JAMA | Original Investigation

Association of Intracerebral Hemorrhage Among Patients Taking Non–Vitamin K Antagonist vs Vitamin K Antagonist Oral Anticoagulants With In-Hospital Mortality

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IMPORTANCE Although non–vitamin K antagonist oral anticoagulants (NOACs) are increasingly used to prevent thromboembolic disease, there are limited data on NOAC-related intracerebral hemorrhage (ICH).

OBJECTIVE To assess the association between preceding oral anticoagulant use (warfarin, NOACs, and no oral anticoagulants [OACs]) and in-hospital mortality among patients with ICH.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of 141 311 patients with ICH admitted from October 2013 to December 2016 to 1662 Get With The Guidelines–Stroke hospitals.

EXPOSURES Anticoagulation therapy before ICH, defined as any use of OACs within 7 days prior to hospital arrival.

MAIN OUTCOMES AND MEASURES In-hospital mortality.

RESULTS Among 141 311 patients with ICH (mean [SD] age, 68.3 [15.3] years; 48.1% women), 15 036 (10.6%) were taking warfarin and 4918 (3.5%) were taking NOACs preceding ICH, and 39 585 (28.0%) and 5783 (4.1%) were taking concomitant single and dual antiplatelet agents, respectively. Patients with prior use of warfarin or NOACs were older and had higher prevalence of atrial fibrillation and prior stroke. Acute ICH stroke severity (measured by the National Institutes of Health Stroke Scale) was not significantly different across the 3 groups (median, 9 [interquartile range, 2-21] for warfarin, 8 [2-20] for NOACs, and 8 [2-19] for no OACs). The unadjusted in-hospital mortality rates were 32.6% for warfarin, 26.5% for NOACs, and 22.5% for no OACs. Compared with patients without prior use of OACs, the risk of in-hospital mortality was higher among patients with prior use of warfarin (adjusted risk difference [ARD], 9.0% [97.5% CI, 7.9% to 10.1%]; adjusted odds ratio [AOR], 1.62 [97.5% CI, 1.53 to 1.71]) and higher among patients with prior use of NOACs (ARD, 3.3% [97.5% CI, 1.7% to 4.8%]; AOR, 1.21 [97.5% CI, 1.11-1.32]). Compared with patients with prior use of warfarin, patients with prior use of NOACs had a lower risk of in-hospital mortality (ARD, −5.7% [97.5% CI, −7.3% to −4.2%]; AOR, 0.75 [97.5% CI, 0.69 to 0.81]). The difference in mortality between NOAC-treated patients and warfarin-treated patients was numerically greater among patients with prior use of dual antiplatelet agents (32.7% vs 47.1%; ARD, −15.0% [95.5% CI, −26.3% to −3.8%]; AOR, 0.50 [97.5% CI, 0.29 to 0.86]) than among those taking these agents without prior antiplatelet therapy (26.4% vs 31.7%; ARD, −5.0% [97.5% CI, −6.8% to −3.2%]; AOR, 0.77 [97.5% CI, 0.70 to 0.85]), although the interaction *P* value (.07) was not statistically significant.

CONCLUSIONS AND RELEVANCE Among patients with ICH, prior use of NOACs or warfarin was associated with higher in-hospital mortality compared with no OACs. Prior use of NOACs, compared with prior use of warfarin, was associated with lower risk of in-hospital mortality.

JAMA. doi:10.1001/jama.2017.21917
Published online January 25, 2018.

Supplemental content

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Non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly used as alternatives to warfarin to prevent thromboembolic complications in high-risk patients with atrial fibrillation.[1,2] Although NOACs have a more favorable safety profile than warfarin, the annual risk of intracerebral hemorrhage (ICH) among NOAC-treated patients is 0.5%.[3-6] Prior studies regarding the outcomes of ICH among patients taking NOAC therapy are limited in size and scope.[7-9] With the rapid adoption of NOACs in clinical practice, there is a need to better understand the outcomes among patients who develop an ICH with prior NOAC therapy compared with those experiencing ICH either with prior warfarin therapy or among those without prior oral anticoagulation.

The goals of the study were to evaluate the characteristics and clinical outcomes in patients who experienced an ICH with preceding use of NOACs compared with no oral anticoagulants (OACs) and warfarin, and to determine the incremental risk of mortality and disability associated with the concomitant prior use of OACs and antiplatelet therapy according to the type of anticoagulants.

Key Points

Question What is the association between preceding oral anticoagulant use (warfarin, non–vitamin K oral anticoagulants [NOACs], and no oral anticoagulants) and in-hospital mortality among patients with intracerebral hemorrhage?

Findings In this registry-based retrospective cohort study including 141 311 patients with intracerebral hemorrhage, prior use of warfarin or NOACs, compared with no prior anticoagulant use, was associated with higher in-hospital mortality, although the use of NOACs, compared with warfarin, was associated with lower in-hospital mortality risk (adjusted risk difference, −5.7%; adjusted odds ratio, 0.75).

Meaning Among patients with intracerebral hemorrhage, prior use of NOACs, compared with prior use of warfarin, was associated with lower risk of in-hospital mortality.

Methods

Data Source

This retrospective cohort study used data from the American Heart Association/American Stroke Association Get With The Guidelines-Stroke (GTWG-Stroke), which is an ongoing, voluntary, continuous registry sponsored by the American Heart Association/American Stroke Association. Details of GWTG-Stroke registry data collection and variable definitions have been previously described.[10] Standardized data collection includes patient demographic information, medical history, diagnostic testing, brain imaging, in-hospital treatment, and outcomes. The validity and reliability of data collection in GWTG-Stroke have been reported in previous research.[11] Quintiles serves as the data collection and coordination center for GWTG-Stroke. The Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for research purposes. Each participating hospital received either human research approval to enroll patients without individual patient consent under the Common Rule or a waiver of authorization and exemption from subsequent review by their institutional review board. This study was approved by the institutional review board of Duke University.

Study Population

All patients with a diagnosis of ICH were identified in the GWTG-Stroke registry database between October 2013 and December 2016. Preceding use of OACs or antiplatelet therapy was recorded as part of routine care and defined as any use within 7 days prior to hospital arrival. For the purpose of the study, preceding anticoagulation treatments were categorized into 3 mutually exclusive groups: (1) warfarin; (2) NOACs; and (3) no OACs (**Figure 1**). NOACs were defined as the preceding use of dabigatran, rivaroxaban, apixaban, or edoxaban. Patients were excluded from the analysis if they were taking 2 or more anticoagulant agents (both NOACs and warfarin, or NOAC or warfarin with other anticoagulants such as heparin and low-molecular-weight heparin).

Antiplatelet treatments were classified into 3 categories: (1) no antiplatelet therapy, (2) single antiplatelet therapy (SAPT); and (3) dual antiplatelet therapy (DAPT) (Figure 1). SAPT was defined as any one of the following antiplatelet agents prior to ICH: aspirin, clopidogrel, ticlopidine, prasugrel, or ticagrelor. DAPT was defined as aspirin/dipyridamole, aspirin plus aspirin/dipyridamole, aspirin plus clopidogrel, ticlopidine, prasugrel, or ticagrelor. Patients who were not in any of these 3 antiplatelet groups were excluded from the analysis.

