Clinical Characteristics and Outcomes Associated With Oral Anticoagulant Use Among Patients Hospitalized With Intracerebral Hemorrhage

Ying Xian, MD, PhD; Shuaiqi Zhang, MS; Taku Inohara, MD, PhD; Maria Grau-Sepulveda, MD, MPH; Roland A. Matsouaka, PhD; Eric D. Peterson, MD, MPH; Jonathan P. Piccini, MD, MHS; Eric E. Smith, MD, MPH; Kevin N. Sheth, MD; Deepak L. Bhatt, MD, MPH; Gregg C. Fonarow, MD; Lee H. Schwamm, MD

Abstract

IMPORTANCE Although the use of factor Xa (FXa) inhibitors has increased substantially over the past decade, there are limited data on characteristics and outcomes of FXa inhibitor–associated intracerebral hemorrhage (ICH).

OBJECTIVE To investigate the association between prior oral anticoagulant use (FXa inhibitors, warfarin, or none) and in-hospital outcomes among patients with nontraumatic ICH.

DESIGN, SETTING, AND PARTICIPANTS This is a cohort study of 219,701 patients with nontraumatic ICH admitted to 1,870 hospitals in the Get With The Guidelines–Stroke registry between October 2013 and May 2018. Data analysis was performed in December 2019.

EXPOSURES Anticoagulation therapy before ICH.

MAIN OUTCOMES AND MEASURES The primary outcome was in-hospital mortality. Secondary outcomes were a composite measure of in-hospital mortality or discharge to hospice, discharge home, independent ambulation, and modified Rankin Scale (mRS) score at discharge.

RESULTS Of 219,701 patients (mean [SD] age, 68.2 [15.3] years; 104,940 women [47.8%]), 9,202 (4.2%) were taking FXa inhibitors, 21,430 (9.8%) were taking warfarin, and 189,069 (86.0%) were not taking any oral anticoagulant before ICH. Patients taking FXa inhibitors or warfarin were older and had higher prevalence of cardiovascular risk factors. Compared with those not taking an oral anticoagulant (42,660 of 189,069 patients [22.6%]), the in-hospital mortality risk was higher for both FXa inhibitors (2,487 of 9,202 patients [27.0%]; adjusted odds ratio [aOR], 1.27; 95% CI, 1.20-1.34; P < .001) and warfarin (7,032 of 21,430 patients [32.8%]; aOR, 1.67; 95% CI, 1.60-1.74; P < .001). Both FXa inhibitors (3,478 of 9,202 patients [37.8%]; aOR, 1.19; 95% CI, 1.13-1.26; P < .001) and warfarin (9,151 of 21,430 patients [42.7%]; aOR, 1.50; 95% CI, 1.44-1.56; P < .001) were associated with higher odds of death or discharge to hospice compared with not taking oral anticoagulation (58,022 of 189,069 patients [30.7%]). Although the rates of discharge home, independent ambulation, mRS scores of 0 or 1, and mRS scores of 0 to 2 were numerically lower among patients taking FXa inhibitors, these differences were not significant compared with patients not taking oral anticoagulants. In contrast, patients taking FXa inhibitors were less likely to die (aOR, 0.76; 95% CI, 0.72-0.81; P < .001) or to experience death or discharge to hospice (aOR, 0.79; 95% CI, 0.75-0.84; P < .001), more likely to be discharged home (aOR, 1.18; 95% CI, 1.10-1.26; P < .001), and had better mRS scores at discharge (eg, mRS scores of 0-1: aOR, 1.24; 95% CI, 1.09-1.40; P < .001) than those treated with warfarin. Concomitant warfarin and antiplatelet therapy (either single or dual) was associated with worse outcomes compared with taking warfarin alone (eg, in-hospital mortality for dual-antiplatelet agents: aOR, 2.07; 95% CI, 1.72-2.50; P < .001). However, such incremental risk was not significant in patients taking FXa inhibitors.

(continued)
CONCLUSIONS AND RELEVANCE In this cohort study, FXa inhibitor–associated ICH was associated with higher risk of mortality or death or discharge to hospice than not taking an oral anticoagulant, but patients taking FXa inhibitors had better outcomes than those with warfarin-related ICH.

Introduction

Intracerebral hemorrhage (ICH) is the most feared complication of oral anticoagulant (OAC) therapy and is associated with high mortality and morbidity. Compared with warfarin, factor Xa (FXa) inhibitors, such as apixaban, rivaroxaban, and edoxaban, reduce the risk of ICH by 52%. Despite their favorable safety profiles, as many as 0.5% of patients taking FXa inhibitors will still experience an intracranial bleeding event with each year of therapy. Although the use of FXa inhibitors has increased substantially over the past decade, prior studies of FXa inhibitor–associated ICH are limited in size and scope. We have characterized ICH in patients taking non–vitamin K antagonist OACs, including direct thrombin inhibitor (dabigatran) and FXa inhibitors as a group. Given their differences in mechanism of action and targets at the coagulation cascade, there remains limited experience with FXa inhibitor–associated ICH. In addition, many patients were taking both anticoagulant and antiplatelet therapy before ICH, but the potential incremental risk associated with concomitant therapy remains unknown.

Using data from the American Heart Association and American Stroke Association Get With The Guidelines–Stroke (GWTG-Stroke) registry, we sought to evaluate the characteristics of patients who experienced a nontraumatic ICH with preceding use of FXa inhibitors compared with no OAC or with warfarin, and to determine the risk of mortality and disability according to the type of anticoagulants, and any incremental risk associated with concomitant antiplatelet therapy in nationwide clinical practice.

