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RESEARCH ARTICLE

Neuroimaging and Clinical Outcomes of Oral Anticoagulant–Associated Intracerebral Hemorrhage

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Objective: Whether intracerebral hemorrhage (ICH) associated with non–vitamin K antagonist oral anticoagulants (NOAC-ICH) has a better outcome compared to ICH associated with vitamin K antagonists (VKA-ICH) is uncertain.
Methods: We performed a systematic review and individual patient data meta-analysis of cohort studies comparing clinical and radiological outcomes between NOAC-ICH and VKA-ICH patients. The primary outcome measure was 30-day all-cause mortality. All outcomes were assessed in multivariate regression analyses adjusted for age, sex, ICH location, and intraventricular hemorrhage extension.
Results: We included 7 eligible studies comprising 219 NOAC-ICH and 831 VKA-ICH patients (mean age = 77 years, 52.5% females). The 30-day mortality was similar between NOAC-ICH and VKA-ICH (24.3% vs 26.5%; hazard ratio = 0.94, 95% confidence interval [CI] = 0.67–1.31). However, in multivariate analyses adjusting for potential confounders, NOAC-ICH was associated with lower admission National Institutes of Health Stroke Scale (NIHSS) score (linear regression coefficient = −2.83, 95% CI = −5.28 to −0.38), lower likelihood of severe stroke (NIHSS > 10 points) on admission (odds ratio [OR] = 0.50, 95% CI = 0.30–0.84), and smaller baseline hematoma volume (linear regression coefficient = −0.24, 95% CI = −0.47 to −0.16). The two groups did not differ in the likelihood of baseline hematoma volume < 30cm^3 (OR = 1.14, 95% CI = 0.81–1.62), hematoma expansion (OR = 0.97, 95% CI = 0.63–1.48), in-hospital mortality (OR = 0.73, 95% CI = 0.49–1.11), functional status at discharge (common OR = 0.78, 95% CI = 0.57–1.07), or functional status at 3 months (common OR = 1.03, 95% CI = 0.75–1.43).
Interpretation: Although functional outcome at discharge, 1 month, or 3 months was comparable after NOAC-ICH and VKA-ICH, patients with NOAC-ICH had smaller baseline hematoma volumes and less severe acute stroke syndromes.

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Intracerebral hemorrhage (ICH) is the most feared complication of oral anticoagulation, with mortality approaching 50%.[1] Despite advances in primary prevention and especially the treatment of hypertension, the global incidence of ICH has remained stable,[2] in part due to the increase of anticoagulant-related ICH in the elderly.[3]

Use of oral anticoagulation with vitamin K antagonists (VKAs) is known to double the ICH risk even under optimal treatment conditions (international normalized ratio [INR] = 2–3); the annual risk of ICH is estimated to range from 0.3 to 0.6% per year.[4,5] Apart from the increased incidence, VKA-associated ICH (VKA-ICH) is associated with larger hematoma volumes, increased case fatality, and poor functional outcome.[6,7] Non–vitamin K antagonist oral anticoagulants (NOACs) have similar efficacy in ischemic stroke prevention in patients with nonvalvular atrial fibrillation (NVAF), with half the incidence of ICH compared to warfarin.[8] Although the pharmacodynamics, short half-life, and discriminate anticoagulant action of NOACs have been associated with the lower risk of incident ICH, findings are conflicting regarding the outcome of patients with NOAC-associated ICH (NOAC-ICH) compared to VKA-ICH.[9,10]

We therefore performed a systematic review and individual patient data meta-analysis (IPDM), including data from available cohort studies comparing clinical and radiological outcomes between NOAC-ICH and VKA-ICH patients.

Patients and Methods

Literature Search and Trial Identification

This meta-analysis is presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Individual Patient Data (PRISMA-IPD) guidelines[11] and was written according to the Meta-analysis of Observational Studies in Epidemiology proposal.[12] We followed a prespecified study protocol that has been published in the International Register PROSPERO (International Prospective Register of Ongoing Systematic Reviews).[13]

Eligible study protocols reporting clinical and radiological characteristics of NOAC-ICH in comparison to VKA-ICH were identified by searching MEDLINE and Scopus. The combination of search strings that was used in all database searches included the terms "intracerebral hemorrhage", "intracranial hemorrhage", "intracranial bleeding", "cerebral hemorrhage", "cerebral hematoma", "vitamin K antagonists" (including also the names of all pharmaceutical substances), "novel oral anticoagulants", "direct oral anticoagulants", and "non-vitamin K antagonist oral anticoagulants" (including also the names of all pharmaceutical substances). No language or other restrictions were imposed. The last literature search was conducted on August 25, 2017. Reference lists of all articles that met our inclusion criteria and of relevant review articles were examined to identify studies that may have been missed by the initial database search. Literature searches were performed by 2 independent teams of reviewers (G.T. and A.H.K., D.W. and D.J.W.), and emerging disagreements were resolved with consensus.

