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Direct oral anticoagulant– vs vitamin K antagonist–related nontraumatic intracerebral hemorrhage

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ABSTRACT

Objective: To compare the neuroimaging profile and clinical outcomes among patients with intracerebral hemorrhage (ICH) related to use of vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) for nonvalvular atrial fibrillation (NVAF).

Methods: We evaluated consecutive patients with NVAF with nontraumatic, anticoagulant-related ICH admitted at 13 tertiary stroke care centers over a 12-month period. We also performed a systematic review and meta-analysis of eligible observational studies reporting baseline characteristics and outcomes among patients with VKA- or DOAC-related ICH.

Results: We prospectively evaluated 161 patients with anticoagulation-related ICH (mean age 75.6 ± 9.8 years, 57.8% men, median admission NIH Stroke Scale [$NIHSS_{adm}$] score 13 points, interquartile range 6–21). DOAC-related (n = 47) and VKA-related (n = 114) ICH did not differ in demographics, vascular risk factors, HAS-BLED and CHA_2DS_2-VASc scores, and antiplatelet pretreatment except for a higher prevalence of chronic kidney disease in VKA-related ICH. Patients with DOAC-related ICH had lower median $NIHSS_{adm}$ scores (8 [3–14] vs 15 [7–25] points, $p = 0.003$), median baseline hematoma volume (12.8 [4–40] vs 24.3 [11–58.8] cm^3, $p = 0.007$), and median ICH score (1 [0–2] vs 2 [1–3] points, $p = 0.049$). Severe ICH (>2 points) was less prevalent in DOAC-related ICH (17.0% vs 36.8%, $p = 0.013$). In multivariable analyses, DOAC-related ICH was independently associated with lower baseline hematoma volume ($p = 0.006$), lower $NIHSS_{adm}$ scores ($p = 0.022$), and lower likelihood of severe ICH (odds ratio [OR] 0.34, 95% confidence interval [CI] 0.13–0.87, $p = 0.025$). In meta-analysis of eligible studies, DOAC-related ICH was associated with lower baseline hematoma volumes on admission CT (standardized mean difference = −0.57, 95% CI −1.02 to −0.12, $p = 0.010$) and lower in-hospital mortality rates (OR = 0.44, 95% CI 0.21–0.91, $p = 0.030$).

Conclusions: DOAC-related ICH is associated with smaller baseline hematoma volume and lesser neurologic deficit at hospital admission compared to VKA-related ICH. *Neurology*® 2017;89:1142–1151

GLOSSARY

CI = confidence interval; **CMB** = cerebral microbleed; **CMB-NOW** = Cerebral Microbleeds During the Non-Vitamin K Antagonist Oral Anticoagulants or Warfarin Therapy in Stroke Patients With Nonvalvular Atrial Fibrillation; **DOAC** = direct oral anticoagulant; **ICH** = intracranial hemorrhage; **INR** = international normalized ratio; **IQR** = interquartile range; **MOOSE** = Meta-Analysis of Observational Studies Epidemiology; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **NVAF** = nonvalvular atrial fibrillation; **OR** = odds ratio; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RE-LY** = Randomized Evaluation of Long-Term Anticoagulation Therapy; **ROCKET AF** = Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; **VKA** = vitamin K antagonist.

Oral anticoagulation prevents thromboembolism and significantly reduces mortality in patients with nonvalvular atrial fibrillation (NVAF).[1] The most feared complication related to the use of oral anticoagulation is intracranial hemorrhage (ICH), which has been associated with a higher

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Supplemental data at Neurology.org

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likelihood of both hematoma expansion and mortality.[2] Even though direct oral anticoagulants (DOACs) have shown to be both safe and effective for ischemic stroke prevention in patients with NVAF[3,4] with half the risk for ICH compared to vitamin K antagonists (VKAs),[5,6] preliminary findings of a recent multicenter registry indicate that DOAC-related ICHs also carry a high risk for both hematoma expansion and unfavorable clinical outcomes.[7] The concern regarding both hematoma expansion and subsequent worse outcomes in DOAC-related ICHs is exacerbated by the lack of approved specific antidotes for DOACs (except for dabigatran) compared to VKAs.[8]

In view of the former considerations, we sought to compare the neuroimaging profiles and clinical outcomes between DOAC- and VKA-related nontraumatic ICHs in a prospective, multicenter, cross-sectional study. Given the scarce available data comparing neuroimaging and clinical outcomes between DOAC- and VKA-related ICH, we also performed a systematic review and meta-analysis to summarize all available literature data and to further evaluate the association of DOAC- (vs VKA-) related ICH with radiologic and clinical outcome measures.