Methods

Data Source

The GWTG-Stroke program is an ongoing, voluntary, national stroke registry and quality improvement initiative sponsored by the American Heart Association and American Stroke Association. Details of GWTG-Stroke registry data collection and variable definitions have been described elsewhere. Standardized data collection includes patient demographic characteristics, medical history, medications taken before admission, diagnostic testing, brain imaging, in-hospital treatment, and outcomes. The validity and reliability of data collection have been reported in previous research. Each participating hospital received either human research approval to enroll patients without individual patient consent under the Common Rule (45 CFR §46) or a waiver of authorization and exemption from subsequent review by their institutional review board. IQVIA, Inc serves as the data collection and coordination center. The Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for research purposes. This study was approved by the institutional review board of Duke University. This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Study Population and Variable of Interest

This is a registry-based cohort study of patients hospitalized for nontraumatic ICH in GWTG-Stroke hospitals between October 2013 and May 2018. For the purpose of our analysis, patients with subarachnoid hemorrhage, subdural hematoma, or those taking dabigatran (direct thrombin

JAMA Network Open. 2021;4(2):e2037438. doi:10.1001/jamanetworkopen.2020.37438
inhibitor) were not included in the study population. Because andexanet-α, a specific reversal agent for rivaroxaban and apixaban, may affect outcomes in ICH and because the GWTG-Stroke registry did not previously collect the name of the reversal agent, we limited our study period until May 3, 2018, before the US Food and Drug Administration’s approval of andexanet-α. Prior use of OACs was defined as documentation of patients taking an OAC within 7 days before hospital arrival. On the basis of this information, we categorized patients into 3 mutually exclusive groups: direct FXa inhibitors, including rivaroxaban, apixaban, or edoxaban; warfarin; and no OAC use before ICH. The Figure shows details of inclusion and exclusion criteria. Briefly, we excluded patients who had in-hospital stroke onset, transferred out to another hospital, had discharge information missing, left against medical advice, had a prosthetic heart valve, or took anticoagulants other than warfarin or FXa inhibitors before their stroke. After these exclusions, the final study population consisted of 219,701 patients with nontraumatic ICH from 1870 GWTG-Stroke hospitals in the US. Because the National Institute of Health Stroke Scale (NIHSS) score (range, 0-42, with a higher score indicating greater stroke severity) is a critical factor associated with outcomes, we further created a subgroup of individuals with complete NIHSS data (143,340 patients [65.2%]) for a sensitivity analysis.

The primary outcome was in-hospital mortality (yes or no). Secondary outcomes included a composite measure of in-hospital mortality or discharge to hospice (yes or no), discharge disposition (home vs other), 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 free from substantial disability, and those with an mRS score of 0 to 2 were classified as functionally independent.

Statistical Analysis
Medians (25th to 75th percentiles) and percentages were used to describe the distribution of continuous and categorical variables, respectively. Baseline characteristics were compared across the 3 prior anticoagulation treatment groups using the Pearson χ² test for categorical variables and Kruskal-Wallis test for continuous variables. Multivariable logistic regression models were performed to investigate the associations of prior anticoagulation therapies with each clinical outcome. Because it is inappropriate to impute outcome measures, complete case analyses were performed for death (100% of cases), discharge disposition (100% of cases), ambulatory status (67.6% of cases), and mRS (67.7% of cases) models.

The prior anticoagulation treatment was included as an independent variable, with no OAC or warfarin as the reference groups. A generalized estimation equations modeling approach was used to account for within-hospital clustering of patients. These analyses adjusted for baseline patient demographic and clinical factors before the index event and hospital characteristics that are expected to be associated with outcome and have been used in prior GWTG-Stroke analyses.9,12
Covariates included age, sex, race/ethnicity (admission staff, medical staff, or both recorded the patient’s self-reported race/ethnicity, usually during the registration), insurance, medical history (atrial fibrillation or flutter, coronary artery disease or prior myocardial infarction, prior stroke, prior transient ischemic attack, carotid stenosis, heart failure, hypertension, peripheral vascular disease, diabetes, dyslipidemia, obesity, renal insufficiency, smoking status, and drug or alcohol abuse), arrival and admission information (emergency medical services arrival vs private transportation, transfer-in, and arrived off-hours), medication taken before admission (antihypertensive, lipid-lowering medication, diabetic medication, single-antiplatelet agent [aspirin, clopidogrel, prasugrel, ticagrelor, or ticlopidine], dual-antiplatelet therapy [aspirin plus dipyridamole or aspirin plus clopidogrel, prasugrel, ticagrelor, or ticlopidine], other antiplatelet or combination), rural hospital, hospital number of beds, academic center, geographic region, primary stroke center, and comprehensive stroke center.

NIHSS score was not included in the primary analysis because NIHSS score may lie somewhere between OAC and outcomes, reflecting more rapid hematoma growth before hospital arrival. Instead, the same analyses were replicated in patients with documented NIHSS scores while adjusting for NIHSS score along with other original covariates (143 340 patients [65.2%]) in the sensitivity analysis. The Glasgow Coma Scale (GCS) and ICH scores are commonly used risk stratification scales for ICH. Use of anticoagulation reversal treatment during the hospitalization may have been associated with outcomes. However, these data elements are available for only 86 800 patients (39.5%) hospitalized in centers that opt to report comprehensive stroke center data element. These variables have high missing rates (GCS score, 29.1%; ICH score, 38.1%; and reversal treatment, 72.2%). Therefore, these data were provided for information purpose only and were not included in the risk-adjustment model.

To evaluate the incremental risk of mortality and disability with the concomitant prior antiplatelet therapy, separate multivariable logistic regression models with generalized estimation equations were performed in each OAC group (FXa inhibitors, warfarin, and no OAC), respectively, with antiplatelet treatment category (no antiplatelet, single-antiplatelet agent, or dual-antiplatelet agents) as the independent variable. Patients who were not in any of these 3 antiplatelet groups were excluded from the analysis.

All statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute). All P values are 2-sided, with P < .05 considered significant. The original analyses were performed in December 2019.

**Results**

Baseline characteristics specific to anticoagulants used are shown in Table 1. Of 219 701 patients with nontraumatic ICH (mean [SD] age, 68.2 [15.3] years; 104 940 women [47.8%]), 9202 patients (4.2%) were receiving FXa inhibitors, 21 430 (9.8%) were receiving warfarin, and 189 069 (86.0%) were not receiving any OAC before ICH. Compared with patients without OAC use, patients with prior FXa inhibitor or warfarin use were more likely to be older and non-Hispanic White and to have Medicare insurance; had a higher prevalence of cardiovascular risk factors, including atrial fibrillation or flutter, prior stroke, prior transient ischemic attack, coronary artery disease, peripheral vascular disease, diabetes, hypertension, heart failure, dyslipidemia, and obesity; and had lower a prevalence of tobacco and drug or alcohol abuse (Table 1).

