Original Contribution

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Endovascular Stroke Treatment and Risk of Intracranial Hemorrhage in Anticoagulated Patients

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Background and Purpose—We aimed to determine the safety and mortality after mechanical thrombectomy in patients taking vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs).

Methods—In a multicenter observational cohort study, we used multiple logistic regression analysis to evaluate associations of symptomatic intracranial hemorrhage (sICH) with VKA or DOAC prescription before thrombectomy as compared with no anticoagulation. The primary outcomes were the rate of sICH and all-cause mortality at 90 days, incorporating sensitivity analysis regarding confirmed therapeutic anticoagulation. Additionally, we performed a systematic review and meta-analysis of literature on this topic.

Results—Altogether, 1932 patients were included (VKA, n=222; DOAC, n=98; no anticoagulation, n=1612); median age, 74 years (interquartile range, 62–82); 49.6% women. VKA prescription was associated with increased odds for sICH and mortality (adjusted odds ratio [aOR], 2.55 [95% CI, 1.35–4.84] and 1.64 [95% CI, 1.09–2.47]) as compared with the control group, whereas no association with DOAC intake was observed (aOR, 0.98 [95% CI, 0.29–3.35] and 1.35 [95% CI, 0.72–2.53]). Sensitivity analyses considering only patients within the confirmed therapeutic anticoagulation range did not alter the findings. A study-level meta-analysis incorporating data from 7462 patients (855 VKAs, 318 DOACs, and 6289 controls) from 15 observational cohorts corroborated these observations, yielding an increased rate of sICH in VKA patients (aOR, 1.62 [95% CI, 1.22–2.17]) but not in DOAC patients (aOR, 1.03 [95% CI, 0.60–1.80]).

Conclusions—Patients taking VKA have an increased risk of sICH and mortality after mechanical thrombectomy. The lower risk of sICH associated with DOAC may also be noticeable in the acute setting. Improved selection might be advisable in VKA-treated patients.

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Symptomatic intracranial hemorrhage (sICH) is a dreaded complication in patients with an acute ischemic stroke (AIS) treated with intravenous thrombolysis (IVT) or endovascular therapy (EVT). The overall risk of sICH in patients receiving mechanical thrombectomy (MT) in 5 large randomized controlled trials was 4.4%.[1]

Therapeutic oral anticoagulation (OAC) was a prominent risk factor for hemorrhagic complications in unselected AIS patients[2]; however, the relative increase in risk in patients taking OAC who undergo MT is unknown. Patients on anticoagulants were often excluded from recent pivotal randomized controlled MT trials, and subgroup analysis of patients on OAC is lacking. Data on efficacy and safety of endovascular treatment in patients on anticoagulants, especially those on direct OACs (DOACs), are hence scarce and observational (Table I in the online-only Data Supplement).[3–17] Additionally, most studies did not differentiate between therapeutic and nontherapeutic activity of OAC.

Therefore, the main objectives of this study were (1) to determine the risk of sICH and mortality in MT patients taking either vitamin K antagonists (VKAs) or DOAC as compared with patients without OAC in a large multicenter registry; (2) to provide a sensitivity analysis including only patients with confirmed therapeutic anticoagulation activity; and (3) to present an up-to-date meta-analysis summarizing the available observational evidence of sICH and mortality risk in patients undergoing endovascular recanalization procedures.

Methods

Data Availability Statement

The deidentified data generated and analyzed in this study will be available and shared on request from any qualified investigator for the purposes of replicating procedures and results, after clearance by the ethics committee.

Observational Cohort Study

The study protocol of the BEYOND-SWIFT registry has been registered (NCT03496064), and details have been published previously.[18] In brief, the registry is a retrospective, international, multicenter, nonrandomized observational study set up to investigate the safety and efficacy of a market-release neurothrombectomy device (applied as initial devices) in AIS patients. Table II in the online-only Data Supplement gives an overview of the patients included, availability of follow-up data for each center, and ethical approval procedure.