Outcome Measures

The primary outcome was in-hospital mortality (yes or no). The exploratory outcomes included discharge disposition (home vs other), in-hospital mortality or discharge to hospice, ambulatory status at discharge (able to ambulate independently vs not), and modified Rankin Scale (mRS) score at discharge (range, 0 [no symptoms] to 6 [death]). Patients with an mRS score of 0 or 1 were classified as having excellent recovery, and those with an mRS score of 0 to 2 were classified as having functional independence.

Statistical Analysis

Baseline characteristics were compared across 3 preceding anticoagulation treatment groups. Medians with interquartile ranges were calculated for continuous variables in each group and compared using a Kruskal-Wallis test. Categorical variables were reported as counts and percentages, and differences among groups were assessed using the χ^2 test.

Multivariable logistic regression models were performed to assess the relationship between preceding anticoagulation therapies with each clinical outcome. These analyses adjusted for baseline demographic and clinical variables prior to the index ICH event including demographics (age, sex, and race/ethnicity [black, Hispanic, Asian, and other vs white: admission staff, medical staff, or both recorded the patient's self-reported race/ethnicity, usually during registration;

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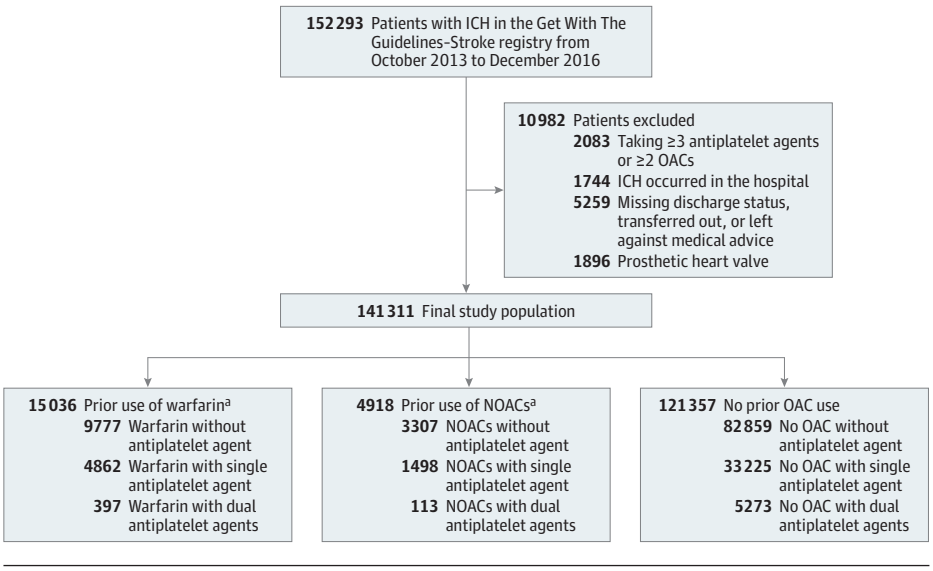
Figure 1. Study Cohort Creation



ICH indicates intracerebral hemorrhage; NOAC, non–vitamin K oral anticoagulants; and OACs, oral anticoagulants.

[a] Prior use was defined as any use within 7 days of hospital arrival.

prior studies have suggested differences in outcomes from intracerebral hemorrhage related to race/ethnicity]), insurance, medical history (atrial fibrillation/flutter, coronary artery disease or prior myocardial infarction, carotid stenosis, diabetes, peripheral vascular disease, hypertension, smoking, dyslipidemia, prior stroke or transient ischemic attack, heart failure, drug or alcohol abuse, obesity or overweight, and renal insufficiency), arrival and admission information (emergency medical services arrival and transfer-in [vs private transportation] and arrived off hours), medications at admission (antihypertensive, lipid-lowering, and diabetic agents), and hospital characteristics (region, rural vs urban, teaching hospital, number of beds, and certified primary stroke center). All continuous variables were tested for linearity and included in the model as a linear variable except for age. A nonlinear relationship exists between in-hospital death and age; therefore, splines with a cutoff point of age 70 years were used in the model. The preceding anticoagulation treatment was included as an independent variable, with no OACs or warfarin as the reference groups.

As a sensitivity analysis, the same analyses were replicated in patients without preceding use of any antiplatelet therapy. Furthermore, sensitivity analyses were also performed in patients with a National Institutes of Health Stroke Scale (NIHSS) score on admission, with the model including NIHSS score along with other covariates. NIHSS was used as a measure of stroke severity (range, 0-42, with a higher score indicating greater stroke severity), but it was not included in the main model because a higher NIHSS score could be the result of hematoma expansion caused by NOACs or OACs and controversies existed about whether NIHSS should be included in the model. The generalized estimation equation (GEE) modeling approach was used to account for within-hospital clustering of patients. In addition, the GEE approach using normal distribution with identity link was used for estimating unadjusted and adjusted risk differences.[12,13]

To evaluate the differences in the incremental risk of mortality and disability with the concomitant prior antiplatelet therapy according to underlying OAC, multivariable logistic regression models with GEE were performed in each OAC group, respectively, with antiplatelet treatment category (no antiplatelet, SAPT, or DAPT) as the independent variable and no antiplatelet as the reference group.

As a sensitivity analysis, multivariable logistic regression models with GEE were performed to compare the in-hospital mortality rate among patients with preceding use of NOACs with that among patients with preceding use of warfarin in the therapeutic range. Additionally, the association of international normalized ratio (INR) level and outcomes was also evaluated among patients with prior use of warfarin. For these additional analyses, patients with prior use of warfarin were classified into 3 categories based on admission INR level: (1) subtherapeutic, defined as INR less than 2; (2) therapeutic, with INR ranging from 2 to 3; and (3) supratherapeutic defined as INR greater than 3.

All variables had less than 2% missing data except for insurance (7.4%) and preadmission medications (18.1% for antihypertensive and 21.8% for diabetic medications). Details of missing values can be found in eTable 1 in the Supplement. To account for missing data, single imputation was used for each variable: men for sex, non-Hispanic white for race/ethnicity, private transportation for emergency medical services arrival and transfer in, and “no” for other. All statistical analyses were performed by the Duke Clinical Research Institute using SAS software version 9.4 (SAS Institute Inc). All P values were 2-sided. For the primary outcome (in-hospital mortality), the Bonferroni correction approach was used to account for multiple comparisons, and $P < .025$ was considered statistically significant and 97.5% CIs instead of 95% CIs were reported. For other outcomes, $P < .05$ was considered statistically significant and 95% CIs were reported.

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Results

A total of 152 293 patients with ICH were admitted to GWTG-Stroke hospitals between October 2013 and December 2016. Of these, 10 982 patients were excluded from the analyses for the following reasons: (1) patients taking 3 or more antiplatelet agents or 2 or more OACs (n = 2083); (2) ICH occurred in the hospital (n = 1744); (3) missing discharge status, transferred out, or left against medical advice (n = 5259); and (4) patients with a prosthetic heart valve (n = 1896) (Figure 1). After these exclusions, the final study population included 141 311 patients from 1662 hospitals.