Overall, approximately one-third of patients were taking some form of antiplatelet therapy before ICH. Patients taking FXa inhibitors or warfarin were more likely to have concomitant aspirin use than those not taking OAC (2492 [27.1%] vs 6445 [30.1%] vs 46 974 [24.8%]) (Table 1). Patients in all 3 groups had a median initial NIHSS score of 9, whereas patients in the warfarin group had higher mean NIHSS scores (mean [SD], 12.5 [11.3]) than patients taking FXa inhibitors (mean [SD], 11.9 [10.7]) and those not taking OACs (mean [SD], 11.9 [10.8]).
Table 1. Baseline Characteristics of Patients and Hospitals by Use of Anticoagulants Before Intracerebral Hemorrhage

| Characteristics                  | Patients or hospitals, No. (%) | Factor Xa inhibitors (n = 9202) | Warfarin (n = 21 430) | No OAC (n = 189 069) | P value |
|----------------------------------|--------------------------------|---------------------------------|-----------------------|----------------------|---------|
| **Patient characteristics**      |                                |                                 |                       |                      |         |
| Age, median (IQR), y             |                                | 77 (70-84)                      | 77 (69-84)            | 68 (56-79)           | <.001   |
| Women                            | 4510 (49.0)                    | 9928 (46.3)                     | 90 502 (47.9)         |                      | <.001   |
| **Race/ethnicity**               |                                |                                 |                       |                      |         |
| Non-Hispanic                     |                                |                                 |                       |                      | <.001   |
| White                            | 7229 (78.6)                    | 16 480 (76.9)                   | 112 656 (59.6)        |                      |         |
| Black                            | 906 (9.9)                      | 2303 (10.8)                     | 36 783 (19.5)         |                      | <.001   |
| Hispanic                         | 422 (4.6)                      | 997 (4.7)                       | 18 292 (9.7)          |                      |         |
| Asian                            | 298 (3.2)                      | 771 (3.6)                       | 10 039 (5.3)          |                      |         |
| Other                            | 347 (3.8)                      | 879 (4.1)                       | 11 299 (6.0)          |                      |         |
| **Insurance**                    |                                |                                 |                       |                      |         |
| Medicare                         | 4844 (52.6)                    | 11 236 (52.4)                   | 73 106 (38.7)         |                      |         |
| Medicaid                         | 629 (6.8)                      | 1569 (7.3)                      | 21 896 (11.6)         |                      |         |
| Private insurance                | 3396 (36.9)                    | 7752 (36.2)                     | 66 084 (35.0)         |                      | <.001   |
| Self-pay                         | 96 (1.0)                       | 278 (1.3)                       | 11 725 (6.2)          |                      |         |
| Not documented                   | 237 (2.6)                      | 595 (2.8)                       | 16 258 (8.6)          |                      |         |
| **Medical history**              |                                |                                 |                       |                      |         |
| Atrial fibrillation or flutter   | 6849 (74.4)                    | 14 317 (66.8)                   | 13 109 (6.9)          |                      | <.001   |
| Previous stroke                  | 2872 (31.2)                    | 6106 (28.5)                     | 37 585 (19.9)         |                      | <.001   |
| Previous transient ischemic attack | 841 (9.1)                     | 1680 (7.8)                      | 8329 (4.4)            |                      | <.001   |
| Coronary artery disease or myocardial infarction | 2772 (30.1) | 6760 (31.5) | 27 103 (14.3) | <.001 |
| Carotid stenosis                 | 240 (2.6)                      | 513 (2.4)                       | 2771 (1.5)            |                      | <.001   |
| Peripheral vascular disease      | 510 (5.5)                      | 1502 (7.0)                      | 4406 (2.3)            |                      | <.001   |
| Hypertension                     | 7620 (82.8)                    | 17 354 (81.0)                   | 135 672 (71.8)        |                      | <.001   |
| Heart failure                    | 1441 (15.7)                    | 4033 (18.8)                     | 9404 (5.0)            |                      | <.001   |
| Diabetes                         | 2839 (30.9)                    | 7189 (33.6)                     | 46 764 (24.7)         |                      | <.001   |
| Dyslipidemia                     | 4515 (49.1)                    | 10 287 (48.0)                   | 60 118 (31.8)         |                      | <.001   |
| Obesity or overweight           | 2000 (21.7)                    | 4783 (22.3)                     | 34 489 (18.2)         |                      | <.001   |
| Renal insufficiency              | 858 (9.3)                      | 2777 (13.0)                     | 13 713 (7.3)          |                      | <.001   |
| Smoker                           | 634 (6.9)                      | 1488 (6.9)                      | 26 560 (14.1)         |                      | <.001   |
| Drug or alcohol abuse            | 331 (3.6)                      | 723 (3.4)                       | 19 001 (10.1)         |                      | <.001   |
| **Arrival and admission information** |                              |                                 |                       |                      |         |
| Arrival by emergency medical services | 4628 (50.3) | 10 228 (47.7) | 87 576 (46.3) | <.001 |
| Arrived off-hours<sup>a</sup>    | 5150 (56.0)                    | 12 176 (56.8)                   | 108 624 (57.5)        | .005                |         |
| Transfer-in                      | 3318 (36.1)                    | 8281 (38.6)                     | 70 962 (37.5)         | <.001               |         |
| Time from symptom onset to arrival, median (IQR), min | 210 (75-484) | 232 (85-525) | 202 (71-494) | <.001 |
| **NIHSS score at presentation<sup>b</sup>** |                          |                                 |                       |                      |         |
| Mean (SD)                        | 11.9 (10.7)                    | 12.5 (11.3)                     | 11.9 (10.8)           |                     | <.001   |
| Median (IQR)                     | 9 (3-20)                       | 9 (3-21)                        | 9 (3-20)              |                     |         |
| **First GCS score<sup>c</sup>**  |                                |                                 |                       |                      | .02     |
| Mean (SD)                        | 11.4 (4.3)                     | 11.1 (4.5)                      | 11.3 (4.4)            |                     |         |
| Median (IQR)                     | 14 (8-15)                      | 14 (7-15)                       | 14 (7-15)             |                     |         |
| **Initial ICH score<sup>d</sup>** |                              |                                 |                       |                      | <.001   |
| Mean (SD)                        | 1.9 (1.4)                      | 2.0 (1.4)                       | 1.7 (1.4)             |                     |         |
| Median (IQR)                     | 2 (1-3)                        | 2 (1-3)                         | 1 (1-3)               |                     |         |

(continued)
Among patients with documented GCS (61,553 patients) or ICH (53,717 patients) scores, the median GCS score was 14 in all 3 groups, and the median ICH scores were 2 for those taking FXa inhibitors (mean [SD], 1.9 [1.4]) and warfarin (mean [SD], 2.0 [1.4]) and 1 for those not taking OAC (mean [SD], 1.7 [1.4]) (Table I). Despite the high missing rates and the lack of the name of the reversal agent, 53.4% (940 of 1,703 patientsexcluding 2,700 missing) of patients taking FXa inhibitors, 69.1% (3,376 of 4,889 patients excluding 3,164 missing) taking warfarin, and 9.2% (1,623 of 17,582 patients excluding 5,696 missing) not taking OAC were treated with some form of reversal or replacement agent during the hospitalization.

