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

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Abstract

Background and Objectives
Ischemic stroke despite a direct oral anticoagulant (DOAC) is increasingly common and portends a high risk of subsequent ischemic stroke. The efficacy and safety of antithrombotic regimens after the condition are unclear. We aimed to compare the outcomes of patients with ischemic stroke despite DOACs 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$_{switch}$), or addition of antiplatelet agents, with those of unchanged DOAC regimen (DOAC$_{same}$) among patients with nonvalvular atrial fibrillation (NVAF) who developed the first ischemic stroke despite a DOAC from January 1, 2015, to December 31, 2020, in Hong Kong. The 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 patients with AF on a DOAC as stroke prophylaxis, 2,908 patients developed ischemic stroke despite a DOAC. A total of 2,337 patients with NVAF were included in the final analyses. Compared with DOAC$_{same}$, warfarin (aHR 1.96, 95% CI 1.27–3.02, $p = 0.002$) and DOAC$_{switch}$ (aHR 1.62, 95% CI 1.25–2.11, $p < 0.001$) were associated with an increased risk of recurrent ischemic stroke. In the DOAC$_{same}$ group, adjunctive antiplatelet agent was not associated with a 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 patients with NVAF with ischemic stroke despite a 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

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Glossary

ACS = acute coronary syndrome; **aHR** = adjusted hazard ratio; **CI** = confidence interval; **DM** = diabetes mellitus; **DOAC** = direct oral anticoagulant; **GBM** = generalized boosted models; **LAD** = large artery atherosclerotic disease; **NVAF** = nonvalvular atrial fibrillation; **PS** = propensity score; **SmPC** = summary of product characteristics.

antiplatelet agent did not seem to reduce ischemic stroke relapse. Because diabetes mellitus, the use of CYP/P-gp modulators, and LAD were predictors of recurrent ischemic stroke, further investigations should evaluate whether 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 NVAF experiencing 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.

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

In practice, there are broadly 3 alternative antithrombotic regimens after ischemic stroke despite DOACs: (1) switching between the 4 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 most 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 epidemiologic study, adjustment of oral anticoagulant therapy collectively did not reduce subsequent ischemic stroke risk.[7] Because ischemic stroke despite DOACs is increasingly common due to surging DOAC prescriptions,[10-12] investigating the outcomes of patients on alternative antithrombotic regimens after an episode of ischemic stroke despite DOACs may inform treatment decisions.

In this population-based analysis, we compared the clinical outcomes of patients with NVAF with ischemic stroke despite DOACs 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 a reduced risk of recurrent ischemic stroke.

Methods

Study Design and Data Source

We performed a population-based retrospective cohort study and recruited all patients with ischemic stroke despite DOACs admitted to public hospitals in Hong Kong from January 1, 2015, to December 31, 2020. Clinical parameters were retrieved through 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. The CDARS had a coding accuracy of 85%–100% according to previous studies.[13] We followed the STROBE reporting guidelines.

Study Subjects

We enrolled patients with NVAF 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), hyperlipidemia, and arterial and venous thromboembolism were retrieved. We collected any documented history of small vessel disease and large intracranial or extracranial artery atherosclerotic disease (LAD). We recorded the use of antiplatelet agents (clopidogrel, aspirin, cilostazol, and ticagrelor), intensity of statins (none, low, moderate, and high[14]), cytochrome P450 or P-glycoprotein (CYP/P-gp) modulators (phenytoin, valproate, carbamazepine, amiodarone, dronedarone, rifampicin, cyclosporin, and verapamil), and nonsteroidal anti-inflammatory drugs (NSAIDs). CHADS2-Vasc and HAS-BLED scores after the first ischemic stroke despite DOACs were calculated.[15] We excluded patients with active malignancy, mitral stenosis, left ventricular thrombus, valvular replacement, left atrial appendage occlusion, atrial septal defect,

polycythemia ruba vera, essential thrombocytosis, and thrombophilia. We also excluded patients who had anticoagulation discontinued after the stroke episode or with an inappropriate DOAC dosage for body weight, renal function, and age at stroke onset. eTable 1 (links.lww.com/WNL/C839) in the Supplement listed the ICD9-CM codes used in the study.

Ischemic Stroke Despite DOACs

Ischemic stroke despite DOACs 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 DOACs were retrieved. Anticoagulation therapy after the first episode of ischemic stroke despite DOACs was classified into (1) unchanged group (DOAC$_{same}$); (2) DOAC-to-warfarin group; or (3) DOAC-to-another DOAC group (DOAC$_{switch}$), that is, 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

The primary outcome was recurrent ischemic stroke after the first episode of ischemic stroke despite DOACs. Secondary outcomes were intracranial hemorrhage, ACS, and all-cause death.