For the primary analysis, we included all patients from BEYOND-SWIFT (Bernese-European Registry for Ischemic Stroke Patients Treated Outside Current Guidelines With Neurothrombectomy Devices Using the Solitaire FR With the Intention for Thrombectomy) for whom information on OAC therapy before stroke onset was available. We grouped patients according to their intake of anticoagulants before admission: VKA (group 1) and DOAC therapy (group 2) were defined as patients with a current prescription for a VKA or DOAC drug at the time of symptom onset. Patients without OAC (group 3) were defined as those with no current prescription of an OAC substance at the time of symptom onset. Intake of antiplatelet therapy did not affect assignment to a group. For the sensitivity analysis, we defined confirmed therapeutic anticoagulation as an international normalized ratio (INR) >1.7 in patients taking VKA or specific drug activity >50 ng/mL[19–23] in patients taking DOAC. If no specific drug activity measurement was available in patients taking DOAC, confirmed therapeutic OAC was defined as either (1) drug intake within the last 24/12 hours for once daily/twice daily medication; (2) thrombin time >38 seconds in patients taking dabigatran[24]; or (3) INR >1.2 in patients taking Xa inhibitors (apixaban, edoxaban, or rivaroxaban; Table III in the online-only Data Supplement).[25,26]

Variables and Image Analysis

Local investigators collected data on OAC medication before stroke onset and records of coagulation assays, which were performed according to local standards. We defined tandem occlusion as the presence of an intracranial large vessel occlusion and >90% extracranial cervical stenosis or occlusion. We defined successful recanalization as reperfusion of at least 50% of the initially occluded target territory, according to the modified treatment in cerebral ischemia score (≥2b).[27]

Outcomes

The primary end point of this analysis was sICH until hospital discharge, which was assessed at each center applying the ECASS II (European Co-Operative Acute Stroke Study-II) criteria.[28] Secondary outcomes were technical efficacy and all-cause mortality at 3 months. For evaluation of the functional outcome at 3 months, we applied the modified Rankin Scale obtained during routinely scheduled clinical visits or standardized telephone interviews. We present the rates of good functional outcome (modified Rankin Scale score, 0–2).

Statistical Analysis

We compared the 3 groups (VKA, DOAC, and patients without OAC) and the 2 OAC groups (VKA versus DOAC; Table IV in the online-only Data Supplement) using appropriate statistical measures (χ^2 test for categorical variables, Kruskal-Wallis H test for non-normally continuous or ordinally scaled variables, and ANOVA for independent, normally distributed data, Fisher exact test for categorical variables, Mann-Whitney *U* test for non-normally continuous or ordinally scaled variables, and Welch *t* test for independent, normally distributed data).

For the analysis of a preinterventional model, the association of OAC type with the binary outcome parameter was assessed separately for each outcome (primary outcome sICH or mortality or good functional outcome) using multiple logistic regression controlling for the following prespecified confounders: age (continuous), sex (categorical), National Institutes of Health Stroke Scale on admission (ordinal, adjusted odds ratio [aOR] per point increase), hypertension (categorical), diabetes mellitus (categorical), dyslipidemia (categorical), cardioembolic stroke subtype (categorical), time from symptom onset to groin puncture (continuous), type of imaging (categorical), tandem occlusion (categorical), and IVT (categorical). The rationale for this model was the combination of known predictors of sICH following EVT[29–34] and baseline differences between patients experiencing sICH and those who did not (Table V in the online-only Data Supplement). Patients with missing data items were excluded from the multivariable analysis. For the sensitivity analysis, the same model was used to assess the association of INR (continuous) with sICH in VKA patients. No corrections for multiple testing were made for secondary and sensitivity analyses.

For the prognostic postinterventional model, the following additional confounders were included: reperfusion success (categorical), use of balloon guide catheter (categorical), maneuver count (ordinal, aOR per one maneuver), time from groin puncture to reperfusion (continuous), and compound complication (categorical). The rationale for this model was the combination of known predictors of sICH following EVT[29–34] and interventional differences between patients with sICH and without sICH (Table IV in the online-only Data Supplement).

Systematic Review and Meta-Analysis

We performed a systematic review and meta-analysis conforming to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[35] and the Meta-Analysis of Observational Studies in Epidemiology checklist[36] (for further details, search strategy, and statistics, see the online-only Data Supplement). The systematic review and meta-analysis was registered at the International Prospective

Register of Systematic Reviews (CRD42019127464). Briefly, prevalences of sICH and mortality in patients undergoing EVT according to whether patients had previously been prescribed DOAC, VKA, or no OAC were used to calculate summary estimates of effect sizes (summarized odds ratios [sORs])[37] using the inverse variance heterogeneity model assuming heterogeneous populations and accounting for multiple true effect sizes. When information was missing in the original publication, we contacted the lead authors to request the additional information. We display summarized point estimates together with the corresponding 95% CIs to express the odds for a comparison between VKA or DOAC and patients without OAC.