Among 141 311 patients with ICH (mean [SD] age, 68.3 [15.3] years; 48.1% women), 121 357 patients (85.9%) were not receiving OACs prior to ICH, 15 036 (10.6%) were receiving warfarin, and 4918 (3.5%) were receiving NOACs. Among patients with preceding use of NOACs, 11.0% were taking dabigatran; 54.0%, rivaroxaban; 34.9%, apixaban; and 0.1%, edoxaban. Patients with prior use of warfarin or NOACs were more likely to have concomitant SAPT than those not taking any OAC, whereas patients without preceding use of OACs were more likely to have DAPT (SAPT: 32.3% for warfarin, 30.5% for NOACs, and 27.4% for no OACs; DAPT: 2.6% for warfarin, 2.3% for NOACs, and 4.4% for no OACs) (**Table 1** and Figure 1). Baseline characteristics by OAC type are shown in Table 1.

Patients with preceding use of warfarin or NOACs were more likely to be older, white, and have a higher prevalence of atrial fibrillation, prior stroke or transient ischemic attack, and atherosclerotic comorbidities (eg, coronary artery disease, diabetes, hypertension, dyslipidemia, and heart failure). The severity of ICH at admission, as measured by NIHSS, was not significantly different across the 3 groups (median [interquartile range]: 9 [2-21], 8 [2-20], and 8 [2-19] for warfarin, NOACs, and no OACs, respectively). When directly comparing patients with preceding use of warfarin with those with preceding use of NOACs, the baseline characteristics were not significantly different except for a higher prevalence of renal disease in patients with prior use of warfarin and a higher prevalence of atrial fibrillation in patients with prior use of NOACs.

Preceding Anticoagulation Treatment and Outcome Measures

The unadjusted in-hospital mortality rates were 32.6% for prior use of warfarin, 26.5% for prior use of NOACs, and 22.5% for no preceding use of OACs. After adjustment for confounders, both prior use of warfarin (adjusted risk difference [ARD], 9.0% [97.5% CI, 7.9% to 10.1%]; adjusted odds ratio [AOR], 1.62 [97.5% CI, 1.53 to 1.71]) and prior use of NOACs (ARD, 3.3% [97.5% CI, 1.7% to 4.8%]; AOR, 1.21 [97.5% CI, 1.11 to 1.32]) were associated with increased odds of in-hospital mortality as compared with no prior use of OACs. Compared with patients with prior use of warfarin, patients with prior use of NOACs had a lower risk of in-hospital mortality (ARD, −5.7% [97.5% CI, −7.3% to −4.2%]; AOR, 0.75 [97.5% CI, 0.69 to 0.81]) (**Table 2**). Ambulatory and functional outcomes were not significantly different between patients with prior use of NOACs vs no prior use of OACs, whereas patients with prior use of NOACs were more likely to be discharged home and have better functional outcomes at discharge than those with prior use of warfarin (Table 2). These findings were consistent when confined to patients without preceding use of any antiplatelet agents (n = 95 943) (eTable 2 in the Supplement). In addition, sensitivity analyses in patients with NIHSS on admission (n = 90 223) also were consistent with the main findings even after the further adjustment with NIHSS score (eTable 3 in the Supplement).

Incremental Risk of Mortality and Disability With Concomitant Anticoagulant and Antiplatelet Therapy

Baseline characteristics by number of antiplatelet agents are shown in eTable 4 in the Supplement. Compared with patients without prior use of antiplatelet therapy, patients with prior use of antiplatelet therapy were older and had higher burden of atherosclerotic comorbidities. In patients with prior use of NOACs and no OACs, SAPT was not associated with an increased risk of in-hospital mortality. By contrast, in patients with prior use of warfarin, SAPT was associated with a higher rate of in-hospital mortality (33.2% vs 31.7%; ARD, 3.2% [97.5% CI, 1.4% to 5.0%]; AOR, 1.17 [97.5% CI, 1.07 to 1.28]) than no prior antiplatelet (**Figure 2**). The preceding use of DAPT was associated with increased risk of in-hospital mortality among patients with prior warfarin use (ARD, 16.5% [97.5% CI, 10.9% to 22.2%]; AOR, 2.13 [97.5% CI, 1.66 to 2.73]) and with no prior OAC use (ARD, 7.3% [97.5% CI, 5.7% to 8.9%]; AOR, 1.50 [97.5% CI, 1.38 to 1.64]). Nevertheless, these differences were not statistically significant among patients with prior use of NOACs (ARD, 7.0% [97.5% CI, −2.9% to 16.8%]; AOR, 1.41 [97.5% CI, 0.87 to 2.28]) (Figure 2).

For ambulatory and functional outcomes, patients with prior use of DAPT were less likely to be discharged home than those without any prior use of antiplatelet agents among patients with prior use of no OAC, but there was no difference in patients with prior use of warfarin or NOACs. When directly compared with prior use of warfarin, patients with prior use of NOACs had lower in-hospital mortality compared with patients with prior use of warfarin regardless of antiplatelet therapy, and the difference in mortality between patients with prior use of NOACs vs prior use of warfarin was numerically greater among patients with prior use of dual antiplatelet agents (32.7% vs 47.1%; ARD, −15.0% [97.5% CI, −26.3% to −3.8%]; AOR, 0.50 [97.5% CI, 0.29 to 0.86]) than among those without prior antiplatelet therapy (26.4% vs 31.7%; ARD, −5.0% [97.5% CI, −6.8% to −3.2%]; AOR, 0.77 [97.5% CI, 0.70 to 0.85]), although the *P* value of interaction (.07) was not statistically significant (eTable 5 in the Supplement).

Comparison of Outcomes in NOAC- vs Warfarin-Treated Patients With Therapeutic Range of INR

There was a dose-response relationship between INR and outcomes in patients with prior use of warfarin who experienced an ICH. The unadjusted in-hospital mortality rates were 25.0% for those with prior use of warfarin with

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Table 1. Baseline Characteristics by Anticoagulant Type