Covariates

We included 5 demographic variables (age, sex, a history of smoking or drinking, and modified Rankin scale after the first ischemic stroke despite DOACs), 12 medical comorbidities (intracranial hemorrhage, congestive heart failure, hypertension, DM, ischemic heart disease, arterial and venous thromboembolism, peripheral vascular disease, chronic kidney and liver disease, small vessel disease, and LAD), 9 baseline laboratory parameters (total cholesterol, low-density and high-density lipoprotein cholesterol, triglycerides, glycated hemoglobin A1c, creatinine, alanine transaminase, hemoglobin, 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 because of the de-identified data.

Statistical Analyses

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$_{switch}$) with the reference group (DOAC$_{same}$) by inverse probability of treatment weighting. We estimated the PS of each patient by generalized boosted models (GBMs) that included the covariates mentioned earlier. The optimal iteration of GBMs was determined by 4 stopping rules previously described[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 DOACs 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 DOACs and the earliest date among (1) study end, (2) death, and (3) discontinuation of oral anticoagulation. The 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 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 2-sided test with a p value <0.05 was considered statistically significant.

Secondary Analyses

We performed 3 planned secondary analyses.

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 DOACs, vs patients with no antiplatelet therapy before and after the event. We confined the analysis to the DOAC$_{same}$ group.

DOAC Regimen After the Index Ischemic Stroke During DOACs

In an exploratory analysis, we compared the outcomes of patients who received 5 mg of apixaban twice daily (API10), 110 mg of dabigatran twice daily (DAB220), 150 mg of dabigatran twice daily (DAB300), 60 mg of edoxaban daily (EDO60), or 20 mg of rivaroxaban (RIV20) daily after the first ischemic stroke despite DOACs, regardless of the initial DOAC regimen in a PS-weighted analysis. We excluded patients who took 2.5 mg of apixaban twice daily, 30 mg of edoxaban daily, or 15 mg of rivaroxaban 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 110 mg of dabigatran twice daily in this comparison because the regimen was considered a standard dosage locally, that is, dabigatran recipients who received DAB220 may otherwise be eligible for DAB300, in contrast to European summary of product characteristics (SmPC) on dabigatran dosage.[18]

Risk Factors Associated With Recurrent Ischemic Stroke

To identify the risk factors of recurrent ischemic stroke, we compared the demographics, medical comorbidities, laboratory

Figure 1 Study Flow Diagram
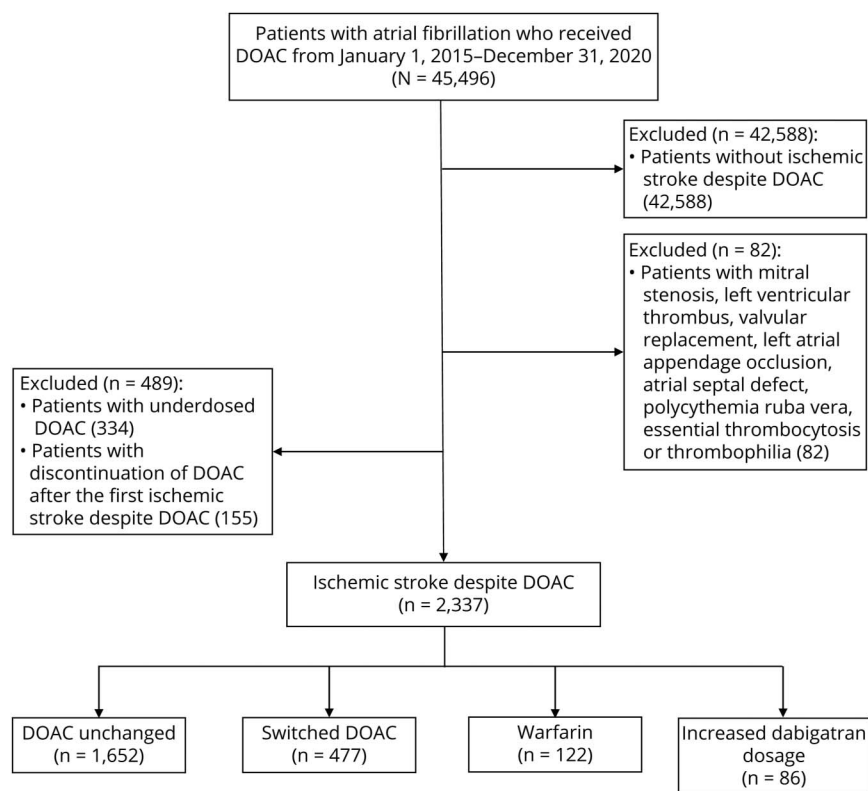
parameters, and medications among patients with and without recurrent ischemic stroke in an unweighted logistic regression analysis. We limited this analysis to the DOAC$_{same}$ group. Covariates that were clinically relevant or reached a p value ≤0.25 in the univariate logistic regression model were subjected to a final multivariate logistic regression model. Schoenfeld residual plots were 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 ± 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 datasets after the first 20 iterations. In the descending order of missing information, missing data on HbA1c (17.9%), lipid profile (13.8%), alkaline phosphatase (0.1%), alanine transferase (0.04%), hemoglobin (0.04%), and 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
Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