METHODS

Multicenter study population and methods. We prospectively enrolled consecutive patients with nontraumatic ICH and positive history of oral anticoagulant intake who presented in the emergency rooms of the participating tertiary care stroke centers during a 1-year period (June 2015–July 2016). More specifically, the definition of VKA-related ICH required effective use of VKA with an international normalized ratio (INR) of >1.5 on hospital admission as previously described.[9] Patients with major head trauma or known underlying structural or vascular cause of ICH were excluded from further evaluation. We also excluded patients with cerebral ischemia and hemorrhagic transformation. Details of the complete list of participating institutions, the parameters that were recorded, and the statistical analysis are available in the supplemental material at Neurology.org.[10]

Noncontrast head CT scans were performed for all patients both at baseline and within 24 hour after ictus. CT findings were interpreted and extracted independently by either neurologists or neuroradiologists in each participating institution who were unaware of each patient's clinical data. Hematoma volume in both baseline and follow-up (within the first 24 hours) CT scans was calculated from the slices of CT images in each patient with the ABC/2 method,[11] while expansion of hematoma at 24 hours was defined as an absolute increase of >12.5 mL or a relative increase of >33% in hematoma volume at the 24-hour CT scan compared to the admission CT scan.[12] Repeat CT scans were also systematically evaluated and compared with the admission CT scan for the presence of edema or midline shift within the first 24 hours from the index event.

For each included patient, we additionally calculated the corresponding body mass index score, creatinine clearance on admission estimated by the Cockcroft-Gault equation, CHA_2DS_2-VASc score,[13] HAS-BLED score,[14] and ICH score.[15] Severe ICH on admission was defined as an index event with an ICH score of >2. This specific cutoff was selected because in the original cohort an ICH score of >2 was associated with a significant increase in 30-day mortality (72% vs 26%).[15]

In the participating centers, all eligible patients were treated according to current guidelines for the management of spontaneous ICH.[16] Intubation, surgical decompression, or external ventricular drainage was indicated by case on the basis of both neurologic deterioration and findings on the repeat CT scan. NIH Stroke Scale (NIHSS) score at 24 hours and hospital discharge and modified Rankin Scale (mRS) scores at both discharge and 3 months were obtained as standard of care for all patients. Disability at 3 months was defined as an mRS score of >2.[12]

Standard protocol approvals, registrations, and patient consents. The study was approved by the corresponding institutional ethical standards committees in each participating center, and written informed consent was obtained from all patients or guardians.

Search strategy and data extraction from previous studies. The meta-analysis has adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses[17] and was written according to the Meta-Analysis of Observational Studies Epidemiology (MOOSE) proposal.[18] Eligible observational studies reporting baseline characteristics and outcomes among patients with VKA-related or DOAC-related ICH were identified by searching MEDLINE and SCOPUS.

In each study that met the inclusion criteria, for the quantitative analysis, the Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses tool was used.[19] Quality control and bias identification were performed independently by 3 reviewers (G.T., A.H.K., and A.V.A.), and all emerging conflicts were resolved with consensus. For each included study, the numbers of events in patients with VKA-related or DOAC-related ICH were identified, and the corresponding odds ratios (ORs) were calculated. For studies with a zero cell, we used a continuity correction of 0.5 as appropriate. Continuous outcomes were pooled as standardized mean differences, calculated as the mean differences divided by the corresponding pooled SDs. Further details on the meta-analysis protocol are available in the supplemental material.

Statistical analyses. ***Multicenter cross-sectional study.*** Statistical comparisons between different subgroups were performed with appropriate tests. The distribution of the 3-month mRS scores among groups was compared with the Cochran-Mantel-Haenszel test and univariable/multivariable ordinal logistic regression (shift analysis).[20]

Univariable and multivariable regression analyses were also used to evaluate the associations between baseline characteristics and outcomes of interest. In all linear regression analyses, baseline hematoma volume and admission NIHSS ($NIHSS_{adm}$) score were cube root and log transformed, respectively, to satisfy statistical assumptions regarding normality of the distribution.[21,22] We reported all associations as linear regression coefficients in linear regression models, ORs in logistic regression models, and common ORs in ordinal regression models.