### Prior Anticoagulation Treatment and In-hospital Outcomes

The unadjusted in-hospital mortality rates were 22.6% (42,660 of 189,069 patients) for patients not taking OAC, 27.0% (2,487 of 9,202 patients) for those taking FXa inhibitors, and 32.8% (7,032 of 21,430 patients) for those taking warfarin. After risk adjustment, both FXa inhibitors (adjusted odds ratio [aOR], 1.27; 95% CI, 1.20-1.34; P < .001) and warfarin (aOR, 1.67; 95% CI, 1.60-1.74; P < .001) were associated with greater odds of in-hospital mortality compared with no OAC (Table 2). Similarly,
both FXa inhibitors (3478 of 9202 patients [37.8%]; aOR, 1.19; 95% CI, 1.13-1.26; P < .001) and warfarin (9151 of 21,430 patients [42.7%]; aOR, 1.50; 95% CI, 1.44-1.56; P < .001) were associated with greater odds of death or discharge to hospice than no OAC (58,022 of 189,069 patients [30.7%]). Although the rates of discharge home, independent ambulation, freedom from substantial disability (mRS score 0-1), and functional independence (mRS score 0-2) were numerically lower among patients taking FXa inhibitors, these differences were not significant compared with those not taking OACs. Similar findings were found in the sensitivity analyses after further adjustment with NIHSS score in the subgroup of 143,340 patients with documented NIHSS score at admission (eTable in the Supplement).

Compared with those treated with warfarin, patients receiving FXa inhibitors were less likely to die (aOR, 0.76; 95% CI, 0.72-0.81; P < .001) and were less likely to die or be discharged to hospice (aOR, 0.79; 95% CI, 0.75-0.84; P < .001) (Table 2). In addition, patients taking FXa inhibitors were more likely to be discharged home (aOR, 1.18; 95% CI, 1.10-1.26; P < .001) and have better mRS scores at discharge (aOR, 1.24 [95% CI, 1.09-1.40] for mRS scores of 0-1 and aOR 1.25 [95% CI, 1.13-1.39] for mRS scores of 0-2; P < .001 for both) than those taking warfarin. These findings were consistent after further adjustment with NIHSS score.

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

Among patients with ICH with prior use of FXa inhibitors, there were no significant incremental risks of mortality or functional outcomes at discharge with either single-antiplatelet or dual-antiplatelet agents compared with patients without concomitant antiplatelet use (Table 3). By contrast, in patients with prior use of warfarin, both single-antiplatelet and dual-antiplatelet agents were

### Table 2. Outcomes by Use of Anticoagulant Prior to Intracerebral Hemorrhage

| Outcomes and anticoagulant | Event rate, No./total No. (%) | Adjusted OR (95% CI) | P value | Adjusted OR (95% CI) | P value |
|----------------------------|-----------------------------|---------------------|---------|---------------------|---------|
| In-hospital mortality      |                             |                     |         |                     |         |
| Factor Xa inhibitors       | 2487/9202 (27.0)            | 1.27 (1.20-1.34)    | <.001   | 0.76 (0.72-0.81)    | <.001   |
| Warfarin                   | 7032/21,430 (32.8)          | 1.67 (1.60-1.74)    | <.001   | 1 [Reference]       | NA      |
| No OAC                     | 42,660/189,069 (22.6)       | 1 [Reference]      | NA      | 0.60 (0.57-0.62)    | <.001   |
| Death or discharge to hospice |                           |                     |         |                     |         |
| Factor Xa inhibitors       | 3478/9202 (37.8)            | 1.19 (1.13-1.26)    | <.001   | 0.79 (0.75-0.84)    | <.001   |
| Warfarin                   | 9151/21,430 (42.7)          | 1.50 (1.44-1.56)    | <.001   | 1 [Reference]       | NA      |
| No OAC                     | 58,022/189,069 (30.7)       | 1 [Reference]      | NA      | 0.67 (0.64-0.70)    | <.001   |
| Discharge home             |                             |                     |         |                     |         |
| Factor Xa inhibitors       | 1685/9202 (18.3)            | 0.95 (0.89-1.01)    | .12     | 1.18 (1.10-1.26)    | <.001   |
| Warfarin                   | 3491/21,430 (16.3)          | 0.81 (0.76-0.85)    | <.001   | 1 [Reference]       | NA      |
| No OAC                     | 48,893/189,069 (25.9)       | 1 [Reference]      | NA      | 1.24 (1.18-1.31)    | <.001   |
| Independent ambulation at discharge | |                     |         |                     |         |
| Factor Xa inhibitors       | 1745/6259 (27.9)            | 0.99 (0.93-1.07)    | .87     | 1.06 (0.98-1.14)    | .14     |
| Warfarin                   | 3664/13,256 (27.6)          | 0.94 (0.89-0.99)    | <.001   | 1 [Reference]       | NA      |
| No OAC                     | 45,027/129,036 (34.9)       | 1 [Reference]      | NA      | 1.07 (1.01-1.12)    | <.02    |
| Modified Rankin Scale score 0-1 |                         |                     |         |                     |         |
| Factor Xa inhibitors       | 466/6,667 (7.0)             | 0.95 (0.85-1.07)    | .40     | 1.24 (1.09-1.40)    | <.001   |
| Warfarin                   | 906/15,720 (5.8)            | 0.77 (0.70-0.84)    | <.001   | 1 [Reference]       | NA      |
| No OAC                     | 13,043/126,239 (10.3)       | 1 [Reference]      | NA      | 1.30 (1.19-1.42)    | <.001   |
| Modified Rankin Scale score 0-2 |                    |                     |         |                     |         |
| Factor Xa inhibitors       | 724/6,667 (10.8)            | 0.95 (0.86-1.05)    | .29     | 1.25 (1.13-1.39)    | <.001   |
| Warfarin                   | 1,420/15,720 (9.0)          | 0.76 (0.70-0.82)    | <.001   | 1 [Reference]       | NA      |
| No OAC                     | 19,346/126,239 (15.3)       | 1 [Reference]      | NA      | 1.32 (1.22-1.42)    | <.001   |

Abbreviations: NA, not applicable; OAC, oral anticoagulant; OR, odds ratio.