From January 1, 2015, to December 31, 2020, 2,908 of 45,496 patients with AF developed ischemic stroke despite DOACs. We excluded 571 patients with valvular AF, thrombophilia, underdosed DOACs, or discontinuation of anticoagulation after the first ischemic stroke despite DOACs (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$_{same}$), 477 (20.4%) patients received an alternative DOAC (DOAC$_{switch}$), 122 (5.2%) patients were prescribed warfarin, and 86 (3.7%) patients stepped up from 110 mg of dabigatran twice daily to 150 mg of dabigatran twice daily. We excluded patients with an increased dabigatran dosage from the primary analysis because of 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 with DOAC$_{same}$, warfarin (adjusted hazard ratio [aHR] 1.96, 95% confidence interval [CI] 1.29–3.02, $p = 0.002$) and DOAC$_{switch}$ (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$_{switch}$ was also associated with an increased risk of ACS (aHR 2.18, 95% CI 1.29–6.67 $p = 0.003$, Figure 1C). DOAC$_{switch}$ and

Table 1 Imputed Patient Characteristics and Covariate Balance Across Different Anticoagulation Regimens After the First Ischemic Stroke Despite DOACs

	DOAC$_{same}$	DOAC$_{switch}$	AMSD	Warfarin	AMSD
N	1,652	477		122	
Demographics					
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 (%)	1,622 (99.0)	482 (99.4)	0.005	119 (98.3)	0.002
Medical comorbidities					
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 (%)	1,132 (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
Nonmajor 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
CHADS2Vasc, mean ± SD	4.6 ± 1.7	4.5 ± 1.7	NA	4.6 ± 1.8	NA
HAS-BLED, mean ± SD	2.4 ± 0.9	2.3 ± 1.0	NA	2.4 ± 1.1	NA
Concurrent medications					
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
Laboratory parameters					
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

Table 1 Imputed Patient Characteristics and Covariate Balance Across Different Anticoagulation Regimens After the First Ischemic Stroke Despite DOACs *(continued)*

	DOAC_same	DOAC_switch	AMSD	Warfarin	AMSD
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 (10^9/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
Annual incidence rate of outcome (%)					
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 = nonsteroidal anti-inflammatory drugs; P-gp = p-glycoprotein; PT = prothrombin time.

warfarin groups were not associated with intracranial hemorrhage or death (Tables 1 and 2, Figure 2, A–D).

Secondary Analyses

Adjunctive Antiplatelet Therapy
Among 1,652 patients in the DOAC_same group, 249 (15.1%) patients were started on antiplatelet agents within 8 weeks of the first ischemic stroke despite DOACs (eTable 2, links.lww.com/WNL/C839 in the Supplement), and 1,166 (70.6%) patients did not receive any antiplatelet therapy. Adjunctive antiplatelet treatment did not reduce the 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 ≤0.25 in the univariate logistic regression analyses (eTable 3, links.lww.com/WNL/C839 in the Supplement), our multivariable logistic regression analysis within the DOAC_same group revealed that advanced age (aHR 1.02, 95% CI 1.00–1.03, p = 0.029), a history of DM (aHR 1.49 95% CI 0.73–1.20, p = 0.002), the 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 tests 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 DOACs, 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 because of the small sample size (n = 47). Covariate balance was listed in eTable 5 (links.lww.com/WNL/C839) with API10 as the reference group. The risks of recurrent ischemic stroke were comparable among the 4 DOAC regimens. Compared with API10, DAB220 was associated with a lower risk of intracranial hemorrhage (aHR 0.27, 95% CI 0.15–0.99, p = 0.019), and RIV20 was associated with a 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_switch were associated with an increased risk of recurrent ischemic stroke. Addition of antiplatelet after the first ischemic stroke despite DOACs was not associated with a lower risk of subsequent