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval was granted by local ethical standards committees (see Table II in the online-only Data Supplement for details of each center). Additionally, ethical approval was obtained for centrally pooling the data in Bern (KEK Bern, Bern, Switzerland, Local Ethics Committee study identifier: 2018-00766). The registry is registered at https://www.clinicaltrials.gov (NCT03496064) and the systematic review and meta-analysis at the Prospective Register of Systematic Reviews (CRD42019127464).

Results

Baseline

For 1942 of 2046 patients in the registry, information on OAC medication was available (222 VKAs, 98 DOACs, and 1622 no OAC) hence excluding 104 patients for whom information on OAC medication was missing. For 317 of 320 (99.1%) patients on OAC, information on sICH was available, and 267 of 320 (83.4%) had documented 90-day follow-up. INR was available for 138 of 222 (62.2%) patients taking VKA. Information on DOAC compliance was available for 35 of 98 (36%) patients (23, medication certainly taken; 12, certainly not taken; 63, not documented). Reliable assessments of DOAC activity were available for 44 of 98 (45%) patients. Either documented information on compliance or a reliable assessment of DOAC activity was available for 70 of 98 (71%) patients. Altogether, 1596 of 1942 (82.2%) patients were included in the primary multiple regression analysis (Figure I in the online-only Data Supplement). The main data item missing was a record of symptom to groin time (258/1942); other missing items concerned <2% of patients.

Baseline characteristics and univariable comparisons of patients according to OAC status before AIS are presented in Table IV in the online-only Data Supplement.

Characteristics and univariable comparisons of patients experiencing sICH and those not experiencing sICH after MT are presented in Table V in the online-only Data Supplement. Patients who had an sICH were more often on OAC, underwent magnetic resonance imaging as the initial imaging modality less often, and more often had a more proximal large vessel occlusion. Furthermore, there was a trend toward higher baseline National Institutes of Health Stroke Scale and tandem occlusions in patients with an sICH.

Univariable Analysis

Univariable outcomes are presented in the Table. Univariable logistic regression analysis showed that VKA significantly increased the odds of sICH (aOR, 1.920 [95% CI, 1.164–3.166]) and mortality (aOR, 1.680 [95% CI, 1.212–2.327]) compared with patients not receiving OAC (Table VI in the online-only Data Supplement). No significant associations regarding sICH (aOR, 0.989 [95% CI, 0.391–2.497]) and mortality (aOR, 1.482 [95% CI, 0.871–2.523]) were found for DOAC patients when compared with patients not receiving OAC.

Preinterventional Model

According to the preinterventional multiple logistic regression analysis, after adjusting for prespecified confounders, VKA therapy was associated with increased odds for sICH and mortality (aOR, 2.554 [95% CI, 1.349–4.836] and 1.639 [95% CI, 1.086–2.473], respectively) compared with the control group, whereas DOAC therapy showed no significant associations with either (aOR, 0.982 [95% CI, 0.288–3.346] and 1.351 [95% CI, 0.722–2.527]). Of the prespecified confounders, IVT (aOR, 1.648 [95% CI, 1.015–2.677]) and tandem occlusion (aOR, 1.897 [95% CI, 1.118–3.218]) were associated with sICH (Table VII in the online-only Data Supplement). When considering only patients previously prescribed VKA, the INR on admission was not associated with sICH occurrence (aOR, 0.770 [95% CI, 0.206–2.883] per 1.0 increase). Those results were consistent in propensity score matching and nearest-neighbor matching (online-only Data Supplement).

In the sensitivity analysis considering only patients with confirmed therapeutic VKA therapy, the point estimate for sICH was similar to that for control patients although not statistically significant (aOR, 2.314 [95% CI, 0.831–6.443]). Confirmed therapeutic VKA therapy was associated with higher mortality (aOR, 1.969 [95% CI, 1.058–3.665]). Comparison of patients on confirmed therapeutic DOAC with controls showed a trend toward higher mortality (aOR, 2.044 [95% CI, 0.916–4.561]). For patients on therapeutic DOAC, no point estimate could be calculated for sICH owing to the low incidence of the outcome. Characteristics of patients with and without missing values in the primary analysis of the multivariable preinterventional model are presented in Table VIII in the online-only Data Supplement. DOAC patients had fewer missing data items, but no univariable predictor of sICH was significantly different between patients with and those without missing data items.