Data Transfer and Verification

Anonymized data were transferred from participating centers to the Coordinating and Data Management Centre (National Hospital for Neurology and Neurosurgery, Queen Square University College Hospitals, National Health Service Foundation Trust). The data obtained from each participating study were checked with respect to range, internal consistency, consistency with published reports, and missing items.[14] Inconsistencies or missing data were discussed with the individual principal investigators, and emerging problems were resolved with consensus. Finally, data supplied were either recoded or transformed to reflect common definitions and common units of measurement across the generated individual patient database, and computer-generated detailed summary tabulations based on the converted data were returned to each collaborator for review and verification.

Inclusion Criteria, Exclusion Criteria, and Outcomes of Interest

To be eligible for inclusion in the IPDM, individual studies, registries, or databases (reported variously as prospective or retrospective observational cohort studies or trials) were asked to include data available for compulsory baseline characteristics of interest (age, sex, oral anticoagulant agent, ICH location [lobar vs nonlobar], intraventricular hemorrhage [IVH] extension in baseline neuroimaging) and survival data (number of days from index event to death). The list of noncompulsory variables that were requested is available in Supplementary Table 1.

Hematoma volume was calculated with the same method for NOAC-ICH and VKA-ICH using either the ABC/2 method or planimetric measurement with adjustments made for multilobar hemorrhage and scans with nonuniform slice thickness.[15] Hematoma expansion at follow-up neuroimaging was defined as an absolute increase of >12.5cm^3 or a relative increase of >33% in hematoma volume at the follow-up scan compared to the admission neuroimaging.[16] In patients with sufficient data, we additionally calculated the corresponding CHA_2DS_2-VASc scores,[17] if these were not provided in the original databases.

In the present IPDM, we included patients older than 18 years with diagnosis of acute primary ICH who were confirmed to be receiving VKAs (with INR > 1.5 on admission)[18] or NOACs (definite evidence of intake within 24 hours before the ICH onset). We excluded patients with ICH secondary to trauma (ie, major head trauma thought to be sufficient to have caused the ICH in the previous 24 hours), vascular malformation, tumor, cavernoma, aneurysm, or hemorrhagic transformation of ischemic stroke. We additionally excluded patients with primary subarachnoid hemorrhage (with or without an ICH component), isolated intraventricular bleeding, and VKA-ICH patients with INR ≤ 1.5 on admission.[13]

The primary outcome was 30-day all-cause mortality between NOAC-ICH and VKA-ICH. Secondary outcomes were admission stroke severity (assessed with the National Institutes of Health Stroke Scale score [NIHSS]), severe stroke (NIHSS > 10) on admission,[19] level of consciousness (quantified by Glasgow Coma Scale score [GCS]) on admission, hematoma volume on admission, small hematoma volume (<30cm^3) on admission,[20] hematoma expansion rate on follow-up neuroimaging, in-hospital mortality, and functional status at discharge and at 3 months, quantified by the distribution of modified Rankin Scale (mRS) scores.

Quality Assessment in Included Studies

We used the Newcastle-Ottawa Scale to assess the quality of each observational study that met our inclusion

criteria.[21] According to this scale, a maximum of 1 star can be awarded for each item within the selection and exposure/outcome categories and a maximum of 2 stars for the comparability category; studies can earn a maximum of 9 star-points. Quality control and bias identification were performed by 2 independent reviewers (D.W. and G.A.), and all disagreements were resolved with consensus.[21]

Statistical Analysis

We summarized normally distributed continuous variables as means with corresponding standard deviations, whereas nonnormally distributed variables were reported as medians with their corresponding interquartile ranges. All categorical variables were presented as absolute numbers with corresponding percentages.

Univariate Kaplan–Meier survival probabilities were estimated for each anticoagulant group; the log-rank test was used to compare groups. For the primary prespecified outcome analysis, we fitted a Cox proportional hazards model with a frailty term for study. In this observational study, the exposure (NOAC vs VKA) precedes acute ICH and thus the exposure itself might affect some of the markers of ICH severity (ICH volume and GCS). For multivariate models of the outcome variables (mortality, functional outcomes), we therefore only included covariates that should not be affected by anticoagulant choice (age, sex, ICH location, and IVH extension); we added a shared frailty term to allow for possible site-related factors (eg, general ICH management, resources, ethnicity). The assumption of proportional hazards was assessed using Schoenfeld residuals.