Table 1 Baseline characteristics of patients pretreated with DOACs and VKAs

Variable	DOACs (n = 47)	VKAs (n = 114)	*p* Value
Baseline clinical characteristics			
Age, mean ± SD, y	76.6 ± 9.5	75.2 ± 9.9	0.417
Male, %	57.4	57.9	0.958
BMI, mean ± SD, kg/m^2	27.0 ± 5.5	28.4 ± 6.6	0.248
Race, %			
White	87.2	72.8	
Black	6.4	16.7	
Asian	6.4	8.8	
Hispanic	0	1.7	
CHA_2DS_2-VASc score, mean ± SD	4.5 ± 1.8	4.4 ± 1.6	0.771
HAS-BLED score, mean ± SD	2.7 ± 1.0	2.9 ± 1.1	0.143
Hypertension, %	95.7	93.8	0.636
Diabetes mellitus, %	44.7	41.2	0.687
Hyperlipidemia, %	51.1	57.9	0.427
Heart failure, %	21.3	24.6	0.655
Current smoking, %	6.4	11.4	0.333
Coronary artery disease, %	23.4	39.5	0.052
Chronic kidney disease, %	6.5	21.9	0.020
History of any stroke, %	39.5	38.3	0.889
History of ischemic stroke, %	38.3	37.7	0.945
History of ICH, %	6.4	6.1	0.954
Statin pretreatment, %	47.7	59.1	0.199
Antiplatelet pretreatment, %	27.3	38.5	0.187
Dual antiplatelet pretreatment, %	2.3	7.3	0.231
DOAC type, n (%)			
Dabigatran	8 (17)	—	—
Rivaroxaban	24 (51)		
Apixaban	15 (32)		
NIHSS score at admission, median (IQR)	8 (3–14)	15 (7–25)	0.003
GCS score at admission, median (IQR)	14 (12–15)	13 (7–15)	0.008
SBP admission, mean ± SD, mm Hg	175.1 ± 31.9	172.5 ± 32.1	0.639
DBP admission, mean ± SD, mm Hg	94.4 ± 20.4	91.4 ± 18.5	0.377
Baseline laboratory values			
INR at admission, mean ± SD	1.6 ± 0.72	2.9 ± 1.14	<0.001
aPTT at admission, mean ± SD, s	34.8 ± 6.1	40.3 ± 11.2	0.002
Platelet count, median (IQR), n × 10^3/μL	195 (172–233)	206 (166–256)	0.635
CrCl on admission, mean ± SD, mL/min	66.4 ± 18.4	66.5 ± 34.1	0.980
Baseline CT findings			
Lobar hemorrhage, %	44.7	58.8	0.102
Intraventricular hemorrhage, %	36.2	43.0	0.424
Baseline ICH volume, median (IQR), cm^3	12.8 (4–40)	24.3 (11–58.8)	0.007
Baseline ICH volume >30 cm^3, %	25.5	45.6	0.018

Continued

Table 1 Continued

Variable	DOACs (n = 47)	VKAs (n = 114)	*p* Value
ICH score, median (IQR)	1 (0–2)	2 (1–3)	0.049
Severe ICH, %[a]	17.0	36.8	0.013

Abbreviations: aPTT = activated partial thromboplastin time; BMI = body mass index; CrCl = creatinine clearance; DBP = diastolic blood pressure; DOAC = direct oral anticoagulant; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; INR = international normalized ratio; IQR = interquartile range; NIHSS = NIH Stroke Scale; SBP = systolic blood pressure; VKA = vitamin K antagonist.
[a] Defined as an ICH score of >2.

RESULTS **Multicenter cross-sectional study.** A total of 161 consecutive patients with ICH (mean age 75.6 ± 9.8 years, 57.8% men, median $NIHSS_{adm}$ score 13 points, interquartile range [IQR] 6–21) were admitted in the 13 participating institutions during the 1-year period with DOAC-related (n = 47) and VKA-related (n = 114) ICH. The 47 patients with DOAC-related ICH were pretreated with dabigatran (n = 8), rivaroxaban (n = 24), and apixaban (n = 15).

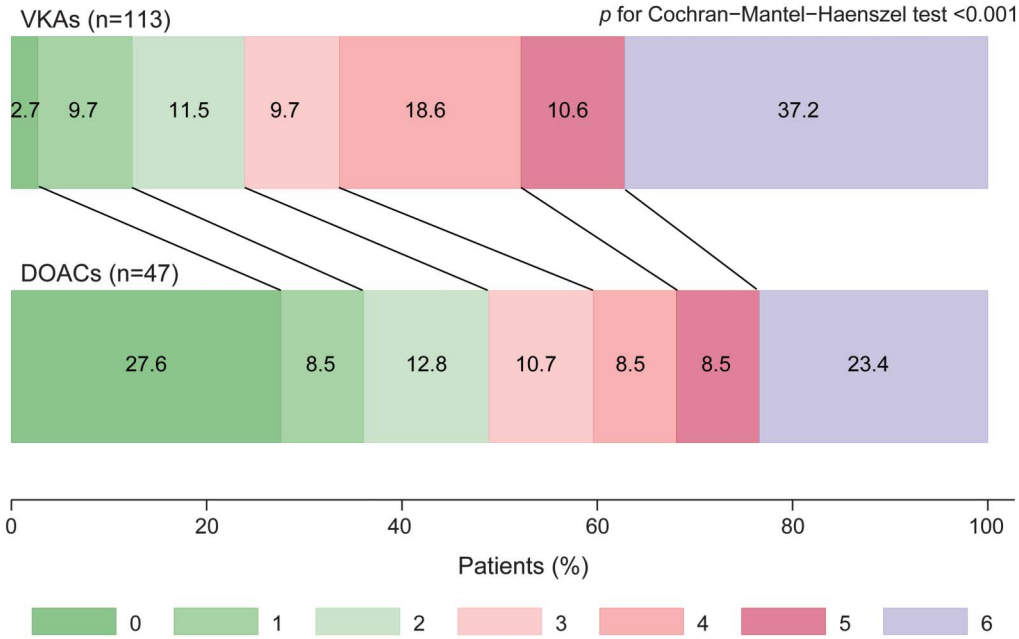
Patients with VKA- and DOAC-related ICH did not differ in demographics, HAS-BLED and CHA_2DS_2-VASc scores, antithrombotic medications, or vascular risk factors, except for a higher