Postinterventional Model

Also in the postinterventional multiple regression model adjusting for additional interventional confounders, VKA therapy significantly increased the odds of sICH compared with patients not receiving OAC (aOR, 2.553 [95% CI, 1.034–6.301]). VKA therapy approached significance to increase the odds of all-cause mortality at day 90 as compared with patients without OAC (aOR, 1.697 [95% CI, 0.992–2.904]). No statistically significant associations were found between DOAC and sICH (aOR, 0.715 [95% CI, 0.088–5.806]) or DOAC and mortality (aOR, 1.565 [95% CI, 0.710–3.451]) as compared with patients without OAC. Of the confounders, the National Institutes of Health Stroke Scale on admission (aOR, 1.041 [95% CI, 1.001–1.083]) and occurrence of complications (aOR, 3.467 [95% CI, 1.753–6.854]) were associated with sICH (Table IX in the online-only Data Supplement).

Table. Outcome Data Comparing Patients According to Status of Oral Anticoagulation on Univariable χ^2 Analysis

Outcome	DOAC (n=98)	VKA (n=222)	Other (n=1622)	*P* Value	*P* for All DOACs vs All VKAs	Warranted Therapeutic DOAC (n=49)	Warranted Therapeutic VKA (n=69)	*P* for Therapeutic DOAC vs Therapeutic VKA
sICH ECASS II	5 (5.2%)	21 (9.5%)	84 (5.2%)	0.033	0.267	2 (4.2%)	5 (7.4%)	0.698
Mortality at 3 mo	21 (31.8%)	64 (34.6%)	347 (23.9%)	0.004	0.763	15 (42.9%)	21 (35.0%)	0.513
Systemic bleeding	0 (0%)	6 (6.5%)	22 (3.4%)	0.287	0.408	0 (0%)	2 (5.3%)	1.000
mRS 0–2 at 3 mo	29 (43.9%)	61 (33%)	648 (44.7%)	0.010	0.135	16 (45.7%)	21 (35.0%)	0.384

DOAC indicates direct oral anticoagulant; mRS, modified Rankin Scale; sICH ECASS II, symptomatic intracranial hemorrhage according to the European Co-Operative Acute Stroke Study-II definition; and VKA, vitamin K antagonist.

Technical Efficacy

The rate of successful reperfusion was higher in DOAC patients (93.2%; Table X in the online-only Data Supplement) than VKA patients (81.5%), although the rate of excellent reperfusion was similar. The procedure duration was shorter in DOAC patients, and general anesthesia was less often used. Extracranial stenting was more often performed in patients not receiving OAC.

Functional Outcome

Patients on VKA had lower rates of good functional outcome at 3 months than patients who did not receive OAC in the univariable analysis, although the differences were nonsignificant in the multivariable analysis. No significant difference in functional outcome, either in univariable or multivariable analysis, was found between patients on DOAC and those who were not on OAC (Table; Table VI in the online-only Data Supplement).

Meta-Analysis

The database searches and citation tracking yielded 751 hits. After removing duplicates, 381 abstracts and 45 full-text records were screened as potentially relevant. In total, 14 publications met the inclusion criteria of reporting the risk of sICH after EVT for large vessel occlusion in AIS patients with OAC pretreatment and inclusion of a control group receiving no OAC (13 for VKA and 10 for DOAC; Figure II in the online-only Data Supplement). The definitions of sICH and comparator groups across studies were somewhat heterogeneous (Table I in the online-only Data Supplement). We included a total of 855 VKA cases, 318 DOAC cases, and 6289 controls in the meta-analysis. Pooled analysis of these studies showed a significant difference in sICH rate (sOR, 1.62 [95% CI, 1.22–2.17]) and mortality rate (sOR, 1.66 [95% CI, 1.28–2.15]) between patients on VKA undergoing EVT and patients in the comparator groups (Figure; Figures III and IV in the online-only Data Supplement). No such difference was observed for DOAC patients as compared with the control groups for either sICH (sOR, 1.03 [95% CI 0.60–1.80]) or mortality (sOR, 1.35 [95% CI, 0.97–1.87]). There was no signal of either pronounced heterogeneity (I^2 sICH for VKA, 11%; Cochrans Q, 13.5; df, 12; χ^2; P=0.33) or of publication bias (funnel plot, Figures V through IX in the online-only Data Supplement).