For the secondary outcomes of interest, we performed mixed effects multivariate logistic or ordinal regression analyses, as indicated. Anticoagulant (NOAC vs VKA), age, sex, IVH extension, and ICH location were treated as fixed effects and registry as a random effect in each analysis exploring clinical severity or functional outcome/mortality, whereas anticoagulant (NOAC vs VKA), age, sex, and ICH location were treated as fixed effects and registry as a random effect in the analysis exploring ICH volume and ICH expansion. Associations in all logistic and ordinal regression analyses are presented using odds ratios (ORs) and common ORs (cORs), respectively, with their corresponding 95% confidence intervals (CIs).[13] In the final multivariate analyses, statistical significance was achieved if 2-sided $p < 0.05$, calculated using the likelihood ratio test. In multivariate models, we excluded patients with missing data from the analysis; we did not impute missing data.

Where applicable, the adjusted individual study results were displayed using a forest plot and a 2-stage meta-analysis was performed to calculate I^2, a measure of heterogeneity across studies, and τ^2, a measure of variance of the true effect sizes.[22] The pooled estimate was suppressed in these plots, because their sole purpose here is to display the results from each individual study.

Finally, we performed prespecified subgroup analyses on the primary outcome according to the NOAC drug used (apixaban, dabigatran, rivaroxaban), reporting the relevant p value for interaction for each one.

Results

Study Selection and Study Characteristics

Systematic search of MEDLINE and Scopus databases yielded 600 and 684 results, respectively. After removing duplicates, the titles and abstracts from the remaining 974 studies were screened and 12 potentially eligible studies for the meta-analysis were retained. After retrieving the full-text version of the aforementioned 12 studies, 3 studies were excluded because they included patients with traumatic brain injury[23–25] and 1 study due to the lack of a VKA-ICH comparator group (Supplementary Table 2).[26] In the final presentation of the literature search results, there was no conflict or disagreement between the reviewers and the corresponding authors from the 8 studies that met the protocol's inclusion criteria were contacted by email. Individual patient data were obtained from all study protocols, except for one,[27] and the 7 eligible studies were finally included in the qualitative and quantitative synthesis (Fig 1).[28–34]

Prior to applying our own inclusion and exclusion criteria, we received 100% of expected patient numbers from each study (Supplementary Table 3). No important issues with IPD integrity were identified after checks according to PRISMA checklist recommendations. Quality assessment of included studies highlighted one study[32] that reported enrollment of some VKA patients before the start of enrollment of their first NOAC patient (Supplementary Table 4).

After excluding 74 patients on a VKA with an initial INR value ≤1.5, we were left with a total of 1,050 patients (219 on NOACs and 831 on a VKA) from 7 individual studies. Baseline characteristics and outcomes of the total 1,050 eligible ICH patients (NOAC-ICH, n = 219; VKA-ICH, n = 831; mean age = 77 years, 52.5% women) are summarized in Supplementary Table 5. The use of any reversal strategy was approximately 3 times more common ($p < 0.001$) in VKA-ICH patients (n = 621, 89%) compared to NOAC-ICH patients (n = 58, 31%). More specifically, use of vitamin K was reported in 25% and 75% of NOAC-ICH and VKA-ICH patients, respectively. Protein complex concentrate