Characteristic	Warfarin (n = 15 036)	NOACs (n = 4918)	No OACs (n = 121 357)	*P* Value
Patient Characteristics				
Age, median (IQR), y	77 (68-84)	78 (70-84)	68 (56-79)	<.001
Women, No. (%)	7042 (46.8)	2436 (49.6)	58 441 (48.2)	<.001
Race/ethnicity, No. (%)				
Non-Hispanic white	11 607 (77.3)	3947 (80.3)	73 022 (60.3)	<.001
Non-Hispanic black	1583 (10.5)	446 (9.1)	23 264 (19.2)	
Hispanic	689 (4.6)	213 (4.3)	11 557 (9.5)	
Asian	522 (3.5)	137 (2.8)	6303 (5.2)	
Other	617 (4.1)	172 (3.5)	7001 (5.8)	
Insurance, No. (%)				
Private	5590 (38.1)	1900 (39.6)	43 263 (38.8)	<.001
Medicare	7786 (53.1)	2554 (53.2)	46 701 (41.9)	
Medicaid	1094 (7.5)	305 (6.4)	13 776 (12.4)	
Self-pay	195 (1.3)	44 (0.9)	7658 (6.9)	
Medical history, No. (%)				
Atrial fibrillation or flutter	10 006 (66.6)	3801 (77.4)	8669 (7.2)	<.001
Previous stroke or TIA	4996 (33.3)	1781 (36.2)	27 333 (22.8)	<.001
CAD or myocardial infarction	4786 (31.9)	1479 (30.1)	17 534 (14.6)	<.001
Carotid stenosis	353 (2.4)	124 (2.5)	1800 (1.5)	<.001
Diabetes	5082 (33.8)	1539 (31.3)	29 752 (24.8)	<.001
Peripheral vascular disease	1068 (7.1)	288 (5.9)	2819 (2.4)	<.001
Hypertension	12 132 (80.7)	4071 (82.8)	86 667 (72.3)	<.001
Smoker	1039 (6.9)	331 (6.7)	17 071 (14.2)	<.001
Dyslipidemia	7132 (47.5)	2376 (48.4)	38 261 (31.9)	<.001
Heart failure	2812 (18.7)	763 (15.5)	5932 (5.0)	<.001
Drugs or alcohol abuse	485 (3.2)	148 (3.0)	11 656 (9.7)	<.001
Obesity or overweight	3087 (20.5)	936 (19.1)	19 933 (16.6)	<.001
Renal insufficiency	2284 (15.2)	495 (10.1)	11 801 (9.7)	<.001
Arrival and admission information, No. (%)				
EMS arrival	7222 (48.0)	2462 (50.1)	55 964 (46.1)	<.001
Transfer in	5699 (37.9)	1740 (35.4)	44 557 (36.7)	
Arrived off hours[a]	7974 (53.0)	2557 (52.0)	64 240 (52.9)	.41
NIHSS score at presentation, No. (%)[b]				
Median (IQR)	9 (2-21)	8 (2-20)	8 (2-19)	<.001
>21	2178 (23.4)	690 (20.9)	16 069 (20.7)	<.001
14-21	1474 (15.9)	544 (16.4)	12 946 (16.7)	
8-13	1260 (13.6)	466 (14.1)	11 522 (14.9)	
0-7	4389 (47.2)	1608 (48.6)	37 077 (47.8)	
Preadmission medication, No. (%)				
Antiplatelet agents				
Single	4862 (32.3)	1498 (30.5)	33 225 (27.4)	
Dual	397 (2.6)	113 (2.3)	5273 (4.4)	
Antihypertensive	10 505 (83.1)	3481 (84.1)	52 550 (53.1)	<.001
Cholesterol reducer	8398 (56.0)	2757 (56.2)	37879 (31.8)	<.001
Diabetic medications	3259 (27.4)	971 (25.0)	16 024 (16.9)	<.001
Vital signs[c]				
Heart rate, median (IQR), bpm	80 (69-94)	80 (69-93)	81 (70-94)	.01
Systolic blood pressure, median (IQR), mm Hg	157 (137-180)	158 (138-182)	160 (140-186)	<.001
Diastolic blood pressure, median (IQR), mm Hg	84 (72-98)	86 (72-100)	87 (74-102)	<.001
INR, median (IQR)	2.2 (1.6-3.0)	1.2 (1.1-1.4)	1.0 (1.0-1.1)	<.001

(continued)

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Table 1. Baseline Characteristics by Anticoagulant Type (continued)

Characteristic	Warfarin (n = 15 036)	NOACs (n = 4918)	No OACs (n = 121 357)	*P* Value
INR category (only warfarin-treated patients)[d]				
Subtherapeutic (<2)	4361 (39.4)	NA	NA	
Therapeutic (2-3)	4134 (37.3)	NA	NA	
Supratherapeutic (>3)	2574 (23.3)	NA	NA	
Hospital Characteristics				
Bed size, median (IQR)	438 (305-634)	439 (315-635)	443 (308-657)	<.001
Academic center, No. (%)	10804 (72.8)	3366 (69.4)	87513 (72.9)	<.001
Primary stroke center, No. (%)	5158 (34.3)	1730 (35.2)	42 999 (35.4)	.02
Rural hospital, No. (%)	460 (3.1)	133 (2.7)	3163 (2.6)	.006

Abbreviations: bpm, beats per minute; CAD, coronary artery disease; EMS, emergency medical services; IQR, interquartile range; INR, international normalized ratio; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; NOACs, non–vitamin K oral anticoagulants; OACs, oral anticoagulants; TIA, transient ischemic attack.

[a] Arrival at the hospital that did not occur from Monday to Friday, 7 AM to 6 PM.

[b] NIHSS score at presentation was missing for 51 088 patients (36.2%). NIHSS ranges from 0 to 42 and a higher score indicates greater stroke severity.

[c] Vital signs indicate first values on admission.

[d] Among patients with the preceding use of warfarin, INR was missing for 3967 patients (26.4%).

subtherapeutic INR, 32.4% for therapeutic INR, and 37.9% for supratherapeutic INR (**Table 3**). This dose-response relationship was similar even after adjusting for measured confounders (eTable 6 in the Supplement). The in-hospital mortality rate in patients with prior use of NOACs (26.5%) was significantly lower than among patients with prior use of warfarin with therapeutic INR (33.4%) (ARD, −6.1% [97.5% CI, −8.2% to −4.0%]; AOR, 0.73 [97.5% CI, 0.66 to 0.81]) or supratherapeutic INR (39.2%) (ARD, −12.0% [97.5% CI, −14.7% to −9.4%]; AOR, 0.56 [97.5% CI, 0.49 to 0.63]), although there was no significant difference compared with patients with prior warfarin treatment with subtherapeutic INR (Table 3). These findings were consistent when confined to patients without prior use of concomitant antiplatelet therapy.

Discussion

To our knowledge, this study is the largest clinical experience with anticoagulation-related ICH. Of more than 141 000 ICH hospitalizations, 10.6% of patients were receiving warfarin and 3.5% were receiving NOACs prior to ICH. While both prior use of warfarin and prior use of NOACs were associated with the increased odds of mortality compared with no prior use of OACs, patients with prior use of NOACs compared with those with prior use of warfarin were more likely to have favorable outcomes in terms of in-hospital mortality and disability. Moreover, prior use of concomitant antiplatelet therapy was associated with increased odds of in-hospital mortality among patients with preceding warfarin therapy, but such significant differences were not observed among patients with preceding NOAC therapy, likely because of the smaller sample size of patients with prior NOAC use.

Prior studies have demonstrated that warfarin users were at increased risk of ICH, and warfarin-associated ICH was associated with larger hematoma volumes,[14] higher rates of hematoma expansion,[15] and worse clinical outcomes as compared with spontaneous ICH.[16] Although randomized clinical trials comparing the efficacy and safety of NOACs with warfarin showed lower incidence of ICH in patients receiving NOACs, there have been limited data regarding the potential effect of preceding NOACs on ICH outcomes. Two previous studies evaluated anticoagulation-related ICH and found that mortality in NOAC-treated patients was numerically lower than that in warfarin-treated patients; however, the differences were not statistically significant, which was likely due to the small number of ICH cases in the NOAC groups (n = 97 and 101).[17,18] Other studies with a limited number of cases suggested that smaller ICH volume, lower likelihood of hematoma expansion, and better functional outcomes occurred in patients taking NOACs compared with warfarin.[19-21]

Unlike previous research, the current analysis included a large contemporary cohort of ICH from 1662 US hospitals. This study found that among these patients with ICH, prior use of warfarin and prior use of NOACs were associated with increased odds of in-hospital mortality compared with spontaneous ICH among patients not taking any OAC. Nonetheless, preceding use of NOACs was associated with a decreased risk of in-hospital mortality and better in-hospital outcomes than preceding use of warfarin, and importantly, this association was consistent when patients with prior use of NOACs were compared with patients with prior use of warfarin whose INR levels were controlled within the therapeutic range. Because many of these patients should be taking OACs for prevention of thromboembolic complications,[22] these findings suggest that NOACs may be a better option than warfarin, considering the lower mortality risk among patients with ICH with prior use of NOACs. Furthermore, NOACs have been shown to be cost-effective relative to warfarin despite the assumption that outcomes after ICH would be identical regardless of OAC types.[23] The findings of this analysis further support the cost-effectiveness of NOACs by showing that ICH outcomes are less severe among patients with prior use of NOACs compared with patients with prior use of warfarin.