Table 2 Clinical and radiologic outcomes of patients with ICH pretreated with DOACs and VKAs

Variable	DOACs (n = 47)	VKAs (n = 114)	*p* Value
Therapies/interventions, %			
FFP	6.4	27.2	0.003
PCC	34.0	59.6	0.003
Vitamin K	10.8	71.9	<0.001
Idarucizumab	2.2	—	—
Surgical decompression	6.3	7.9	0.740
External ventricular drainage	14.9	15.8	0.887
Intubation	23.4	32.4	0.254
Radiologic outcomes at 24 h			
ICH volume at 24 h, cm^3 median (IQR)	19.8 (6.9–43.6)	28.4 (12.6–56)	0.217
ICH volume >30 cm^3 at 24 h, %	42.5	56.1	0.117
Absolute ICH growth at 24 h, median (IQR)	1.12 (−0.83 to 5.6)	2.6 (−1.73 to 15)	0.347
Hematoma expansion, %	23.1	37.1	0.116
Cerebral edema, %	53.2	71.0	0.030
Midline shift, %	26.1	45.6	0.022
Clinical outcomes			
NIHSS score at 24 h, median (IQR)	6 (2–15)	15 (6–23)	0.007
Absolute NIHSS decrease at 24 h, median (IQR)	0 (−1 to 1)	0 (−2 to 0)	0.274
Days of hospitalization, median (IQR)	8 (4–17)	8.5 (4–14)	0.446
NIHSS score at discharge, median (IQR)	3 (1–10)	6 (3.5–15)	0.011
mRS score at discharge, median (IQR)	3 (1–5)	4 (3–6)	0.002
In-hospital mortality, %	21.2	33.3	0.128
mRS score at 3 mo, median (IQR)[b]	3 (0–5)	4 (3–6)	0.001
Disability at 3 mo,[a] %[b]	51.1	76.3	0.002
Mortality at 3 mo, %[b]	21.7	36.3	0.075

Abbreviations: DOAC = direct oral anticoagulant; FFP = fresh frozen plasma; ICH = intracerebral hemorrhage; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; PCC = prothrombin complex concentrates; VKA = vitamin K antagonist.
[a] Defined as mRS score of >2.
[b] One patient lost to follow-up.

Figure 1 Horizontal "Grotta" bars



Distribution of modified Rankin Scale scores at 3 months in patients with intracerebral hemorrhage pretreated with direct oral anticoagulants (DOACs) or vitamin K antagonists (VKAs).

prevalence of chronic kidney disease in VKA-pretreated patients (21.9% vs 6.5%, $p = 0.020$). No differences were found in the baseline laboratory parameters except for higher INR (2.9 ± 1.14 vs 1.6 ± 0.72, $p < 0.001$) and activated partial thromboplastin time (40.3 ± 11.2 vs 34.8 ± 6.1, $p = 0.002$) values found as expected in patients with VKA- compared to DOAC-related ICH (table 1). Patients with DOAC-related ICH had lower median $NIHSS_{adm}$ scores (8 [IQR 3–14] vs 15 [IQR 7–25] points, $p = 0.003$), higher median admission Glasgow Coma Scale scores (14 [IQR 12–15] vs 13 [IQR 7–15] points, $p = 0.008$), and lower baseline median ICH volume (12.8 [IQR 4–40] vs 24.3 [IQR 11–58.8] cm^3, $p = 0.007$). Moreover, baseline ICH volume >30 cm^3 was less prevalent in DOAC-related ICH (25.5% vs 45.6%, $p = 0.018$). The median ICH score was also lower in DOAC-related ICH (1 [IQR 0–2] vs 2 [IQR 1–3] points, $p = 0.049$), while severe ICH (ICH score >2) was less prevalent in DOAC-related ICH (17% vs 36.8%, $p = 0.013$).

Pharmacologic interventions during hospitalization, including the administration of fresh-frozen plasma, prothrombin complex concentrates, and vitamin K, were more common ($p < 0.01$) in patients with VKA- compared to those with DOAC-related ICH. However, no differences were detected in the rate of invasive procedures (intubation, surgical decompression, or external ventricular drainage) between the 2 groups during hospitalization (table 2). One patient pretreated with dabigatran received treatment with idarucizumab.