* Adjusted for age, sex, race/ethnicity, insurance, medical history (atrial fibrillation or flutter, coronary artery disease or prior myocardial infarction, prior stroke, prior transient ischemic attack, carotid stenosis, heart failure, hypertension, peripheral vascular disease, diabetes, dyslipidemia, obesity, renal insufficiency, smoking status, and drug or alcohol abuse), transport by emergency medical services, transfer in, arrived during off-hours, medication prior to admission (antihypertensive, lipid-lowering medication, diabetic medication, single-antiplatelet agent [aspirin, clopidogrel, prasugrel, ticagrelor, or ticlopidine], dual-antiplatelet therapy [aspirin plus dipyridamole or aspirin plus clopidogrel, prasugrel, ticagrelor, or ticlopidine], other antiplatelet, or combination), rural hospital, hospital number of beds, academic center, geographic regions, primary stroke center, and comprehensive stroke center.

b Reference values are for no OAC.

c Reference values are for warfarin.
Table 3. Incremental Risk of Concomitant Antiplatelet Therapy by the Type of Anticoagulant Prior to Intracerebral Hemorrhage

| Outcomes and antiplatelet | Event rate, No./total No. (%) | Adjusted OR (95% CI)* | P value |
|---------------------------|-------------------------------|----------------------|---------|
| **Factor Xa inhibitors**  |                               |                      |         |
| In-hospital mortality      |                               |                      |         |
| No antiplatelet agent      | 1701/6257 (27.2)              | 1 [Reference]        | NA      |
| Single-antiplatelet agent  | 729/2740 (26.6)               | 1.07 (0.96-1.19)     | .22     |
| Dual-antiplatelet agents   | 55/198 (27.8)                 | 1.19 (0.86-1.66)     | .30     |
| Death or discharge to hospice |                             |                      |         |
| No antiplatelet agent      | 2392/6257 (38.2)              | 1 [Reference]        | NA      |
| Single-antiplatelet agent  | 1009/2740 (36.8)              | 1.06 (0.96-1.18)     | .23     |
| Dual-antiplatelet agents   | 74/198 (37.4)                 | 1.21 (0.89-1.66)     | .23     |
| Discharge home             |                               |                      |         |
| No antiplatelet agent      | 1146/6257 (18.3)              | 1 [Reference]        | NA      |
| Single-antiplatelet agent  | 505/2740 (18.4)               | 0.95 (0.83-1.09)     | .48     |
| Dual-antiplatelet agents   | 34/198 (17.2)                 | 0.69 (0.45-1.05)     | .08     |
| Independent ambulation at discharge | |                      |         |
| No antiplatelet agent      | 1158/4249 (28.2)              | 1 [Reference]        | NA      |
| Single-antiplatelet agent  | 506/1868 (27.1)               | 0.89 (0.77-1.03)     | .11     |
| Dual-antiplatelet agents   | 41/137 (29.9)                 | 0.92 (0.63-1.35)     | .67     |
| Modified Rankin Scale score 0-1 |                             |                      |         |
| No antiplatelet agent      | 318/4553 (7.0)                | 1 [Reference]        | NA      |
| Single-antiplatelet agent  | 137/1986 (6.9)                | 0.85 (0.67-1.08)     | .19     |
| Dual-antiplatelet agents   | 11/144 (7.6)                  | 0.88 (0.48-1.63)     | .69     |
| Modified Rankin Scale score 0-2 |                             |                      |         |
| No antiplatelet agent      | 500/4553 (11.0)               | 1 [Reference]        | NA      |
| Single-antiplatelet agent  | 208/1986 (10.5)               | 0.82 (0.66-1.01)     | .06     |
| Dual-antiplatelet agents   | 16/144 (11.1)                 | 0.79 (0.47-1.32)     | .37     |
| **Warfarin**               |                               |                      |         |
| In-hospital mortality      |                               |                      |         |
| No antiplatelet agent      | 4472/13 966 (32.0)            | 1 [Reference]        | NA      |
| Single-antiplatelet agent  | 2306/6921 (33.3)              | 1.16 (1.09-1.24)     | <.001   |
| Dual-antiplatelet agents   | 246/524 (46.9)                | 2.07 (1.72-2.50)     | <.001   |
| Death or discharge to hospice |                             |                      |         |
| No antiplatelet agent      | 5916/13 966 (42.4)            | 1 [Reference]        | NA      |
| Single-antiplatelet agent  | 2944/6921 (42.5)              | 1.13 (1.06-1.21)     | <.001   |
| Dual-antiplatelet agents   | 280/524 (53.4)                | 1.86 (1.54-2.26)     | <.001   |
| Discharge home             |                               |                      |         |
| No antiplatelet agent      | 2285/13 966 (16.4)            | 1 [Reference]        | NA      |
| Single-antiplatelet agent  | 1134/6921 (16.4)              | 0.96 (0.88-1.05)     | .39     |
| Dual-antiplatelet agents   | 72/524 (13.7)                 | 0.71 (0.55-0.94)     | .01     |
| Independent ambulation at discharge | |                      |         |
| No antiplatelet agent      | 2391/8727 (27.4)              | 1 [Reference]        | NA      |
| Single-antiplatelet agent  | 1195/4264 (28.0)              | 1.00 (0.92-1.10)     | .91     |
| Dual-antiplatelet agents   | 76/255 (29.8)                 | 1.04 (0.78-1.38)     | .81     |
| Modified Rankin Scale score 0-1 |                             |                      |         |
| No antiplatelet agent      | 599/10 220 (5.9)              | 1 [Reference]        | NA      |
| Single-antiplatelet agent  | 283/5071 (5.6)                | 0.81 (0.69-0.96)     | .02     |
| Dual-antiplatelet agents   | 23/412 (5.6)                  | 0.73 (0.45-1.19)     | .21     |
| Modified Rankin Scale score 0-2 |                             |                      |         |
| No antiplatelet agent      | 927/10 220 (9.1)              | 1 [Reference]        | NA      |
| Single-antiplatelet agent  | 459/5071 (9.1)                | 0.87 (0.75-1.00)     | .05     |
| Dual-antiplatelet agents   | 33/412 (8.0)                  | 0.66 (0.43-1.01)     | .05     |

(continued)
associated with higher odds of in-hospital mortality (eg, dual-antiplatelet agent: aOR, 2.07; 95% CI, 1.72-2.50; P < .001) and death or discharge to hospice (eg, dual-antiplatelet agent: aOR, 1.86; 95% CI, 1.54-2.26; P < .001). In addition, these patients were less likely to be discharged home or have better mRS score at discharge, although some of these differences were not significant. Among patients without prior use of OAC, only dual-antiplatelet agents were associated with worse outcomes at discharge. In contrast, patients taking single-antiplatelet agents were more likely to be discharged to home, ambulate independently, and have mRS scores of 0 to 2 at discharge.