Discussion

The main findings of this registry study and meta-analysis of endovascular treatment in patients with preceding OAC treatment were as follows:

(1) Patients on VKA, but not DOAC, had an increased risk of sICH after MT (aOR, 2.55 [95% CI, 1.35–4.84]) compared with patients not on OAC in our registry; (2) the meta-analysis incorporating data from a total of 7462 patients (855 VKAs, 318

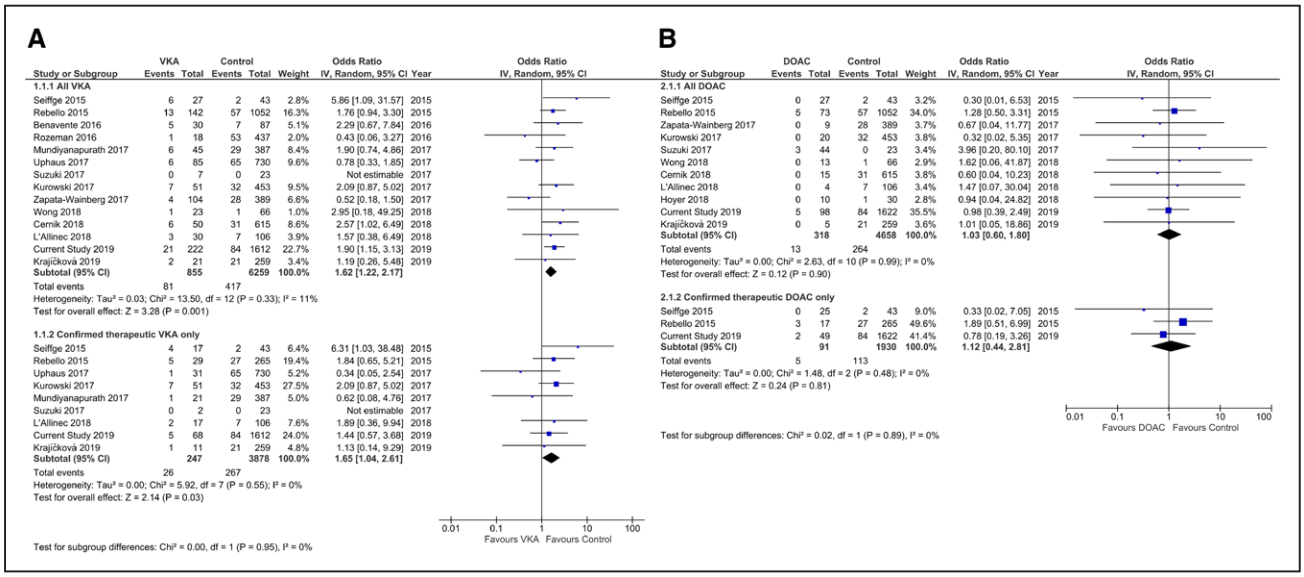

Figure. Meta-analysis of risk of symptomatic intracranial hemorrhage of patients with anticoagulation as compared to controls.[38–43] Forest plot of unadjusted odds ratios for symptomatic intracranial hemorrhage in patients on vitamin K antagonist (VKA; **A**) and direct oral anticoagulant (DOAC; **B**) as compared with patients not on anticoagulation. IV indicates inverse variance.

DOACs, and 6289 controls) corroborated this observation, suggesting that only preceding VKA treatment increases the risk of sICH after endovascular procedures (aOR, 1.62 [95% CI, 1.22–2.17]); (3) in both the registry and meta-analysis, the mortality was higher in patients on OAC than in controls, although statistical significance was only reached in VKA patients; (4) endovascular procedures were feasible and technically successful in a similar proportion of OAC patients to that in controls; and (5) even in tertiary stroke centers, the assessment of compliance and laboratory diagnosis of OAC activity is inadequate.