The 2 groups did not differ in neuroimaging parameters at 24 hours except for cerebral edema and midline shift, which were less prevalent in DOAC-related ICH (53.2% vs 71.0%, $p = 0.030$; and 26.1% vs 45.6%, $p = 0.022$). Moreover, the rates of hematoma expansion (23.1% vs 37.1%, $p = 0.116$) and ICH volume >30 cm^3 at 24 hours (42.5% vs 56.1%, $p = 0.117$) tended to be lower in patients with DOAC-related ICH. Patients with DOAC-related ICH had lower median NIHSS scores at 24 hours (6 [IQR 2–15] vs 15 [IQR 6–23] points, $p = 0.007$) and at hospital discharge (3 [IQR 1–10] vs 6 [IQR 3.5–15] points, $p = 0.011$). They also presented with lower median mRS scores at discharge (3 [IQR 1–5] vs 4 [IQR 3–6] points, $p = 0.002$) and at 3 months (3 [IQR 0–5] vs 4 [IQR 3–6] points, $p = 0.001$). In addition, patients with DOAC-related ICH had lower disability (mRS score >2) rates at 3 months (51.1% vs 76.3%, $p = 0.002$) and greater 3-month functional improvement (shift analysis in mRS scores) compared to VKA-related ICH ($p < 0.001$ by Cochran-Mantel-Haenszel test; figure 1). The 2 groups did not differ in terms of in-hospital (21.2% vs 33.3%, p for log-rank test = 0.128) and 3-month (21.7% vs 36.3%, p for log-rank test = 0.092; figure e-1) mortality rates.

In univariable and multivariable regression analyses, DOAC-related ICH was independently associated with lower baseline hematoma volume

Table 3 Simple and multiple linear regression analyses evaluating the association of baseline characteristics with cube root of hematoma volume on hospital admission

	Simple linear regression		Multiple linear regression	
	Linear regression coefficient (95% CI)	p	Linear regression coefficient (95% CI)	p
Age	0.002 (−0.02 to 0.021)	0.863	—	—
Male	−0.093 (−0.473 to 0.286)	0.628	—	—
BMI	0.007 (−0.025 to 0.039)	0.670	—	—
CHA_2DS_2-VASc score	0.088 (−0.024 to 0.200)	0.123	—	—
HAS-BLED score	0.239 (0.069 to 0.409)	0.006	0.212 (0.031 to 0.393)	0.022
Hypertension	0.125 (−0.692 to 0.942)	0.764	—	—
Diabetes mellitus	0.060 (−0.320 to 0.440)	0.756	—	—
Hyperlipidemia	−0.190 (−0.567 to 0.186)	0.320	—	—
Heart failure	−0.088 (−0.530 to 0.354)	0.694	—	—
Current smoking	0.213 (−0.414 to 0.840)	0.503	—	—
Coronary artery disease	0.335 (−0.056 to 0.725)	0.103	—	—
Kidney failure	−0.008 (−0.504 to 0.488)	0.975	—	—
History of ischemic stroke	0.150 (−0.236 to 0.536)	0.445	—	—
History of ICH	−0.509 (−1.282 to 0.265)	0.196	—	—
Statin pretreatment	−0.120 (−0.510 to 0.271)	0.545	—	—
Antiplatelet pretreatment	0.618 (0.221 to 1.014)	0.002	0.462 (0.068 to 0.855)	0.022
Dual antiplatelet pretreatment	−0.133 (−0.961 to 0.695)	0.751	—	—
DOAC pretreatment	−0.571 (−0.974 to −0.168)	0.006	−0.569 (−0.974 to −0.163)	0.006
Admission SBP	0.004 (−0.002 to 0.010)	0.199	—	—
Admission DBP	0.009 (−0.001 to 0.018)	0.084	0.010 (0.001 to 0.020)	0.035