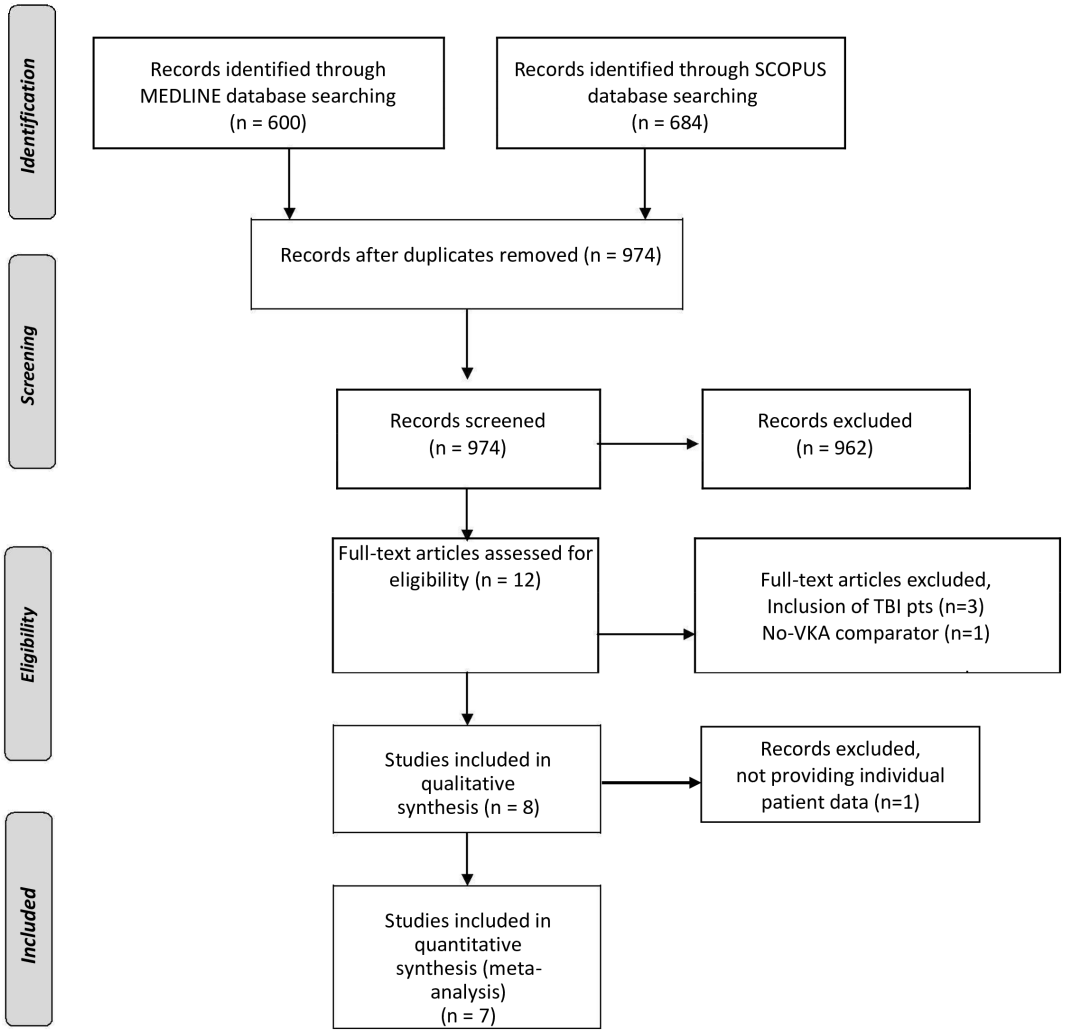

FIGURE 1: Flow chart presenting the selection of eligible studies. TBI = traumatic brain injury; VKA = vitamin K antagonist.

was used in 21% and 79% of NOAC-ICH and VKA-ICH patients, whereas fresh frozen plasma was used in 22% and 78% of NOAC-ICH and VKA-ICH patients, respectively. Use of a specific reversal agent (idarucizumab) was reported in only one patient with NOAC-ICH.[33]

Primary Analysis

Two studies had follow-up times that were too short to allow inclusion into our primary outcome of 30-day mortality. Therefore, our primary analysis comprised 909 patients from 5 studies. In survival analysis, adjusting for age, sex, ICH location, and IVH extension as well as clustering by center, NOAC-ICH and VKA-ICH patients did not differ in the risk of 30-day mortality (24.3% vs 26.5%; adjusted hazard ratio [HR] = 0.94, 95% CI = 0.67–1.31, $p = 0.702$; Fig 2, Supplementary Table 6). The proportional hazard assumption was not violated (global test $p = 0.247$). Unadjusted Kaplan–Meier plots for each included study on the primary outcome of 30-day mortality are available in Figure 3.

In a post hoc sensitivity analysis, including the 74 VKA-ICH patients with INR values ≤1.5 and the patients from the 2 centers with short follow-up times

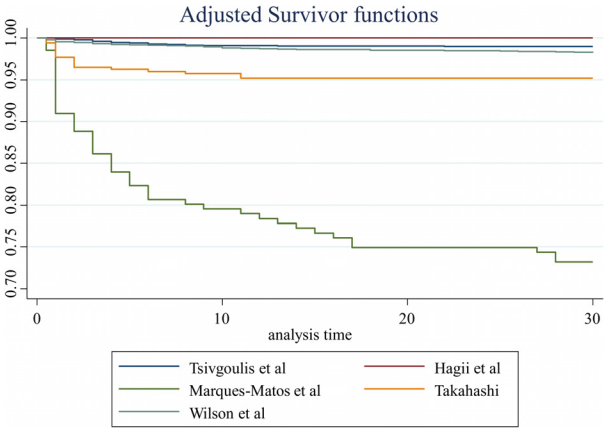

FIGURE 2: Cox regression analyses adjusted for each included study on the primary outcome of 30-day mortality between patients receiving pretreatment with non–vitamin K antagonist oral anticoagulants and patient receiving treatment with vitamin K antagonist oral anticoagulants. [Color figure can be viewed at www.annalsofneurology.org]