In patients receiving OACs, concomitant use of antiplatelet therapy was associated with a 3-fold increase in ICH (0.9% vs 0.3%); therefore, a large portion of patients with ICH were

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Table 2. Outcome Measures by Anticoagulant Type

Outcome Measures	Warfarin	NOACs	No OACs
Primary Outcome: In-Hospital Death			
No./total No. (%)	4903/15 036 (32.6)	1305/4918 (26.5)	27 297/121 357 (22.5)
Adjusted RD (97.5% CI), %[a]	[Reference]	−5.7 (−7.3 to −4.2)	−9.0 (−10.1 to −7.9)
Adjusted OR (97.5% CI)[a]	[Reference]	0.75 (0.69 to 0.81)	0.62 (0.58 to 0.65)
Adjusted RD (97.5% CI), %[a]	9.0 (7.9 to 10.1)	3.3 (1.7 to 4.8)	[Reference]
Adjusted OR (97.5% CI)[a]	1.62 (1.53 to 1.71)	1.21 (1.11 to 1.32)	[Reference]
In-Hospital Death or Discharge to Hospice			
No./total No. (%)	6367/15 036 (42.4)	1822/4918 (37.1)	36 744/121 357 (30.3)
Adjusted RD (95% CI), %[a]	[Reference]	−5.6 (−7.1 to −4.1)	−8.3 (−9.3 to −7.2)
Adjusted OR (95% CI)[a]	[Reference]	0.77 (0.72 to 0.83)	0.67 (0.64 to 0.71)
Adjusted RD (95% CI), %[a]	8.3 (7.2 to 9.3)	2.7 (1.2 to 4.2)	[Reference]
Adjusted OR (95% CI)[a]	1.48 (1.41 to 1.56)	1.14 (1.06 to 1.23)	[Reference]
Able to Ambulate Independently at Discharge[b]			
No./total No. (%)	2642/9269 (28.5)	993/3340 (29.7)	29 632/81 472 (36.4)
Adjusted RD (95% CI), %[a]	[Reference]	1.8 (0 to 3.5)	2.1 (1.0 to 3.3)
Adjusted OR (95% CI)[a]	[Reference]	1.10 (1.00 to 1.20)	1.11 (1.04 to 1.18)
Adjusted RD (95% CI), %[a]	−2.1 (−3.3 to −1.0)	−0.4 (−1.9 to 1.2)	[Reference]
Adjusted OR (95% CI)[a]	0.90 (0.85 to 0.96)	0.99 (0.91 to 1.08)	[Reference]
Discharge Home			
No./total No. (%)	2523/15 036 (16.8)	978/4918 (19.9)	32 482/121 357 (26.8)
Adjusted RD (95% CI), %[a]	[Reference]	3.3 (2.0 to 4.5)	3.0 (2.2 to 3.8)
Adjusted OR (95% CI)[a]	[Reference]	1.28 (1.17 to 1.40)	1.24 (1.16 to 1.31)
Adjusted RD (95% CI), %[a]	−3.0 (−3.8 to −2.2)	0.3 (−0.9 to 1.5)	[Reference]
Adjusted OR (95% CI)[a]	0.81 (0.76 to 0.86)	1.04 (0.95 to 1.12)	[Reference]
Modified Rankin Scale Score 0-1[c]			
No./total No. (%)	683/9162 (7.5)	270/2939 (9.2)	8813/67 496 (13.1)
Adjusted RD (95% CI), %[a]	[Reference]	1.6 (0.4 to 2.8)	2.0 (1.3 to 2.8)
Adjusted OR (95% CI)[a]	[Reference]	1.27 (1.07 to 1.50)	1.30 (1.16 to 1.46)
Adjusted RD (95% CI), %[a]	−2.0 (−2.8 to −1.3)	−0.4 (−1.6 to 0.7)	[Reference]
Adjusted OR (95% CI)[a]	0.77 (0.69 to 0.86)	0.97 (0.84 to 1.13)	[Reference]
Modified Rankin Scale Score 0-2[c]			
No./total No. (%)	1045/9162 (11.4)	416/2939 (14.2)	12 711/67 496 (18.8)
Adjusted RD (95% CI), %[a]	[Reference]	2.5 (1.1 to 3.9)	3.1 (2.3 to 4.0)
Adjusted OR (95% CI)[a]	[Reference]	1.29 (1.13 to 1.48)	1.34 (1.22 to 1.47)
Adjusted RD (95% CI), %[a]	−3.1 (−4.0 to −2.3)	−0.7 (−2.0 to 0.7)	[Reference]
Adjusted OR (95% CI)[a]	0.75 (0.68 to 0.82)	0.96 (0.85 to 1.10)	[Reference]

Abbreviations: NOACs, non–vitamin K oral anticoagulants; OACs, oral anticoagulants; OR, odds ratio; RD, risk difference.

[a] Adjusting for patient and hospital characteristics as follows: demographics (age, sex, and race/ethnicity [black, Hispanic, Asian, and other vs white]), insurance (Medicare, Medicaid, and private insurance/Veterans Affairs/other vs no insurance), medical history (atrial fibrillation or flutter, prior coronary artery disease or myocardial infarction, carotid stenosis, diabetes, peripheral vascular disease, hypertension, smoker, dyslipidemia, prior stroke or transient ischemic attack, heart failure, drug or alcohol abuse, obesity or overweight, and renal insufficiency), arrival and admission information (emergency medical services arrival and transfer in [vs private transportation], arrived off hours), medications prior to admission (antihypertensive, lipid-lowering, and diabetic agents), and hospital characteristics (rural vs urban setting, number of beds, teaching hospital, regions, and certified primary stroke center).

[b] Data were missing for 13 725 patients (12.7%).

[c] Data were missing for 61 714 patients (43.7%). Modified Rankin Scale ranges from 0 to 6, and a higher score indicates worse functional outcome and 6 indicates death. Patients with modified Rankin Scale score of 0 or 1 were classified as having excellent recovery, and those with modified Rankin Scale score of 0 to 2 were classified as having functional independence.

taking both anticoagulant and antiplatelet therapy prior to stroke in this study and that of Shireman et al.[24] Given the potential risk of hematoma expansion, concomitant use of OACs and antiplatelet therapy might affect the outcomes of ICH; however, few studies have evaluated the incremental risk of mortality and disability in patients with ICH taking both anticoagulants and antiplatelet agents, especially in the era of NOACs. A prior meta-analysis, which was conducted before the advent of NOACs, reported higher in-hospital mortality in patients with preceding use of antiplatelet therapy.[25] Similarly, a recent report from the GWTG-Stroke registry showed that patients with prior use of multiple antiplatelet agents, but not SAPT, were at increased risk of in-hospital mortality.[26] Yet in these analyses, patients with concomitant use of OACs were excluded and the incremental risk of antiplatelet therapy in patients treated with OACs could not be evaluated.