Table 2 Outcome Comparisons Among Antithrombotic Strategies After the First Ischemic Stroke Despite DOACs

	Warfarin (n = 122) vs DOAC$_{same}$ (reference, n = 1,652)			DOAC$_{switch}$ (n = 477) vs DOAC$_{same}$ (reference, n = 1,652)			New antiplatelet (n = 249) vs No antiplatelet (reference, n = 1,166)		
	Median follow-up (mo)	aHR (95% CI)	p Value	Median follow-up (mo)	aHR (95% CI)	p Value	Median follow-up (mo)	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$_{same}$ group.

ischemic stroke. eTables 7–12 (links.lww.com/WNL/C839) in the Supplement listed the details of sensitivity analyses.

Classification of Evidence

This study provides Class II evidence that in patients with NVAF experiencing 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 patients with NVAF with an episode of ischemic stroke despite DOACs, we found the following: (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.

A key finding of our study is that switching from DOAC to warfarin in patients with NVAF 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 with that with DOAC.[20] The lower time within therapeutic range in warfarin recipients might play a role in the increased recurrent ischemic stroke risk observed.[21] Because switching to warfarin after a recurrent thrombotic episode with DOACs 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]

Of interest, DOAC-to-DOAC switch was associated with an increased risk of recurrent ischemic stroke compared with 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* allelic variants may predispose to cardioembolic ischemic strokes.[26,27] The resultant cortical or wedge-shaped infarct topography may prompt DOAC switching after 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 whether these factors would have influenced the decision on DOAC switching.

Adjunctive antiplatelet therapy to DOAC did not seem to reduce the 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 patients with NVAF. Some studies even found a higher risk of major cardiovascular events in patients with AF 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] when compared with 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 patients with NVAF who developed ischemic stroke despite DOACs.

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 patients with AF,[15] the mean glycated hemoglobin A1c levels were not significantly different among DOAC recipients with and without recurrent cerebral ischemia in our cohort.

Figure 2 Cumulative Incidence of (A) Ischemic Stroke, (B) Intracranial Hemorrhage, (C) Acute Coronary Syndrome, and (D) Death in Patients With Ischemic Stroke Despite Direct Oral Anticoagulant With Different Anticoagulation Strategies
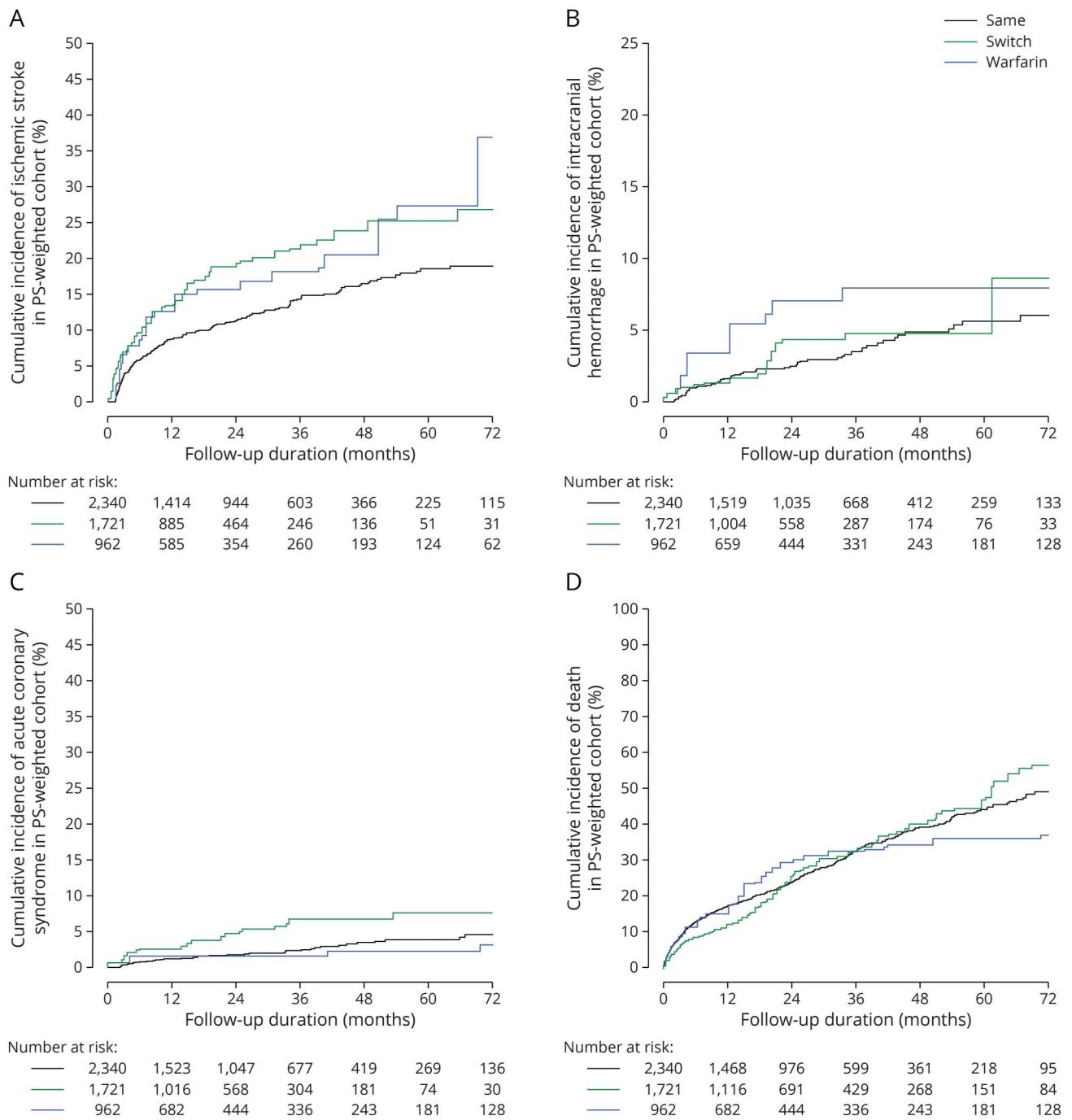