TABLE 1. Overview of Primary and Secondary Adjusted Analyses

Outcome	Studies, n	Patients, n	Effect Size for NOAC (95% CI)	*p*
Primary outcome				
30-day mortality	5	909	HR = 0.94 (0.67 to 1.31)	0.702
30-day mortality, sensitivity analysis[a]	7	1,098	HR = 0.90 (0.66 to 1.21)	0.476
Secondary outcomes				
Admission NIHSS	4	398	LRC = −2.83 (−5.28 to −0.38)	0.024
Admission NIHSS > 10	4	398	OR = 0.50 (0.30 to 0.84)	0.009
Baseline GCS	4	845	LRC = −0.01 (−0.57 to 0.55)	0.979
Baseline ICH volume[b]	7	1,006	LRC = −0.24 (−0.47 to −0.16)	0.036
Baseline hematoma volume < 30 cm^3[b]	7	1,006	OR = 1.14 (0.81 to 1.62)	0.447
Hematoma expansion[b]	7	617	OR = 0.97 (0.63 to 1.48)	0.883
In-hospital mortality	6	824	OR = 0.73 (0.49 to 1.11)	0.140
mRS at hospital discharge	6	824	cOR = 0.78 (0.57 to 1.07)	0.127
mRS at 90 days	3	748	cOR = 1.03 (0.75 to 1.43)	0.842

[a]Including the 74 vitamin K antagonist–ICH patients with international normalized ratio values ≤ 1.5 and after imputation of the patients from 2 centers with short follow-up times.

[b]Adjusted for age, sex, and ICH location. The remainder adjusted for age, sex, intraventricular hemorrhage extension, and ICH location.

CI = confidence interval; cOR = common odds ratio; GCS = Glasgow Coma Scale; HR = hazard ratio; ICH = intracerebral hemorrhage; LRC = linear regression coefficient; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; NOAC = non–vitamin K antagonist oral anticoagulant; OR = odds ratio.

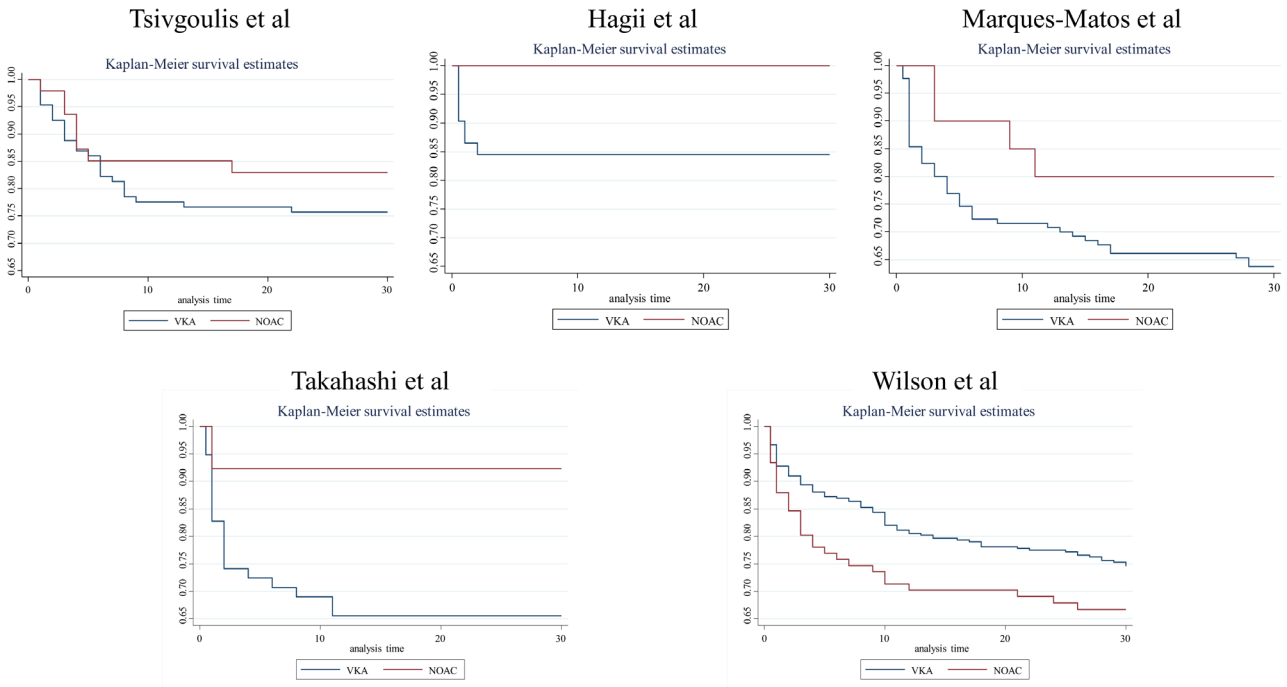

FIGURE 3: Unadjusted Kaplan–Meier plots for each included study on the primary outcome of 30-day mortality. NOAC = non–vitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist. [Color figure can be viewed at www.annalsofneurology.org]

(after imputation of missing baseline values), we documented similar results for the risk of 30-day mortality between NOAC-ICH and VKA-ICH patients (HR = 0.90, 95% CI 0.66–1.21, p = 0.476; see Table 1).

