP/P-gp modulators n(%)	237(14.3)	74(15.5)	0.003	29(23.8)	0.099
Low-intensity statin n(%)	460(27.8)	126(26.4)	0.021	27(22.3)	0.001
Moderate-intensity statin n(%)	359(21.7)	146(30.6)	0.003	57(47.1)	0.027
High-intensity statin n(%)	32(1.9)	80(16.8)	0.003	28(23.1)	0.004
<b>Laboratory Parameters</b>					
HbA1c(%) mean±sd	6.3±1.1	6.2±1.0	0.043	6.3±1.2	0.081
ALT(IU/L) mean±sd	29.5±34.6	32.6±65.2	0.054	47.0±160.7	0.136
Creatinine(umol/L) mean±sd	99.4±45.7	97.1±40.6	0.037	132.7±109.4	0.323

HDL-C(mmol/L) mean±sd	1.2±0.3	1.3±0.4	0.037	1.2±0.3	0.108
Hemoglobin(g/dL) mean±sd	12.2±1.9	12.3±1.8	0.011	12.0±1.8	0.106
LDL-C(mmol/L) mean±sd	1.9±0.6	2.0±0.7	0.040	1.9±0.6	0.060
Platelet(10 <sup>9</sup> /L) mean±sd	218.6±72.1	225.5±78.8	0.048	222.7±79.2	0.025
Total cholesterol(mmol/L) mean±sd	3.7±0.8	3.8±0.8	0.033	3.6±0.8	0.021
Triglyceride(mmol/L) mean±sd	1.2±0.6	1.1±0.5	0.063	1.2±0.6	0.061
ALP(IU/L) mean±sd	91.9±67.4	92.9±58.9	0.006	96.8±47.8	0.060
APTT(s) median(iqr)	35.6±8.5	33.8±6.6	0.102	40.1±7.7	NA
PT(s) median(iqr)	15.4±3.8	15.6±3.8	0.038	25.4±7.8	NA
<b>Annual incidence rate of outcome (%)</b>					
Ischemic stroke	8.7%	12.8%	NA	12.6%	NA
Intracranial hemorrhage	1.5%	1.6%	NA	5.3%	NA
Acute coronary syndrome	0.8%	2.4%	NA	0.6%	NA
Mortality	16.0%	12.0%	NA	15.0%	NA

**Abbreviations:** ALT: alanine transferase; AMSD: absolute mean standardized difference; APTT: activated partial thromboplastin time; CYP: cytochrome P450; DOAC: direct oral anticoagulant; HbA1c: glycated hemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; mRS: modified Rankin scale; NA: not applicable; NSAIDs: non-steroidal anti-inflammatory drugs; P-gp: p-glycoprotein; PT: prothrombin time



**Table 2. Outcome comparisons among antithrombotic strategies after the first ischemic stroke despite DOAC**

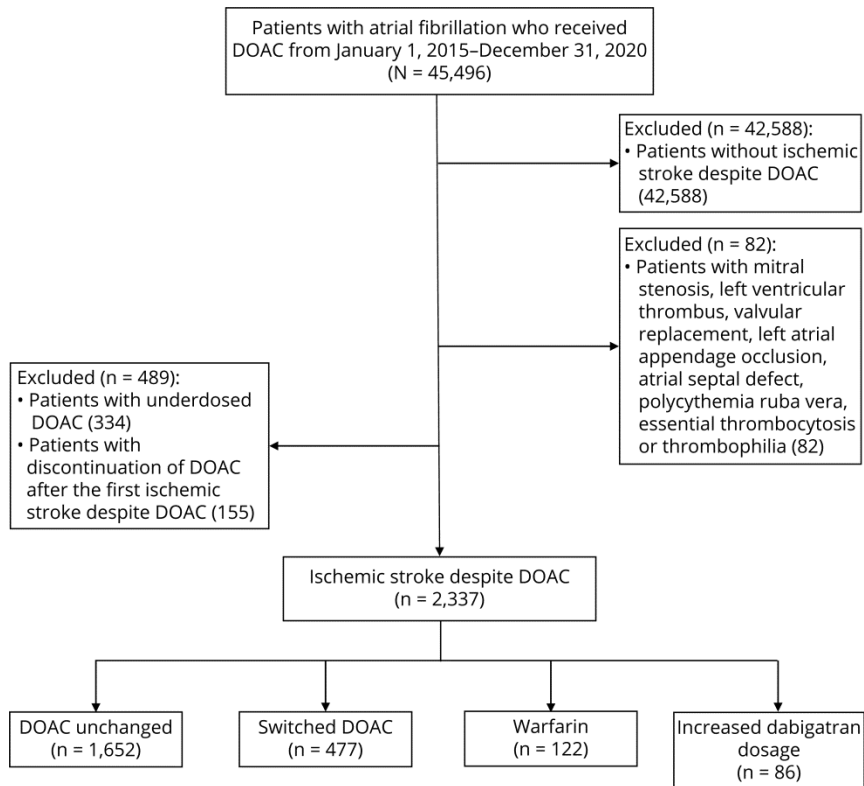
	Warfarin (n=122) vs DOAC <sub>same</sub> (Reference, n=1652)			DOAC <sub>switch</sub> (n = 477) vs DOAC <sub>same</sub> (Reference, n=1652)			New antiplatelet (n=249) vs No antiplatelet (Reference, n=1166)		
	Median follow-up (months)	aHR (95%CI)	p-value	Median follow-up (months)	aHR (95%CI)	p-value	Median follow-up (months)	aHR (95%CI)	p-value
Ischemic stroke	17	1.96 (1.27-3.02)	0.002	16	1.62 (1.25-2.11)	<0.001	17	1.28 (0.88-1.84)	0.188
Intracranial hemorrhage	19	1.51 (0.64-3.54)	0.342	18	1.06 (0.59-1.90)	0.837	19	1.20 (0.54-2.68)	0.654
ACS	20	1.69 (0.33-8.81)	0.529	18	2.18 (1.29-3.67)	0.003	19	1.71 (0.80-3.66)	0.167
Death	18	1.36 (0.92-2.01)	0.122	18	0.98 (0.81-1.19)	0.833	18	1.09 (0.84-1.41)	0.512