Another study also found that most patients with ischemic stroke despite DOACs had satisfactory glycemic control at stroke onset.[33] Further longitudinal studies should determine whether a stringent long-term glycemic control may lower the risk of recurrent ischemic stroke among DOAC recipients. Apart 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 underanticoagulation from drug-drug interactions between DOAC and CYP/P-gp modulators.[16,34]

In our exploratory comparison of different DOAC regimens, all 4 drug regimens had a comparable risk of recurrent ischemic stroke. The lower risk of intracranial hemorrhage with 110 mg of dabigatran twice daily was similar to that observed in population-based studies that included patients

Figure 3 Cumulative Incidence of (A) Ischemic Stroke, (B) Intracranial Hemorrhage, (C) Acute Coronary Syndrome, and (D) Death in Patients With Ischemic Stroke Despite Direct Oral Anticoagulant With or Without Newly Added Antiplatelet Therapy
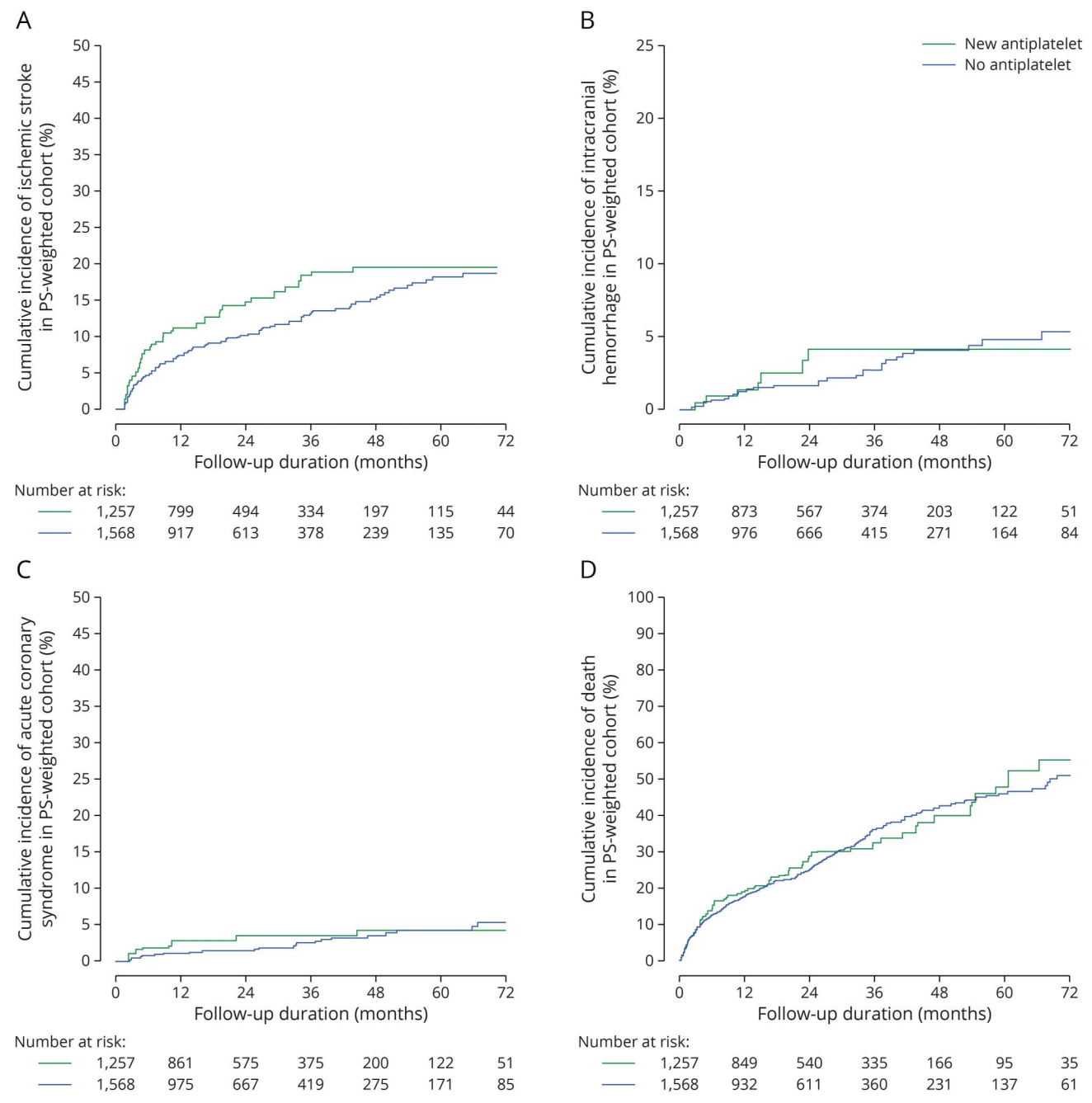
without ischemic stroke despite DOACs.[35] This observation may be related to the preservation of blood-brain barrier function through direct thrombin inhibition.[36] On the contrary, the reason behind the lower risk of ischemic heart disease with 5 mg of apixaban twice daily compared with 20 mg of rivaroxaban daily is unclear because previous studies reported only a lower risk of major cardiovascular events with DOAC compared with warfarin without robust comparisons among DOACs.[37,38] Although the pharmacologic 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 150 mg of dabigatran twice daily, however, could be biased by younger age, better functional status, and renal function. It should also be noted that there were no prespecified dosage adjustment criteria for dabigatran in patients with normal renal function during the study period. Patients on 110 mg of dabigatran twice daily might otherwise be eligible for the 150 mg of dabigatran twice daily regimen. In comparison with the European SmPC recommendation on