In several clinical settings, patients are eligible for both anticoagulation and antiplatelet therapies, such as patients with atrial fibrillation who received recent percutaneous coronary intervention. Particularly in patients with atrial fibrillation, the combination of OAC and DAPT is considered required in those who require coronary stent implantation up to 6 months, depending on the individualized ischemic and bleeding risks.[27,28] Although warfarin and NOACs are recommended for the combination strategy of antiplatelet and anticoagulation therapies,[27] a recent trial comparing 3 different antithrombotic strategies (low-dose rivaroxaban plus a $P2Y_{12}$ inhibitor, very-low-dose rivaroxaban plus DAPT, and warfarin plus DAPT) demonstrated lower bleeding rates in the rivaroxaban strategies than in the warfarin strategy, with similar efficacy.[29-31]

The current study found significantly increased odds of in-hospital mortality among patients with prior warfarin

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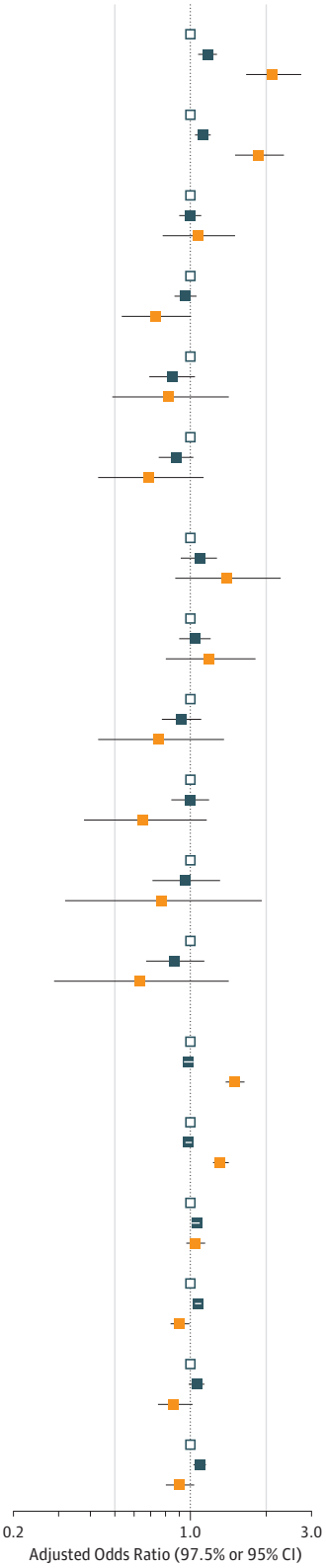
Figure 2. Incremental Risk of Antiplatelet Therapy by the Type of Concomitant Anticoagulant

	No. With Event/ Total No. (%)	Adjusted Risk Difference (97.5% or 95% CI)	Adjusted Odds Ratio (97.5% or 95% CI)
Warfarin			
In-hospital mortality			
No antiplatelet agent	3101/9777 (31.7)	[Reference]	[Reference]
Single antiplatelet agent	1615/4862 (33.2)	3.2 (1.4 to 5.0)[a]	1.17 (1.07 to 1.28)[a]
Dual antiplatelet agents	187/397 (47.1)	16.5 (10.9 to 22.2)[a]	2.13 (1.66 to 2.73)[a]
In-hospital mortality or hospice			
No antiplatelet agent	4108/9777 (42.0)	[Reference]	[Reference]
Single antiplatelet agent	2049/4862 (42.1)	2.5 (0.8 to 4.3)	1.12 (1.04 to 1.21)
Dual antiplatelet agents	210/397 (52.9)	14.1 (9.1 to 19.1)	1.87 (1.50 to 2.34)
Able to ambulate independently			
No antiplatelet agent	1720/6087 (28.3)	[Reference]	[Reference]
Single antiplatelet agent	861/2991 (28.8)	0.1 (-1.9 to 2.1)	1.00 (0.90 to 1.11)
Dual antiplatelet agents	61/191 (31.9)	1.5 (-5.0 to 8.0)	1.08 (0.78 to 1.49)
Discharge home			
No antiplatelet agent	1655/9777 (16.9)	[Reference]	[Reference]
Single antiplatelet agent	812/4862 (16.7)	-0.5 (-1.8 to 0.8)	0.96 (0.87 to 1.06)
Dual antiplatelet agents	56/397 (14.1)	-3.7 (-7.3 to -0.2)	0.74 (0.54 to 1.01)
Modified Rankin Scale score 0-1			
No antiplatelet agent	452/5916 (7.6)	[Reference]	[Reference]
Single antiplatelet agent	211/2980 (7.1)	-0.9 (-2.1 to 0.4)	0.85 (0.69 to 1.04)
Dual antiplatelet agents	20/266 (7.5)	-1.4 (-4.7 to 1.9)	0.83 (0.49 to 1.41)
Modified Rankin Scale score 0-2			
No antiplatelet agent	684/5916 (11.6)	[Reference]	[Reference]
Single antiplatelet agent	334/2980 (11.2)	-1.0 (-2.5 to 0.5)	0.88 (0.75 to 1.03)
Dual antiplatelet agents	27/266 (10.2)	-3.3 (-7.2 to 0.6)	0.70 (0.43 to 1.12)
Non-vitamin K oral anticoagulants			
In-hospital mortality			
No antiplatelet agent	873/3307 (26.4)	[Reference]	[Reference]
Single antiplatelet agent	395/1498 (26.4)	1.4 (-1.7 to 4.5)[a]	1.08 (0.91 to 1.28)[a]
Dual antiplatelet agents	37/113 (32.7)	7.0 (-2.9 to 16.8)[a]	1.41 (0.87 to 2.28)[a]
In-hospital mortality or hospice			
No antiplatelet agent	1241/3307 (37.5)	[Reference]	[Reference]
Single antiplatelet agent	536/1498 (35.8)	0.7 (-2.3 to 3.8)	1.04 (0.90 to 1.20)
Dual antiplatelet agents	45/113 (39.8)	4.1 (-4.8 to 13.0)	1.20 (0.80 to 1.81)
Able to ambulate independently			
No antiplatelet agent	668/2247 (29.7)	[Reference]	[Reference]
Single antiplatelet agent	306/1020 (30.0)	-1.6 (-5.1 to 1.8)	0.92 (0.77 to 1.11)
Dual antiplatelet agents	19/73 (26.0)	-4.9 (-14.9 to 5.1)	0.76 (0.43 to 1.35)
Discharge home			
No antiplatelet agent	658/3307 (19.9)	[Reference]	[Reference]
Single antiplatelet agent	303/1498 (20.2)	-0.2 (-2.5 to 2.1)	1.00 (0.84 to 1.18)
Dual antiplatelet agents	17/113 (15.0)	-4.9 (-11.3 to 1.5)	0.66 (0.38 to 1.16)
Modified Rankin Scale score 0-1			
No antiplatelet agent	174/1965 (8.9)	[Reference]	[Reference]
Single antiplatelet agent	90/904 (10.0)	-0.3 (-2.6 to 2.0)	0.96 (0.71 to 1.30)
Dual antiplatelet agents	6/70 (8.6)	-1.3 (-7.8 to 5.2)	0.78 (0.32 to 1.90)
Modified Rankin Scale score 0-2			
No antiplatelet agent	280/1965 (14.3)	[Reference]	[Reference]
Single antiplatelet agent	128/904 (14.2)	-1.6 (-4.4 to 1.2)	0.87 (0.67 to 1.13)
Dual antiplatelet agents	8/70 (11.4)	-4.1 (-11.4 to 3.3)	0.64 (0.29 to 1.41)
No oral anticoagulant			
In-hospital mortality			
No antiplatelet agent	18526/82859 (22.4)	[Reference]	[Reference]
Single antiplatelet agent	7209/33225 (21.7)	-0.2 (-0.9 to 0.5)[a]	0.99 (0.94 to 1.03)[a]
Dual antiplatelet agents	1562/5273 (29.6)	7.3 (5.7 to 8.9)[a]	1.50 (1.38 to 1.64)[a]
In-hospital mortality or hospice			
No antiplatelet agent	24276/82859 (29.3)	[Reference]	[Reference]
Single antiplatelet agent	10445/33225 (31.4)	-0.4 (-1.1 to 0.2)	0.98 (0.95 to 1.01)
Dual antiplatelet agents	2023/5273 (38.4)	5.8 (4.3 to 7.2)	1.32 (1.23 to 1.42)
Able to ambulate independently			
No antiplatelet agent	20714/54193 (38.2)	[Reference]	[Reference]
Single antiplatelet agent	7868/23887 (32.9)	1.0 (0.2 to 1.7)	1.05 (1.01 to 1.09)
Dual antiplatelet agents	1050/3392 (31.0)	1.0 (-0.7 to 2.7)	1.05 (0.96 to 1.14)
Discharge home			
No antiplatelet agent	23486/82859 (28.3)	[Reference]	[Reference]
Single antiplatelet agent	7920/33225 (23.8)	1.2 (0.6 to 1.8)	1.07 (1.04 to 1.11)
Dual antiplatelet agents	1076/5273 (20.4)	-1.3 (-2.5 to -0.1)	0.91 (0.84 to 0.99)
Modified Rankin Scale score 0-1			
No antiplatelet agent	6324/44925 (14.1)	[Reference]	[Reference]
Single antiplatelet agent	2207/19357 (11.4)	0.5 (-0.2 to 1.1)	1.06 (0.99 to 1.13)
Dual antiplatelet agents	282/3214 (8.8)	-0.9 (-2.0 to 0.3)	0.87 (0.75 to 1.02)
Modified Rankin Scale score 0-2			
No antiplatelet agent	8944/44925 (19.9)	[Reference]	[Reference]
Single antiplatelet agent	3327/19357 (17.20)	0.9 (0.2 to 1.7)	1.08 (1.02 to 1.15)
Dual antiplatelet agents	440/3214 (13.7)	-0.9 (-2.3 to 0.4)	0.91 (0.80 to 1.03)