Secondary Outcomes

Results of adjusted analyses on secondary outcomes of interest are presented in Table 1 and Supplementary Tables 7 to 15. An overview of unadjusted analyses on the primary and secondary outcomes of interest is provided in Supplementary Table 16 and Figure 4. Four studies comprising 398 patients had information available on NIHSS. NOAC-ICH was associated with lower admission NIHSS scores (adjusted linear regression coefficient = −2.83, 95% CI = −5.28 to −0.38) and a lower likelihood of severe stroke (NIHSS > 10 points) on admission (adjusted OR = 0.50, 95% CI = 0.30–0.84).

Four studies comprising 845 patients had data available on GCS. In adjusted analysis, the two groups did not differ on GCS on hospital admission (adjusted linear regression coefficient = −0.01, 95% CI = −0.57 to 0.55).

Seven studies comprising 1,006 patients had data available on ICH volume. NOAC-ICH was associated with smaller baseline hematoma volumes on admission (adjusted linear regression coefficient = −0.24, 95% CI = −0.47 to −0.16). However, the odds of admission hematoma volume being <30cm^3 did not differ between the groups (adjusted OR = 1.14, 95% CI = 0.81–1.62)

Seven studies comprising 617 patients had data available on ICH expansion on follow-up neuroimaging, which did not differ between the two groups (adjusted OR = 0.97, 95% CI = 0.63–1.48).

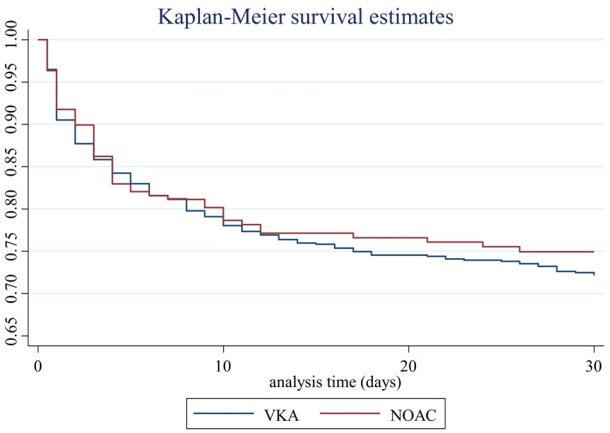

FIGURE 4: Unadjusted Kaplan–Meier curves on the probability of 30-day survival between patients with intracerebral hemorrhage related to non–vitamin K antagonist oral anticoagulants (NOACs) and patients with intracerebral hemorrhage related to vitamin K antagonist (VKA) oral anticoagulants. [Color figure can be viewed at www.annalsofneurology.org]

Seven studies comprising 902 patients had data on in-hospital mortality and mRS at discharge. However, one of the studies did not collect data on IVH extension and thus could not be included in multivariate analysis. In adjusted analysis comprising 824 patients from 6 studies, no significant differences between the two groups were found regarding in-hospital mortality (adjusted OR = 0.73, 95% CI = 0.49–1.11) and functional status at hospital discharge (adjusted cOR per 1-point increase in mRS-score = 0.78, 95% CI = 0.57–1.07).

Three studies comprising 748 patients had data available on 90-day mRS, which again shows no statistical difference between the groups (adjusted cOR = 1.03, 95% CI = 0.75–1.43).

Analysis of individual NOAC drug type (Table 2) revealed no significant differences in their 30-day mortality risk compared with VKAs (apixaban: adjusted HR = 0.56, 95% CI = 0.20–1.51; dabigatran: adjusted HR = 0.69, 95% CI = 0.34–1.40; rivaroxaban: adjusted HR = 1.11, 95% CI = 0.78–1.68; overall p = 0.267; Fig 5).

Discussion

Our IPDM showed comparable 30-day mortality rates after NOAC-ICH and VKA-ICH, with no statistically significant differences in risk for different NOAC agents. However, NOAC-ICH was independently associated with less severe acute ICH as measured by baseline hematoma volume and stroke severity (NIHSS) on admission. VKA-ICH and NOAC-ICH had similar functional outcome at discharge and at 3-month follow-up.