**Abbreviations:** ACS: acute coronary syndrome; aHR: adjust hazard ratio; CI: confidence interval; DOAC: direct oral anticoagulant

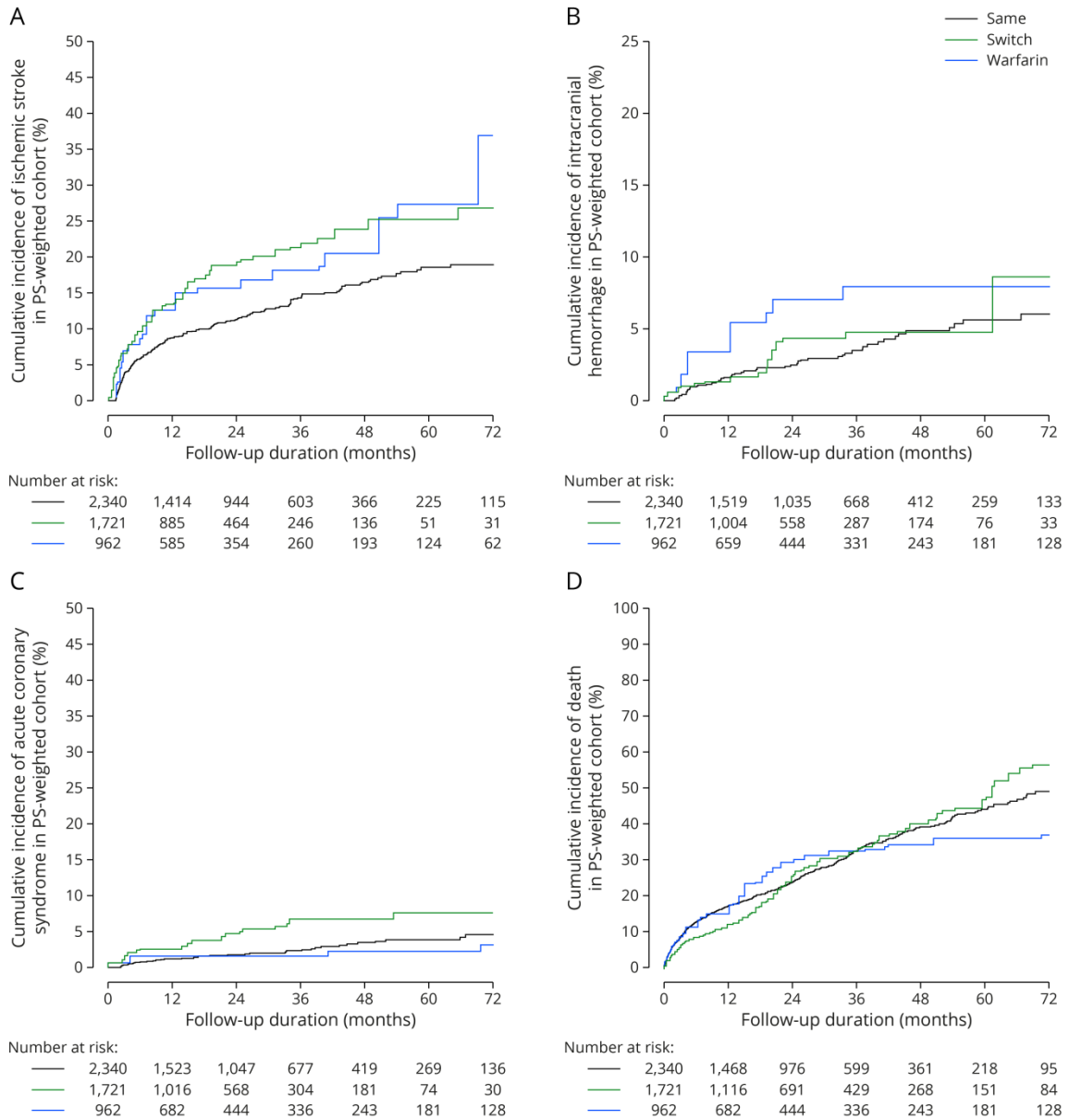
**N.B.:** Comparisons between antiplatelet regimens were within the DOAC<sub>same</sub> group