For model covariates, see the Methods section.

[a] 97.5% CIs are reported for in-hospital mortality; 95% CIs for other outcomes.

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Table 3. Comparison of In-Hospital Mortality Between NOACs vs Warfarin by INR Category

Reference Warfarin Category	No. of Deaths/Total No. (%)		Adjusted RD (97.5% CI), %[a]	Adjusted OR (97.5% CI)[a]
	Warfarin	NOACs		
All Patients With ICH Receiving NOACs or Warfarin[b]				
Subtherapeutic (<2)	1119/4361 (25.7)	1305/4918 (26.5)	−0.3 (−2.4 to 1.9)	0.99 (0.88 to 1.11)
Therapeutic (2-3)	1382/4134 (33.4)		−6.1 (−8.2 to −4.0)	0.73 (0.66 to 0.81)
Supratherapeutic (>3)	1008/2574 (39.2)		−12.0 (−14.7 to −9.4)	0.56 (0.49 to 0.63)
Patients With ICH Receiving NOACs or Warfarin Without Concomitant Antiplatelet Therapy[c]				
Subtherapeutic (<2)	700/2797 (25.0)	873/3307 (26.4)	0.1 (−2.3 to 2.6)	1.01 (0.88 to 1.16)
Therapeutic (2-3)	860/2657 (32.4)		−5.2 (−7.7 to −2.6)	0.76 (0.67 to 0.86)
Supratherapeutic (>3)	635/1675 (37.9)		−11.3 (−14.6 to −8.1)	0.57 (0.49 to 0.67)

Abbreviations: ICH, intracerebral hemorrhage; INR, international normalized ratio; NOACs, non–vitamin K oral anticoagulants; OR, odds ratio; RD, risk difference.

[a] Adjusting for patient and hospital characteristics as follows: demographics (age, sex, and race/ethnicity [black, Hispanic, Asian, and other vs white]), insurance (Medicare, Medicaid, and private insurance/Veterans Affairs/other vs no insurance), medical history (atrial fibrillation or flutter, prior coronary artery disease or myocardial infarction, carotid stenosis, diabetes, peripheral vascular disease, hypertension, smoker, dyslipidemia, prior stroke or transient ischemic attack, heart failure, drug or alcohol abuse, obesity or overweight, and renal insufficiency), arrival and admission information (emergency medical services arrival and transfer in [vs private transportation], arrived off hours), medications prior to admission (antihypertensive, lipid-lowering, and diabetic agents), and hospital characteristics (rural vs urban setting, number of beds, teaching hospital, regions, and certified primary stroke center).

[b] Among patients with the preceding use of NOACs or warfarin, after excluding 3967 warfarin-treated patients who had missing INR data, a total of 15 987 patients were analyzed.

[c] Among patients receiving NOACs or warfarin without concomitant antiplatelet therapy, after excluding 2648 warfarin-treated patients who had missing INR data, a total of 10 436 patients were analyzed.

and antiplatelet therapy, whereas such differences were not observed in patients with prior NOAC treatment. Furthermore, the direct comparison between NOACs and warfarin demonstrated that the lower in-hospital mortality among patients with prior NOAC therapy was numerically more prominent among patients with prior concomitant antiplatelet therapy. While these findings are not conclusive given the relatively small of number of patients with concomitant NOAC and antiplatelet therapy, they may support the hypothesis that NOACs could be a reasonable choice with better safety profiles when combination strategy is required. The recently published Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) trial also confirmed this hypothesis.[32]

The major concern regarding NOACs is a lack of specific reversal agents. Immediate management is necessary for patients with life-threatening bleeding including ICH, and appropriate reversal agents should be administered. Idarucizumab, a specific antidote for dabigatran, is commercially available in the United States,[33] while a reversal agent for factor Xa inhibitors, such as andexanet alfa, has not yet been approved.[34] In this study, more than half of patients with ICH (63%) were admitted before the approval of idarucizumab, but the preceding use of NOACs was associated with lower odds of mortality and disability compared with prior use of warfarin for which an established reversal strategy could be applied.