110 mg of dabigatran twice daily in patients older than 80 years, on concomitant verapamil or with high bleeding risks,[18] patients who received 110 mg of dabigatran 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.

Last, 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 DOACs, as reflected by the risk of recurrent ischemic stroke in patients with LAD.

Our study has 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 an 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 after an episode of ischemic stroke despite DOACs.[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 the warfarin group than in the DOAC$_{same}$ 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. Last, because 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 patients with NVAF who developed ischemic stroke despite DOACs, 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 seem to reduce ischemic stroke relapse. Because DM, the use of CYP/P-gp modulators, and LAD were predictors of recurrent ischemic stroke, further investigations should evaluate whether strict glycemic control, DOAC level monitoring, and routine screening for carotid and intracranial atherosclerosis may reduce ischemic stroke recurrence in these patients.

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Publication History

Appendix Authors

Name	Location	Contribution
Yiu Ming Bonaventure Ip, MD	Department of Medicine and Therapeutics, Faculty of Medicine, The Prince of Wales Hospital, Chinese University of Hong Kong	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Kui Kai Lau, DPhil	Department of Medicine, Queen Mary Hospital, University of Hong Kong	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Ho Ko, PhD	Department of Medicine and Therapeutics, The Prince of Wales Hospital; Li Ka Shing Institute of Health Sciences, Faculty of Medicine, Chinese University of Hong Kong	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data

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