**Discussion**

In this cohort study of more than 200 000 patients with nontraumatic ICH, 4.2% were receiving FXa inhibitors and 9.8% were receiving warfarin before stroke. Although patients receiving FXa inhibitors were more likely to have favorable outcomes than those taking warfarin in terms of mortality and functional outcomes, prior use of FXa inhibitors was associated with increased odds of mortality and death or discharge to hospice compared with those not taking OAC, with more than 1 in 4 patients still dying in the hospital. These findings highlight the need to identify optimal strategies to care for these complex but increasingly common clinical challenges. In addition, concomitant antiplatelet use was common in patients with ICHs associated with use of FXa inhibitors and warfarin. Although both single-antiplatelet and dual-antiplatelet therapy were associated with increased odds of worse outcome among patients taking warfarin, such significant differences were not observed among patients with ICH taking concomitant FXa inhibitors and antiplatelet agents.

The current US and European guidelines recommend FXa inhibitors and direct thrombin inhibitor over warfarin for stroke prevention in high-risk patients with atrial fibrillation. 13,14 FXa

### Table 3. Incremental Risk of Concomitant Antiplatelet Therapy by the Type of Anticoagulant Prior to Intracerebral Hemorrhage (continued)

| Outcomes and antiplatelet | Event rate, No./total No. (%) | Adjusted OR (95% CI)* | P value |
|---------------------------|-------------------------------|-----------------------|---------|
| No OAC                    |                               |                       |         |
| In-hospital mortality     |                               |                       |         |
| No antiplatelet agent     | 28749/128 754 (22.3)          | 1 [Reference]         | NA      |
| Single-antiplatelet agent | 11400/51 874 (22.0)           | 1.01 (0.98-1.05)      | .42     |
| Dual-antiplatelet agents  | 2466/8244 (29.9)              | 1.56 (1.47-1.65)      | <.001   |
| Death or discharge to hospice |                             |                       |         |
| No antiplatelet agent     | 38096/128 754 (29.6)          | 1 [Reference]         | NA      |
| Single-antiplatelet agent | 16637/51 874 (32.1)           | 1.00 (0.97-1.03)      | .95     |
| Dual-antiplatelet agents  | 3228/8244 (39.2)              | 1.38 (1.30-1.46)      | <.001   |
| Discharge home            |                               |                       |         |
| No antiplatelet agent     | 35360/128 754 (27.5)          | 1 [Reference]         | NA      |
| Single-antiplatelet agent | 11823/51 874 (22.8)           | 1.04 (1.01-1.07)      | .008    |
| Dual-antiplatelet agents  | 1657/8244 (20.1)              | 0.91 (0.85-0.97)      | .004    |
| Independent ambulation at discharge |                 |                       |         |
| No antiplatelet agent     | 31591/86 122 (36.7)           | 1 [Reference]         | NA      |
| Single-antiplatelet agent | 11782/37 441 (31.5)           | 1.04 (1.01-1.07)      | .02     |
| Dual-antiplatelet agents  | 1606/5333 (30.1)              | 1.03 (0.96-1.10)      | .40     |
| Modified Rankin Scale score 0-1 |                 |                       |         |
| No antiplatelet agent     | 9445/84 302 (11.2)            | 1 [Reference]         | NA      |
| Single-antiplatelet agent | 3163/35 801 (8.8)             | 1.04 (0.98-1.10)      | .17     |
| Dual-antiplatelet agents  | 425/6013 (7.1)                | 0.86 (0.76-0.97)      | .02     |
| Modified Rankin Scale score 0-2 |                 |                       |         |
| No antiplatelet agent     | 13734/84 302 (16.3)           | 1 [Reference]         | NA      |
| Single-antiplatelet agent | 4929/35 801 (13.8)            | 1.07 (1.02-1.13)      | .006    |
| Dual-antiplatelet agents  | 665/6013 (11.1)               | 0.87 (0.78-0.97)      | .01     |

Abbreviations: NA, not applicable; OAC, oral anticoagulant; OR, odds ratio.  
* Adjustment for age, sex, race/ethnicity, insurance, medical history (atrial fibrillation or flutter, coronary artery disease or prior myocardial infarction, prior stroke, prior transient ischemic attack, carotid stenosis, heart failure, hypertension, peripheral vascular disease, diabetes, dyslipidemia, obesity, renal insufficiency, smoking status, and drug or alcohol abuse), transport by emergency medical services, transfer in, arrived during off-hours, antihypertensive, lipid-lowering medication prior to admission, rural hospital, hospital number of beds, academic center, geographic regions, primary stroke center, and comprehensive stroke center.
inhibitors do not require therapeutic monitoring and are associated with fewer adverse effects and lower rates of bleeding complications, particularly hemorrhagic stroke, than warfarin. As a result, FXa inhibitors are increasingly used in clinical practice. Nonetheless, the rapid adoption of FXa inhibitors will most likely lead to a further increase of FXa inhibitor–associated ICH, highlighting the need to better understand the characteristics, treatment patterns, and prognosis of these patients. However, such studies are challenging because of the improved safety profile of FXa inhibitors and the lower event rates of FXa inhibitor-associated ICH. For instance, of 30 300 patients randomized to receive rivaroxaban, apixaban, or edoxaban in pivotal FXa inhibitor trials, only 141 patients experienced a hemorrhagic stroke.