The intensity of anticoagulation is predictive of outcomes in warfarin-treated patients who experienced an ICH. An evaluation of patients with supratentorial ICH suggested that warfarin therapy increased the risk of mortality from 25.8% for patients not receiving warfarin to 52.0%, and the risk increased further with higher INR levels.[35] The result of this study was consistent with this previous finding and additionally showed that supratherapeutic warfarin was associated with the increased risk of poor neurological outcome. In clinical practice, maintaining INR within the therapeutic range could be challenging. Even in the clinical trials comparing warfarin with NOACs in terms of efficacy and safety, time in therapeutic range went from only 55.2% to 64.9%.[3-6] NOACs might be a better option in broader clinical situations, given the risk of worse outcomes of ICH with supratherapeutic INR (even with therapeutic INR) and the challenge in achieving time in therapeutic range with warfarin.

Limitations

This study has several limitations. First, despite the use of a large number of characteristics to adjust for potential confounding, residual or unmeasured confounding may exist and it may be most prominent in terms of comparison with the no OAC group. Because it is not feasible to randomize patients with ICH to different antithrombotic regimens prior to ICH, our observational findings provide important clinical insights in the context of oral anticoagulation–related ICH, especially in the era of NOACs. Second, the data were obtained from hospitals participating in the GWTG-Stroke program and may not be able to be extrapolated to patients treated in hospitals outside the registry. Nonetheless, to our knowledge, GWTG-Stroke is the largest stroke registry in the United States, covering about three-fourths of the US population. Furthermore, ICH tends to be concentrated at large teaching hospitals. Given the higher representation of high-volume and academic centers in GWTG-Stroke,[36] the study population of this investigation is potentially quite representative of patients with ICH in the United States.

Third, despite the large sample size, in the analysis evaluating the incremental risk of mortality and morbidity with concomitant preceding use of antiplatelet and anticoagulant

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therapies, statistical power might be insufficient in patients with prior use of NOACs. Fourth, timing of the last anticoagulant or antiplatelet agents prior to ICH was not available. Also, the dose of NOAC or antiplatelet agents was not recorded. Patients with renal dysfunction or receiving concomitant antiplatelet therapy may have been receiving a lower dose of NOACs and, consequently, better outcomes. Fifth, OAC reversal strategies, such as the use of vitamin K, fresh frozen plasma, or intravenous factor concentrates, were not collected in the database. Idarucizumab was approved by the US Food and Drug Administration on October 19, 2015, but only 37.0% of patients taking NOACs were admitted after the approval date and potentially eligible to receive idarucizumab.

Sixth, some patients were missing data on mRS at discharge (43.7%), which could skew the results for this exploratory outcome; however, it is unlikely that physicians will report ICH severity differently according to anticoagulation type prior to admission. Seventh, in our database, ICH volume, hematoma expansion, and commonly used clinical scores (eg, ICH score)[37] were not available, yet these variables are surrogate markers for predicting mortality and disability. Because harder end points, such as in-hospital death, functional outcomes represented by mRS at discharge, and discharge disposition, were evaluated in our study, assessing these surrogate markers may not provide additional insights. In addition, given that greater ICH volume, greater hematoma expansion, and higher ICH score may be caused by the preceding use of NOACs or warfarin resulting in the worse clinical outcomes, including these variables in the models would not be appropriate.

Conclusions

Among patients with ICH, prior use of NOACs or warfarin was associated with higher in-hospital mortality compared with no OACs. Prior use of NOACs, compared with prior use of warfarin, was associated with lower risk of in-hospital mortality.

ARTICLE INFORMATION

Accepted for Publication: January 2, 2018.

Published Online: January 25, 2018. doi:10.1001/jama.2017.21917

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Statistical analysis: Xian, Liang, Matsouaka, Peterson.
Obtained funding: Xian, Peterson, Fonarow.
Administrative, technical, or material support: Xian, Hernandez, Fonarow.
Supervision: Xian, Matsouaka, Saver, Peterson, Fonarow.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Inohara reported receiving grants from JSPS during the conduct of the study and Pfizer Health Research Foundation and Miyata Cardiac Research Promotion Foundation outside of this work. Dr Xian reported receiving grants from Genentech, Janssen, and Daiichi Sankyo during the study. Dr Saver has served as a consultant and/or on the advisory board of Medtronic, Stryker, and Neuravia. Dr Smith was a member of the Get With The Guidelines (GWTG) steering committee and served on a data safety and monitoring board for Massachusetts General Hospital. Dr Schwamm reported serving as the volunteer chair of the American Heart Association/American Stroke Association GWTG-Stroke Clinical Work Group. Dr Hernandez reported receiving grants and/or personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Daiichi, Janssen, Novartis, and Portola Pharmaceuticals. Dr Bhatt reported receiving nonfinancial support from the American Heart Association; personal fees from Duke Clinical Research Institute (clinical trial steering committees), Mayo Clinic, Population Health Research Institute (clinical trial steering committee), American College of Cardiology (senior associate editor, Clinical Trials and News, ACC.org), Belvoir Publications (editor in chief, *Harvard Heart Letter*), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), WebMD (CME steering committees), Elsevier, Society of Cardiovascular Patient Care (secretary/treasurer), HMP Communications (editor in chief, *Journal of Invasive Cardiology*), Harvard Clinical Research Institute (clinical trial steering committee), *Journal of the American College of Cardiology* (guest editor, associate editor), Cleveland Clinic, and Mount Sinai School of Medicine; grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis, The Medicines Company, Roche, Pfizer, Forest Laboratories/AstraZeneca, Ischemix, Amgen, Eli Lilly, Chiesi, and Ironwood; and other support from FlowCo, PLx Pharma, Takeda, Medscape Cardiology, Regado Biosciences, Boston VA Research Institute, *Clinical Cardiology* (deputy editor), Veterans Affairs, St Jude Medical, Biotronik, Cardax, American College of Cardiology, Boston Scientific, and Merck. Dr Bhatt has served as chair of the NCDR-ACTION Registry steering committee and VA CART research and publications committee. Dr Peterson reported receiving grants and/or personal fees from Bayer Pharmaceuticals, Janssen Pharmaceuticals, AstraZeneca, Genentech, and the American Heart Association GWTG-Stroke Analytic and has served as a consultant/advisory board member for Janssen, Boehringer Ingelheim, Sanofi, Bayer, Merck, AstraZeneca, Signal Path, and Venable. Dr Fonarow reported serving on the GWTG steering committee; receiving grant funding from the Patient Centered Outcome Research Institute; being an employee of the University of California, which has a patent on an endovascular therapy device; and serving as a consultant for Janssen. No other disclosures were reported.

Funding/Support: The GWTG-Stroke program is provided by the American Heart Association/American Stroke Association. This study is in part supported by the ARAMIS registry with research funding from Daiichi Sankyo, Genentech, and Janssen.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: Drs Saver and Peterson, associate editors of *JAMA*, and Dr Fonarow, associate editor for health care quality and guidelines of *JAMA Cardiology*, were not involved in the editorial review of or decision to publish this article.

Meeting Presentation: This study was presented at the International Stroke Conference; January 25, 2018; Los Angeles, California.

Additional Contributions: We acknowledge Erin Campbell, MS (Duke Clinical Research Institute) for her editorial contributions; she did not receive compensation for her contributions, except for her employment at the Duke Clinical Research Institute, where the study was conducted.

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