Our findings highlighting similar outcomes in NOAC-ICH and VKA-ICH patients differ from those reported from a recent retrospective analysis from the Get with the Guidelines–Stroke (GWTG-Stroke) registry, including 141,311 total ICH patients admitted to 1,662 US hospitals, suggesting that NOAC-ICH patients have lower risk of in-hospital mortality and functional disability at discharge compared to VKA-ICH patients.[35] This disparity could be attributed to the more stringent definition of oral anticoagulant–related ICH in patients from our cohort compared to that used in the cohort from the GWTG-Stroke registry (any use of oral anticoagulant within 7 days prior to hospital arrival) and the lack of adjustment for baseline stroke severity in the multivariate models of in-hospital mortality and functional outcome in both GWTG-Stroke registry and our protocol.[35] Our study provides an invaluable insight in the anticoagulant-related ICH neuroimaging outcomes, which are known to be significant predictors of clinical outcomes but in turn are less affected by demographic characteristics compared to clinical outcomes. Considering that demographic characteristics have been inadequately assessed in our study

TABLE 2. Adjusted Subgroup Analysis on the Primary Outcome of 30-Day Mortality according to the Type of Non–Vitamin K Oral Anticoagulant Based on 5 Studies and 909 Patients

	HR	95% CI	*p*
VKA	Baseline	—	—
Rivaroxaban	1.11	0.78–1.68	0.494
Dabigatran	0.69	0.34–1.40	0.300
Apixaban	0.56	0.20–1.51	0.249
Age, per year increase	1.02	1.01–1.04	0.006
Sex, female/male	1.13	0.87–1.46	0.370
IVH, yes/no	3.16	2.39–4.16	<0.001
ICH location, lobar/nonlobar	1.19	0.91–1.55	0.211

CI = confidence interval; HR = hazard ratio; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage extension; VKA = vitamin K antagonist.

protocol and in the study by Inohara et al,[35] the importance of findings on neuroimaging outcomes is further highlighted. We also consider that the results from the current IPDM, incorporating data from international multicenter cohorts, are likely to be more easily generalizable to every clinical setting. Finally, it should be noted that findings from a very recent meta-analysis of available randomized clinical trials on the use of NOACs for the prevention of thromboembolism in patients with NVAF, suggesting similar case fatality rates in NOAC-related and VKA-related ICH,[36] corroborate further our results on the similar 30-day mortality risk between NOAC- and VKA-related ICH patients and contradict further the finding of lower in-hospital mortality risk for NOAC-ICH patients reported in the study by Inohara et al.[35]

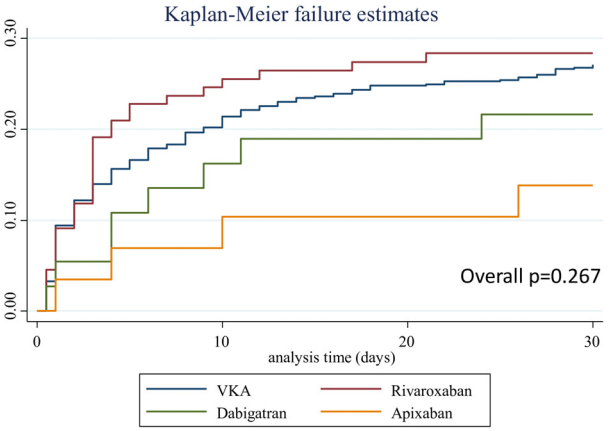

FIGURE 5: Subgroup analysis on the risk of 30-day mortality in patients with intracerebral hemorrhage related to the use of different non–vitamin K antagonist oral anticoagulants. Overall *p* = 0.267. VKA = vitamin K antagonist. [Color figure can be viewed at www.annalsofneurology.org]

Our results are also in accordance with a previously published systematic review and pairwise meta-analysis of aggregate level data from 12 observational studies (393 NOAC-ICH and 3,482 VKA-ICH), suggesting no significant differences in hematoma expansion, mortality, and functional outcome between NOAC-ICH and VKA-ICH patients.[36] A nonsignificant association for lower baseline ICH volume in NOAC-ICH compared to VKA-ICH was also reported in this meta-analysis (standardized mean difference = −0.24, 95% CI −0.52 to 0.04, $p = 0.093$), whereas the association of NOAC-related ICH with 30-day mortality was not evaluated in this meta-analysis.[37]

The finding of lower baseline hematoma volumes in NOAC-ICH compared to VKA-ICH could be attributed to the more favorable pharmacological properties of NOACs, including shorter plasma half-life and selective inhibition of the extrinsic coagulation pathway, compared to VKAs.[38] The one-to-one direct stoichiometric inhibition of thrombin or factor Xa by NOACs favors the physiological cerebrovascular hemostatic response after an ICH, in contrast to the impaired hemostasis due to thrombin substrate deficiency induced by VKAs.[39] However, although hematoma volume on admission is associated with stroke severity[40] and long-term outcome after an ICH,[41] we detected no significant differences between NOAC-ICH and VKA-ICH patients in 30-day mortality risk, the rate of hematoma expansion, in-hospital mortality, or functional outcome at discharge and 3-month follow-up. Because the trajectory of recovery of ICH might be slower than that after ischemic stroke,[42] it is possible that with longer follow-up the apparent benefits of NOACs on acute ICH volume and stroke severity might

translate into better functional outcome. Longer term studies of outcome after VKA-ICH and NOAC-ICH will be needed to investigate this possibility.