## **FIGURE LEGEND**

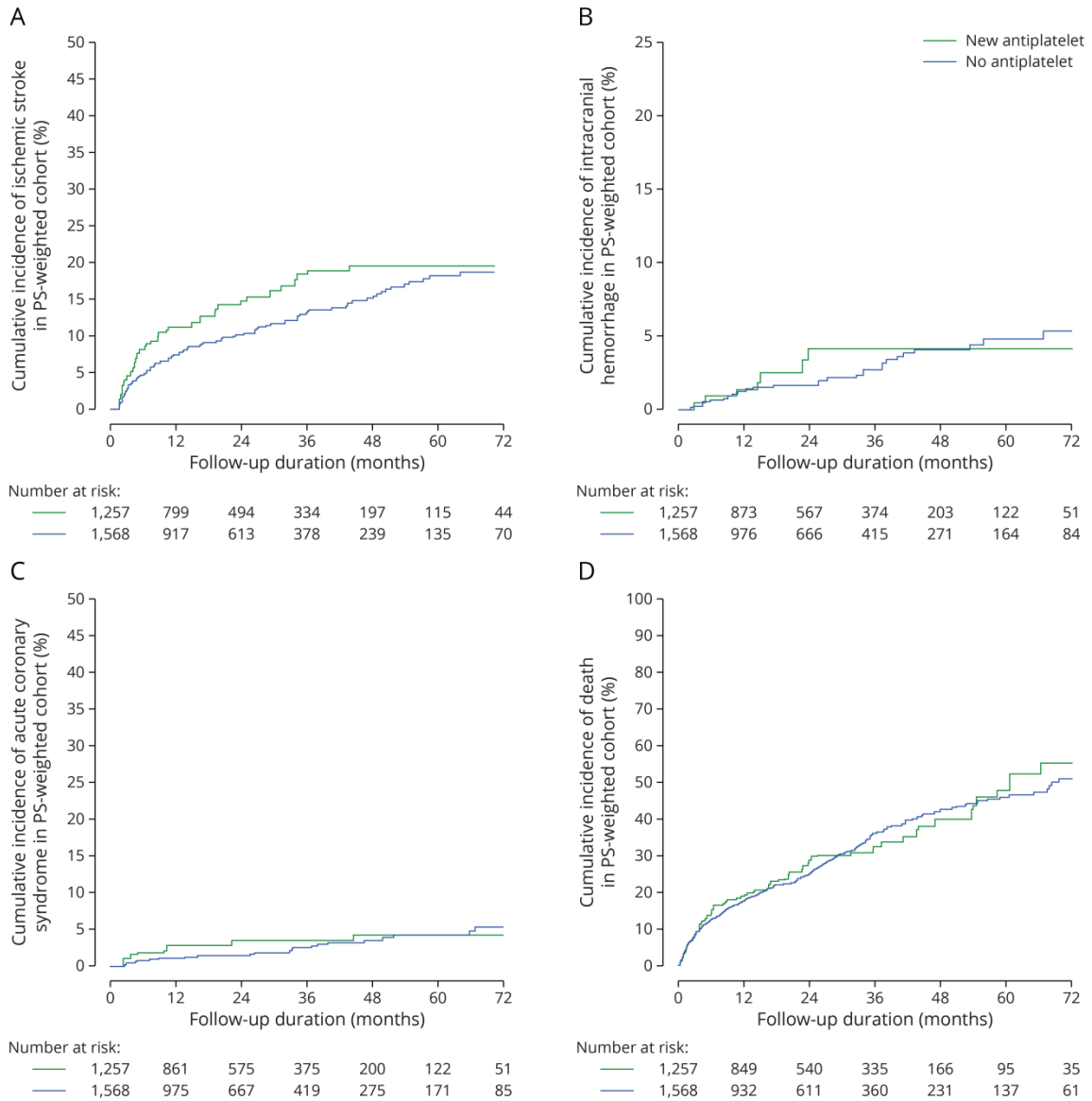
**Figure 1. Study flow diagram**



**Figure 2. Cumulative incidence of A) ischemic stroke, B) intracranial hemorrhage, C) acute coronary syndrome, D) death in patients with ischemic stroke despite direct oral anticoagulant with different anticoagulation strategies**



**Figure 3. Cumulative incidence of A) ischemic stroke, B) intracranial hemorrhage, C) acute coronary syndrome, D) death in patients with ischemic stroke despite direct oral anticoagulant with or without newly added antiplatelet therapy**



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## Association of Alternative Anticoagulation Strategies and Outcomes in Patients With Ischemic Stroke While Taking a Direct Oral Anticoagulant

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*Neurology* published online May 24, 2023

DOI 10.1212/WNL.0000000000207422

**This information is current as of May 24, 2023**

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