To our knowledge, this study provides the largest and most comprehensive assessment of FXa inhibitor–associated ICH. Overall, we observed higher risk profiles in terms of age and comorbidities in patients taking FXa inhibitors than spontaneous ICH without preceding use of OAC. Despite no significant differences in the likelihood of discharge home and functional status at discharge, FXa inhibitor–associated ICH was associated with 27% higher odds (aOR, 1.27) of in-hospital death and 19% higher odds (aOR, 1.19) of death or discharge to hospice than those without preceding use of OAC. In contrast, patients with FXa inhibitor–associated ICH had lower odds of death or discharge to hospice and higher odds of discharge home, freedom from substantial disability, and functional independence compared with patients with warfarin-associated ICH. Although the exact reason for better outcomes for FXa inhibitor–associated ICH vs warfarin-associated ICH remains unknown, we observed less severe stroke at presentation as measured by the NIHSS score in patients with FXa inhibitor–associated ICH. Although the differences in stroke severity may be explained by the underlying risk profiles between patients receiving FXa inhibitor and warfarin, previous studies have suggested smaller ICH volume, less hematoma expansion, and fewer concomitant intraventricular hemorrhage in patients with ICH taking non–vitamin K OACs. Importantly, in certain clinical scenarios, such as atrial fibrillation with recent percutaneous coronary intervention, patients may be required to take both anticoagulant and antiplatelet agents for secondary prevention. Once bleeding complications occurred, however, we found that patients with warfarin-associated ICH had worse outcomes with both single-antiplatelet and dual-antiplatelet therapy. In contrast, such differences were not observed among patients with concomitant FXa inhibitor and antiplatelet agent. These findings suggest that non–vitamin K OACs may be a better choice than warfarin when combination strategy is warranted.

Unlike warfarin-related ICH, the best management strategy for FXa inhibitor–associated ICH remains uncertain. The 2019 European Stroke Organisation Guidelines recommend andexanet-α in ICH with rivaroxaban or apixaban or prothrombin complex concentrate to normalize coagulation tests if specific reversal agents are not available. However, the quality of evidence is low because of a lack of randomized clinical trials and uncertainty regarding the benefit and harm of the reversal treatment. Comparing the impact of various reversal strategies can be difficult because of selection bias and concomitant medication use in ICH, making it hard to disentangle the effectiveness of various treatments. Furthermore, because anticoagulant levels are rarely captured, further research is required to measure clinical outcomes in the context of anticoagulant levels in addition to bleeding size and severity. In the subgroup of patients from hospitals reporting comprehensive stroke center data elements, we found that 53.4% of patients with FXa inhibitors received some form of reversal or replacement agent. Despite the high missing rates and no specific information regarding the reversal strategy, this finding suggests that reversal treatment was not uncommon among patients with ICH occurring during use of FXa inhibitors. Because our study was conducted before the approval of andexanet-α in the US, in the absence of head-to-head clinical trials, these data may be used as a historical control for future research to compare the efficacy and safety of andexanet-α vs nonspecific reversal treatment in patients with FXa inhibitor–associated ICH.
Limitations

There are limitations that should be kept in mind when interpreting these data. First, this was an observational analysis. Treatment selection and residual or unmeasured confounding could affect the validity of study findings and potentially account for the differences in risk-adjusted outcomes. Because treatment was given before the ICH, it is impossible to randomize patients with different OAC regimens. Despite the observational nature, our study still provides important clinical insights to FXa inhibitor–associated ICH, especially given the low incidence rates in pivotal trials. Second, prior use of OAC was defined as documentation of patients taking an OAC within 7 days, yet timing and dose of last OAC intake were not available. It is possible that some patients may have received a lower dose or stopped taking OAC, which consequently influenced ICH outcomes. However, it could be argued that patients are more likely to experience an ischemic stroke rather than an ICH in such scenarios.

Third, some patients were excluded from the ambulatory status or functional outcome models because of missing outcomes. Although this approach may bias the results of this analysis, it is unlikely that physicians will report outcome measures differently according to the type of OAC taken before the stroke. Fourth, ICH volume and location and the presence of hematoma expansion were not available in the registry, which may explain the differences in outcomes between ICH patients with or without OAC use. Fifth, platelet transfusion may have influenced outcomes in patients taking concomitant antiplatelet and anticoagulant therapy. However, such data were not collected in the registry. Sixth, data are 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 or to patients in other countries. Notwithstanding these limitations, GWTG-Stroke is the largest stroke registry in the US, covering approximately three-fourths of the US population. Furthermore, ICH cases tend to be concentrated at or transferred to tertiary hospitals. Given the higher representation of high-volume, academic, and stroke centers in the GWTG-Stroke registry, the study population of this investigation is potentially more representative of OAC-associated ICH in the US.

Conclusions

In conclusion, FXa inhibitor–associated ICH remains a devastating complication of OAC therapy, with 27.0% of patients in this study dying in hospital. Although associated with better outcomes than warfarin, this study found that preceding use of FXa inhibitors was associated with higher risk of mortality and death or discharge to hospice than ICH without prior use of OACs. Further study is warranted to identify the best treatment strategies for FXa inhibitor–associated ICH.
Division of Cardiology, University of California at Los Angeles, Los Angeles (Fonarow); Department of Neurology, Massachusetts General Hospital, Boston (Schwamm).

Author Contributions: Dr Xian had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Xian, Inohara, Sheth, Fonarow.

Acquisition, analysis, or interpretation of data: Xian, Zhang, Grau-Sepulveda, Matsouaka, Peterson, Piccini, Smith, Bhatt, Fonarow, Schwamm.

Drafting of the manuscript: Xian.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Xian, Zhang, Grau-Sepulveda, Matsouaka.

Obtained funding: Xian, Peterson.

Administrative, technical, or material support: Xian, Peterson, Piccini, Sheth.

Supervision: Xian, Matsouaka.

Conflict of Interest Disclosures: Dr Xian reported receiving grants from Portola, the National Institute on Aging, the American Heart Association, Daiichi Sankyo, and Janssen Pharmaceuticals and personal fees from Portola and Boehringer Ingelheim outside the submitted work. Dr Peterson reported receiving grants from Genentech, BMS, AstraZeneca, and Janssen Pharmaceuticals during the conduct of the study. Dr Piccini reported receiving grants for clinical research from Abbott, American Heart Association, Association for the Advancement of Medical Instrumentation, Bayer, Boston Scientific, and Philips and serving as a consultant to Abbott, Abbvie, Altathera, ARCA Biopharma, Biotronik, Boston Scientific, K2P, LivaNova, Medtronic, Milestone, Myokardia, ElectroPhysiology Frontiers, Pfizer, Sanofi, Philips, and UptoDate. Dr Smith reported receiving personal fees from Biogen Consulting, Bayer Consulting, and Javelin Consulting outside the submitted work. Dr Sheth reported receiving grants from the National Institutes of Health, the American Heart Association, Bard, Hyperfine, Biogen, and Novartis; and personal fees from Zoll DSMB, Ceribell, NControl, and Alva Equity outside the submitted work. Dr Bhatt reported serving on the advisory boards of Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, MyoKardia, PhaseBio, PLx Pharma, and Regado Biosciences; serving on the board of directors for Boston VA Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; serving as a member of the American Heart Association Quality Oversight Committee; serving on the data monitoring committees of Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), and Population Health Research Institute; receiving honoraria from the American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (guest editor; associate editor); K2P (cochair, interdisciplinary curriculum), Level Ex, Medintelligence/ReachMD (CME steering committees), M.H. Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and US national coleader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (CME steering committees); serving as deputy editor for Clinical Cardiology, chair of the NCDR-ACTION Registry Steering Committee, and chair of the VA CART Research and Publications Committee; receiving research funding from Abbott, Affirmative, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, MyoKardia, Owkin, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi, Synaptic, and The Medicines Company; receiving royalties from Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald’s Heart Disease); serving as site investigator for Biotronik, Boston Scientific, CSL St Jude Medical (now Abbott), and Svelte; serving as a trustee for American College of Cardiology; and performing unfunded research for FlowCo, Merck, Novo Nordisk, Takeda. Dr Fonarow reported receiving personal fees from AstraZeneca, Bayer, Janssen, and Novartis outside the submitted work and serving as Associate Section Editor for JAMA Cardiology. Dr Schwamm reported receiving personal fees from the Massachusetts Department of Public Health, Genentech, Penumbra, Diffusion Pharma, and Medtronic; grants from Medtronic and the National Institute of Neurological Disorders and Stroke outside the submitted work; and
serving as volunteer chair of the American Heart Association/American Stroke Association Get With the Guidelines (GWTG)-Stroke Clinical Work Group and as a consultant to Coverdell Grant. No other disclosures were reported.