Our study has strengths. We included a large sample of individual participant data, allowing us to perform adjusted analyses for both clinical and radiological outcomes between NOAC-ICH and VKA-ICH. We included high-quality observational studies, using prespecified inclusion criteria at both study and individual patient level. However, there are also several limitations that should be taken into consideration. First, individual participant data from one study including 27 participants was not available,[27] but we consider the potential impact of this to be negligible. Second, although we collected detailed baseline data, we were not able to assess and further adjust the potential impact of some clinical (eg, the degree of blood pressure reduction),[43] laboratory (eg, cholesterol levels on admission),[44] and neuroimaging (eg, presence of cerebral microbleeds or cortical superficial siderosis)[45–48] parameters on the outcomes of interest. It should also be noted that there was no central adjudication in image analysis for both baseline and follow-up neuroimaging scans. Moreover, because patients in the two groups were not randomized to NOAC or VKA administration, imbalances in both baseline characteristics and other potential confounders, including onset-to-neuroimaging time,[49] could be present. Despite adjustment for baseline factors, there is also a risk of residual confounding by indication, which is not completely addressed in the current IPDM or in the previous report from the GWTG-Stroke registry.[35] Moreover, it should also be noted that we were unable to assess for the temporal and geographical differences in ICH care or practice patterns, including the choice and administration timing of reversal agents, which are known to influence ICH outcomes. Due to the complexity of reasons for clinician selection of an anticoagulant regimen for particular patients and the presence of significant disparities in ICH management, we consider that only randomized controlled trial data will be able to firmly account for these potential biases.

The availability of reversal strategies for oral anticoagulants and the timing of their administration after ICH onset could also account for potential difference in outcomes between NOAC-ICH and VKA-ICH patients in the present IPDM. The use of any reversal strategy was approximately 3 times more common in VKA-ICH than in NOAC-ICH cases. Given that NOAC-specific reversal agents may be associated with a lower case fatality rate in NOAC-related ICH,[36] the more widespread future use of these agents might result in a substantial decrease of NOAC-ICH mortality.

Due to the lack of significant differences in clinical outcomes between NOAC-ICH and VKA-ICH, despite the disparities in neuroimaging findings, we performed a post hoc power calculation to investigate for the possibility of a ceiling effect and underpowering; this indicated that our IPDM had 80% power to detect a 10% absolute difference (and a corresponding HR of 0.56) for the primary outcome of interest (30-day mortality) between NOAC-ICH and VKA-ICH patients. Thus, our IPDM was not powered to detect smaller differences in the 1-month mortality rates between NOAC-ICH and VKA-ICH patients. We note that the adjusted absolute risk difference in the in-hospital mortality that was detected in the GWTG-Stroke registry was 6%.[35] The missing functional evaluations in 20% and 30% of our study population at discharge and at 3 months may have diluted the potential beneficial effect of NOACs on functional outcomes in ICH patients, but these were secondary outcomes. Because premorbid mRS scores were not available in the included study protocols, the lack of significant differences on clinical outcomes could also be attributed to the inability for adjustment for the presence of disability prior to index event. Finally, as in the primary analysis, we consider the subgroup analysis according to NOAC regimen underpowered and the risk of residual confounding in the NOAC-ICH subgroup possible.

In conclusion, our IPDM provides preliminary evidence that although 30-day clinical outcomes appear to be comparable between NOAC-ICH and VKA-ICH patients, NOAC-ICH may be related to lower baseline hematoma volumes and lower admission stroke severity scores. This observation requires independent confirmation in larger prospective cohort studies adjusting for all potential confounders, including neuroimaging parameters and pre-ICH functional status. Longer term follow-up studies should determine whether outcomes beyond 30 days differ between VKA-ICH and NOAC-ICH.

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Author Contributions

G.T., D.J.W., A.H.K., D.W., and G.A. contributed to the conception and design of the study; J.S.-F., C.M.-M., E.A., T.A., C.v.d.B., Y.A., H.A., H.T., K.O., J.H., D.J.S., V.-A.L., C.T., P.V., G.B., C.K., J.C.P., V.K.S., T.R., R.M., O.A.S., K.B., H.S., N.G., S.-J.Y., T.K., T.Y.W., K.V., M.F., G.H., R.H., S.G., F.H.B.M.S., J.J.C., L.A.P., M.M., J.-P.M., J.P., J.T., M.B., R.A.-S.S., H.R.J., C.S., Y.Y., P.M.C.C., J.S., C.C., J.-S.J., R.V., D.D., S.T.E., A.R.P.-J., A.M., P.M., and A.V.A. contributed to the acquisition of data; G.T., D.J.W., A.H.K., D.W., and G.A. contributed to analysis of data, drafting the text, and preparing the figures.

Potential Conflicts of Interest

Nothing to report.

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