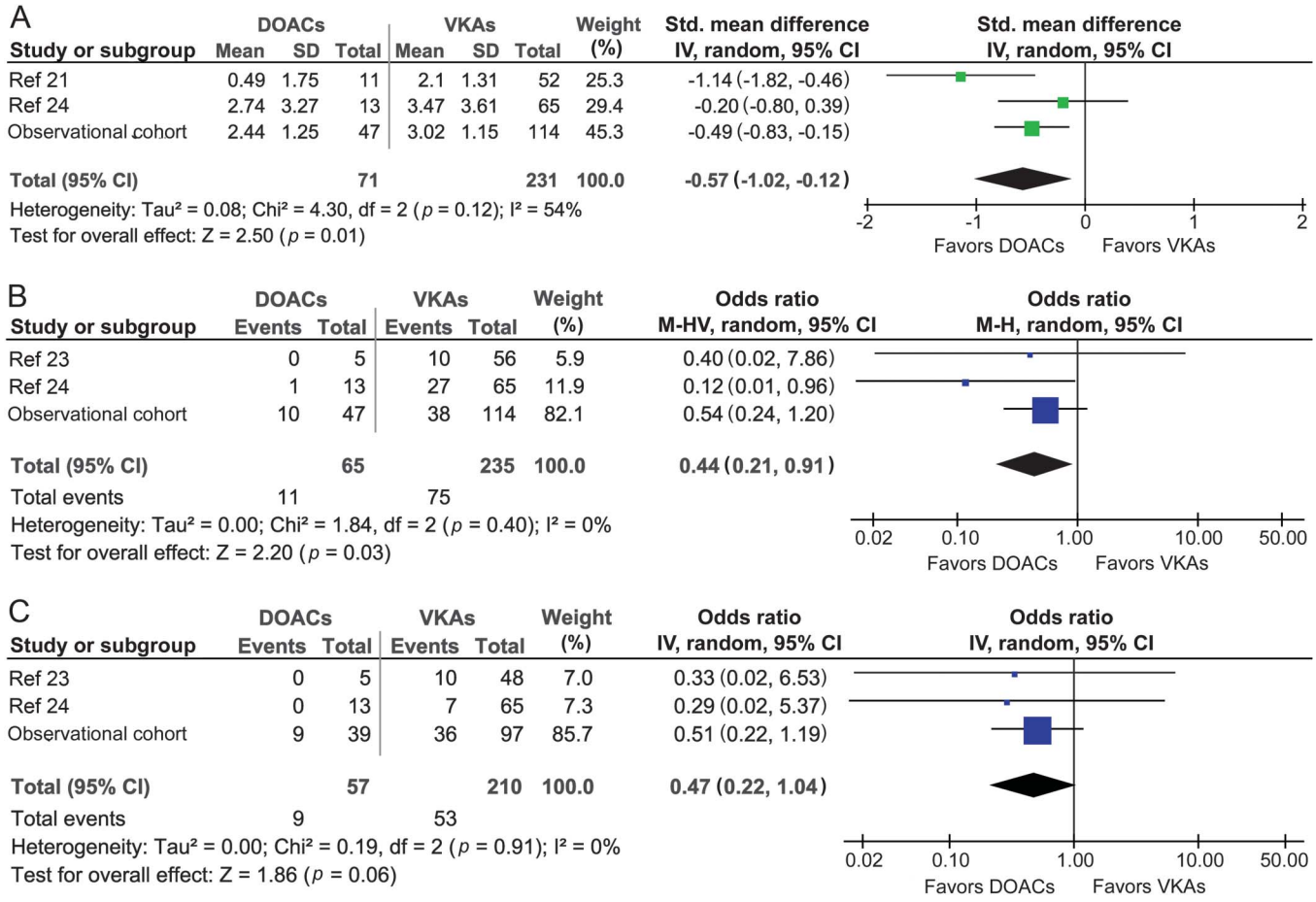
Abbreviations: BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; DOAC = direct oral anticoagulant; ICH = intracerebral hemorrhage; NIHSS = NIH Stroke Scale; SBP = systolic blood pressure.

(linear regression coefficient = −0.569, 95% confidence interval [CI] −0.97 to −0.163, $p = 0.006$; table 3), lower $NIHSS_{adm}$ score (linear regression coefficient = −0.409, 95% CI −0.759 to −0.059, $p = 0.022$; table e-1), and lower likelihood of severe ICH on admission (OR = 0.34, 95% CI 0.13–0.87, $p = 0.025$; table e-2). Moreover, DOAC-related ICH tended to be associated with lower likelihood of baseline hematoma volume of >30 cm^3 on admission CT scan in multivariable logistic regression models adjusted for potential confounders (OR = 0.46, 95% CI 0.20–1.05, $p = 0.067$; table e-3). Even though DOAC-related ICH was associated with lower odds of 3-month disability (OR = 0.32, 95% CI 0.16–0.66, $p = 0.002$; table e-4) and greater likelihood of 3-month functional improvement (common OR = 3.03, 95% CI 1.58–5.88, $p = 0.001$; table e-5) in initial univariable analyses, these associations did not retain their statistical significance in multivariable models adjusted for baseline hematoma volume, $NIHSS_{adm}$ score, and ICH score (OR = 0.77, 95% CI 0.29–2.04, $p = 0.602$; common OR = 1.44, 95% CI 0.69–3.03, $p = 0.324$; tables e-4 and e-5, respectively).

Because of the presence of collinearity regarding the history of DOAC pretreatment with both $NIHSS_{adm}$ score (table e-1) and baseline ICH volume (table 1), we performed additional univariable and multivariable logistic and ordinal regression analyses on the association of DOAC pretreatment with disability and functional improvement after excluding these 2 variables from the multivariable models. In the final multivariable analyses, DOAC-related ICH was associated with lower odds of 3-month disability (OR = 0.45, 95% CI 0.20–0.99, $p = 0.049$; table e-6) and greater likelihood of 3-month functional improvement (common OR = 3.12, 95% CI 1.64–6.25, $p = 0.001$; table e-7).