**Funding/Sponsor:** The GWTG-Stroke registry is organized by the American Heart Association and the American Stroke Association. GWTG-Stroke is sponsored, in part, by Novartis, Boehringer Ingelheim, Lilly, Novo Nordisk, Sanofi, AstraZeneca, Bayer, and Portola Pharmaceuticals. This analysis was supported by a grant from Portola Pharmaceuticals, now a subsidiary of Alexion Pharmaceuticals.

**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.

**Meeting Presentation:** This manuscript was presented at the 2020 Virtual Conference of the European Stroke Organisation and World Stroke Organization; November 7-9, 2020.

**REFERENCES**

1. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955-962. doi:10.1016/S0140-6736(13)62343-0

2. Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992. doi:10.1056/NEJMoa1107039

3. Patel MR, Mahaffey KW, Garg J, et al; ROCET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891. doi:10.1056/NEJMoa090638

4. Giugliano RP, Ruff CT, Braunwald E, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104. doi:10.1056/NEJMoa1310907

5. Lopes RD, Guimarães PO, Kolls BJ, et al. Intracranial hemorrhage in patients with atrial fibrillation receiving anticoagulation therapy. *Blood*. 2017;129(22):2980-2987. doi:10.1182/blood-2016-08-731638

6. Hankey GJ, Stevens SR, Sicciini JP, et al; ROCKET AF Steering Committee and Investigators. Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation. *Stroke*. 2014;45(5):1304-1312. doi:10.1161/STROKEAHA.113.004506

7. Giugliano RP, Ruff CT, Rost NS, et al; ENGAGE AF-TIMI 48 Investigators. Cerebrovascular events in 21,05 patients with atrial fibrillation randomized to edoxaban versus warfarin: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48. *Stroke*. 2014;45(8):2372-2378. doi:10.1161/STROKEAHA.114.006025

8. Hagii J, Tomita H, Metoki N, et al. Characteristics of intracerebral hemorrhage during rivaroxaban treatment: comparison with those during warfarin. *Stroke*. 2014;45(9):2805-2807. doi:10.1161/STROKEAHA.114.006661

9. Inohara T, Xian Y, Liang L, et al. Association of intracerebral hemorrhage among patients taking non-vitamin K antagonist vs vitamin K antagonist oral anticoagulants with in-hospital mortality. *JAMA*. 2018;319(5):463-473. doi:10.1001/jama.2017.21917

10. Fonarow GC, Reeves MJ, Smith EE, et al; GWTG-Stroke Steering Committee and Investigators. Characteristics, performance measures, and in-hospital outcomes of the first one million stroke and transient ischemic attack admissions in get with the guidelines-stroke. *Circ Cardiovasc Qual Outcomes*. 2010;3(3):291-302. doi:10.1161/CIRCOUTCOMES.109.921838

11. Xian Y, Fonarow GC, Reeves MJ, et al. Data quality in the American Heart Association Get With The Guidelines-Stroke (GWTG-Stroke): results from a national data validation audit. *Am Heart J*. 2012;163(2):392-398.e1. doi:10.1016/j.ahj.2011.12.012

12. Xian Y, O’Brien EC, Liang L, et al. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. *JAMA*. 2017;317(10):1057-1067. doi:10.1001/jama.20171371

13. January CT, Wann LS, Callkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. *Circulation*. 2019;140(2):e125-e151. doi:10.1161/CIR.0000000000000665

14. Kirchhof P, Benussi S, Kotecha D, et al; ESC Scientific Document Group. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893-2962. doi:10.1093/eurheartj/ehw210
15. Wilson D, Charidimou A, Shakeshaft C, et al; CROMIS-2 Collaborators. Volume and functional outcome of intracerebral hemorrhage according to oral anticoagulant type. *Neurology*. 2016;86(4):360-366. doi: 10.1212/WNL.0000000000002310

16. Woo HG, Chung I, Gwak DS, et al. Intracerebral hemorrhage associated with warfarin versus non-vitamin K antagonist oral anticoagulants in Asian patients. *J Clin Neurosci*. 2019;61:160-165. doi: 10.1016/j.jocn.2018.10.102

17. Panos NG, Cook AM, John S, Jones GM; Neurocritical Care Society (NCS) Pharmacy Study Group. Factor Xa inhibitor-related intracranial hemorrhage: results from a multicenter, observational cohort receiving prothrombin complex concentrates. *Circulation*. 2020;141(21):1681-1689. doi: 10.1161/CIRCULATIONAHA.120.045769

18. Christensen H, Cordonnier C, Kõrv J, et al. European Stroke Organisation guideline on reversal of oral anticoagulants in acute intracerebral haemorrhage. *Eur Stroke J*. 2019;4(4):294-306. doi: 10.1177/239697319849763

19. Frontera JA, Lewin JJ III, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016;24(1):6-46. doi: 10.1007/s12028-015-0222-x

SUPPLEMENT.

eTable. Outcomes by Use of Anticoagulant Prior to Intracerebral Hemorrhage, With Further Adjustment With National Institute of Health Stroke Scale (NIHSS)