Meta-analysis of observational studies. A MEDLINE and SCOPUS database search yielded 460 and 328 results, respectively. After duplicates were removed, the titles and abstracts from the remaining 768 studies were screened, and 7 potentially eligible studies for the meta-analysis were retained. After retrieval of the

Figure 2 Pairwise meta-analyses of eligible observational studies



Forest plots of the association between direct oral anticoagulant (DOAC)–related intracerebral hemorrhage (ICH) and (A) admission hematoma volumes, (B) in-hospital mortality rates, and (C) hematoma expansion at 24 hours in a pairwise meta-analysis. Comparison group consisted of patients with vitamin K antagonists (VKA)–related ICH. CI = confidence interval; IV = inverse variance; M-HV = Mantel-Haenszel variance.

full-text version of the aforementioned 7 studies, 4 studies were excluded (table e-8). In the final presentation of the literature search results, there was no conflict or disagreement between the 3 reviewers who performed the literature search, and the 3 studies that met the inclusion criteria,[21,23,24] together with the data from the present report, were included in both the qualitative and quantitative syntheses (figure e-2). The characteristics and bias assessment of the included studies (363 total patients with ICH, mean age 76.6 years, men 56.8%) are shown in table e-9.

In the pooled analysis, DOAC-related ICH was associated with lower baseline hematoma volumes on admission CT (standardized mean difference = −0.57, 95% CI −1.02 to −0.12, $p = 0.010$; figure 2A) and lower in-hospital mortality rates (OR = 0.44, 95% CI 0.21–0.91, $p = 0.030$; figure 2B). The association of DOAC-related ICH with hematoma expansion at 24 hours was marginally not achieved (OR = 0.47, 95% CI 0.22–1.04, $p = 0.06$; figure 2C). In all aforementioned analyses, no evidence of heterogeneity was present (p for Cochran Q > 0.1 and $I^2 < 55\%$), while it should also be noted that hematoma expansion definition was univocal in all included studies.[21,23,24]

DISCUSSION The results of this cross-sectional study suggest that DOAC-related ICH has a more favorable neuroimaging and clinical profile on hospital admission compared to VKA-related ICH. More specifically, DOAC-related ICH is associated with lower baseline hematoma volumes, $NIHSS_{adm}$ scores, and ICH scores in multivariable analyses adjusted for numerous potential confounders.

After our results were pooled with the available literature, our pairwise meta-analysis documented a lower in-hospital mortality rate in patients with DOAC-related ICHs. This observation contradicts the findings of both the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)[25] and Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trials,[26] which have

suggested a similar 30-day case fatality risk for DOAC-related and VKA-related ICHs.[6] However, our findings are in accordance with the results of a recent study reporting lower mortality rates in DOAC-treated compared to VKA-treated patients with traumatic ICH.[27] Potential differences in baseline characteristics and in management of patients with ICH during hospitalization may account for these discrepant findings between observational studies and randomized controlled trials. In addition, a marginally nonsignificant lower rate of hematoma expansion (OR = 0.47, 95% CI 0.22–1.04, p = 0.06) was recorded in the pairwise meta-analysis of available studies reporting radiologic outcomes in patients with both DOAC- and VKA-related ICH. This finding is intriguing and deserves further investigation because the pooled prevalence of hematoma expansion reported in all available studies on DOAC-related ICH (17.9%, 95% CI 8.4–34.2; table e-10 and figure e-3) appears to be lower than the respective rates of hematoma expansion reported in previous 3 large studies evaluating patients with VKA-related ICH (36.0%, 50.0%, and 53.8%).[9,28,29]

The difference in baseline hematoma volume reported between DOAC- and VKA-related ICHs, which has already been observed and replicated in animal models,[30] could be partially attributed to the different pharmacologic properties between the 2 oral anticoagulation classes.[21,23,24] DOACs not only have a shorter half-life than VKAs but also selectively inhibit thrombin (dabigatran) or factor Xa (apixaban, rivaroxaban) and thus have no effect on the extrinsic coagulation pathway and the subsequent prothrombin formation and platelet aggregation, in contrast to VKAs.[31] Another potential explanation for the larger hematoma volume observed in VKA-related ICHs could be the higher risk of both cerebral microbleed (CMB) presence[32,33] and CMB progression[34] in stroke patients on VKA treatment, especially in those with higher CHA_2DS_2-VASc scores, increased prothrombin time,[32] and INR variability.[33] Because this increase in CMB number has not yet been evident in DOAC-treated patients,[35] the hypothesis of ICH incidence between DOAC- and VKA- treated patients according to CMB progression will be further tested within the setting of the Cerebral Microbleeds During the Non-Vitamin K Antagonist Oral Anticoagulants or Warfarin Therapy in Stroke Patients With Nonvalvular Atrial Fibrillation (CMB-NOW) study (NCT02356432).[36]

Even though the present report is one of the largest prospective, international, cross-sectional studies to date comparing clinical and radiologic outcomes in patients with DOAC- and VKA-related ICH (table e-9), several limitations should be acknowledged. First, as per the study protocol, no screening log was kept during the recruitment period of the study, and all eligible patients satisfying the predefined inclusion criteria were directly recruited after initial assessment in each participating institution. Second, patients in the 2 groups were not randomized to DOAC or VKA administration; thus, imbalances in both baseline characteristics and other potential confounders could be present. Third, evaluation of premorbid mRS scores was not included in our study protocol. Thus, we cannot provide exact estimates of patients' functional status before the index event. However, it should be noted that the percentages of included patients with history of any stroke, ischemic stroke, or ICH before the index event were equally distributed between the DOAC- and VKA-treated groups (table 1). Moreover, because onset-to-neuroimaging time was not prospectively recorded, potential imbalances in the 2 groups could be present (despite the fact that all patients underwent baseline neuroimaging studies within 24 hours). On the other hand, it should be kept in mind that we detected no differences in baseline characteristics among patients with DOAC- and VKA-related ICH, except for those related directly to the mechanism of anticoagulation (INR, activated partial thromboplastin time values) and the rates of chronic kidney disease history. Despite the reported higher rates of chronic kidney disease in the VKA-related ICH group, no significant differences in the admission creatinine clearance values were documented between the 2 groups.

Fourth, even though patients with VKA-related ICH had higher rates of antiplatelet pretreatment history compared to patients with DOAC-related ICH (38.5% vs 27.3%), this difference was not statistically significant (p = 0.187), while the history of prior antiplatelet intake was incorporated in all univariable/multivariable analyses. Fifth, no subgroup analyses according to DOAC type were feasible because of the low number of patients included in each of the 3 DOAC subgroups. This analysis may be clinically relevant because distinct bleeding patterns and bleeding risks have been reported in different DOACs.[2,37] Sixth, there was no central adjudication of both clinical or imaging outcomes. However, all radiologic parameters were evaluated in the participating institutions by neuroradiologists blinded to the patients' clinical information. Seventh, we did not systematically evaluate patients with MRI on hospital admission for the detection of CMBs; thus, a possible moderating effect of CMB count on the reported associations remains uncertain.[10] Finally, even though we detected no significant differences between patients with DOAC- and VKA-related ICH on the rates of hematoma expansion and in-hospital and 3-month mortality rates, when our data were coupled in pooled analyses with available literature data, the

differences between patients with DOAC- and VKA-related ICH were significant for in-hospital mortality rates ($p = 0.03$) with a tendency ($p = 0.06$) for less hematoma expansion. This observation underlines the fact that even though our multicenter observational study managed to include a high number of patients with DOAC- and VKA-related ICHs, it is presumably still underpowered to detect significant differences in some of the clinical outcomes between the 2 groups. This highlights the need for additional adequately powered and properly designed studies on the topic. We believe that both our observational study data and the pooled estimates from the meta-analysis could provide invaluable insight for future power calculations and sample size estimations.

The present multicenter cross-sectional study suggests that DOAC-related ICHs appear to have more favorable neuroimaging and clinical profiles on hospital admission compared to VKA-related ICH. These findings underscore DOACs as an attractive therapeutic option in terms of risk of severe ICH in patients with NVAF and high risk of intracranial bleeding. This observation requires independent confirmation in larger prospective cohort studies, which will further evaluate comparatively ICH severity and provide robust estimates of cumulative ICH incidence rates between DOAC- and VKA-treated patients.

AUTHOR CONTRIBUTIONS

Georgios Tsivgoulis: literature search, figures, study design, data collection, data analysis, data interpretation, writing. Vasileios-Arsenios Lioutas and Panayiotis Varelas: data collection, data interpretation, writing. Aristeidis H. Katsanos: literature search, figures, data collection, data analysis, data interpretation, writing. Nitin Goyal, Robert Mikulik, Kristian Barlinn, Christos Krogias, Vijay K. Sharma, Konstantinos Vadikolias, Efthymios Dardiotis, and Theodore Karapanayiotides: data collection, data interpretation. Alexandra Pappa, Christina Zompola, and Sokratis Triantafyllou: data collection. Odysseas Kargiotis: data interpretation. Michael Ioakeimidis: data collection. Sotirios Giannopoulos: data collection, data interpretation. Ali Kerro: data collection. Argyrios Tsantes: data interpretation. Chandan Mehta, Mathew Jones, Christoph Schroeder, and Casey Norton: data collection. Anastasios Bonakis: data interpretation. Jason Chang: data collection, data interpretation. Anne W. Alexandrov and Panayiotis Mitsias: data interpretation. Andrei V. Alexandrov: study design, data interpretation.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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