In our registry, the overall rate of OAC pretreatment in MT patients was 16%, similar to published data,[15] emphasizing the importance of this clinical situation.[44] Generally, therapeutic OAC is a prominent risk factor for hemorrhagic complications in AIS patients.[2] However, several studies with small patient numbers failed to show a significant association of OAC with sICH in the subcohort of patients undergoing EVT for AIS (Table I in the online-only Data Supplement). Most of the studies focusing on EVT, however, were limited by different rates of IVT, inclusion of patients with subtherapeutic INR, missing information on OAC reversal before MT, and lack of adjustment for comorbidities. Despite the pathophysiological plausibility of an increased risk of sICH after EVT in OAC cohorts, those limitations might explain the lack of a significant association in previous observational cohort studies. Both our pooled registry analysis and the meta-analysis provided evidence for an increased risk of sICH in VKA patients but not DOAC patients. Our findings of a roughly halved risk of sICH in patients on DOAC as compared with those on VKA after acute recanalization are comparable to the benefits of a lower sICH risk in patients on DOAC observed in randomized controlled trials and real-world data on stroke prevention.[45–47]

Despite an increased risk of sICH, we do not think that this possible downside outweighs the pronounced benefit of MT in patients on VKA with a large vessel occlusion. Nevertheless, this finding has several clinical implications. First, when clinical deterioration occurs after MT, sICH should be suspected with an even lower threshold in patients on VKA than on DOAC or patients not receiving OAC. Second, imaging features should be investigated to identify VKA patients susceptible to sICH. Third, future studies need to clarify whether there is an INR cutoff at which there is a deleterious effect of performing MT in VKA patients. Fourth, further research needs to address the question whether reversal strategies for selected VKA patients undergoing MT could prevent the occurrence of sICH or if the administration of a procoagulant in the setting of an acute thromboembolic event actually carries deleterious effects outweighing the potential benefits. Lastly, it presents an additional reason to start DOAC treatment rather than VKA in patients newly diagnosed with atrial fibrillation. Since therapeutic OAC is a contraindication for IVT, the finding that, overall, MT was feasible, with a similar risk of periprocedural complications, is reassuring.

Despite neither being designed nor powered to address mortality, the point estimates of our analysis indicating an increase in 3-month mortality in patients who had had VKA treatment as compared with patients not on OAC are in line with previously published results.[6,9,10,14,17,48] The increased occurrence of sICH might partially explain this observation. However, patients on DOAC also showed a trend toward increased mortality reflecting the overall worse prognostic profile of patients on OAC as compared with controls (Table IV in the online-only Data Supplement), inherent to indications that led OAC to be prescribed in the first place.

Corroborating previous studies indicating good technical efficacy and feasibility of EVT in OAC patients, we observed comparable rates of successful reperfusion and no excess of periprocedural complications other than sICH. Interestingly, the rates of successful reperfusion were only higher in the DOAC group as compared with the no OAC and VKA groups, potentially reflecting differences in thrombus formation. In our registry, the time from onset of symptoms to recanalization was similar to that reported by other authors,[14,15] without any delay in OAC patients.

In our study, the therapy was proven to be in the therapeutic range in only 50% of patients on VKA and 72% of those on DOAC. This has potentially important repercussions, as patients on therapeutic OAC may present with less severe strokes, less frequently show a target vessel occlusion,[44,49] and differ in terms of eligibility for IVT. Interestingly, this was also observed in our OAC cohort, as the rate of IVT was significantly lower in patients with confirmed therapeutic anticoagulation (VKA, 5.8% versus 34.8%, $P<0.001$; and DOAC, 4.1 % versus 26.3%, $P=0.016$). Those findings highlight the importance of conducting future studies that reliably differentiate between therapeutic and nontherapeutic OAC in patients prescribed VKA and DOAC as those populations may be heterogeneous.

We did not observe any dose dependency of anticoagulant activity in regard to sICH in VKA patients; in fact, the rate of sICH was lower when the INR was within the therapeutic range. However, there are important reasons for this paradoxical observation. First, CIs of sICH in VKA patients with confirmed therapeutic anticoagulation (1.1%–13.4%) and without (5.6%–13.3%) were wide, and the finding that INR was not significantly associated with sICH might have been underpowered. Second, stroke is less severe in patients on therapeutic VKA,[50] which in turn reduces the risk of sICH. Lastly, and most importantly, IVT was used more often in subtherapeutic patients, potentially increasing the risk of sICH in this subgroup and possibly obscuring the dose dependency. The data on the association of IVT with sICH in the setting of EVT, however, are inconclusive.[51]

Strengths and Limitations

Because of the large sample size and good quality of the data, we were able to include many pre- and postinterventional confounders in our model. Despite this potential overadjustment, the association of VKA pretreatment with sICH remained statistically significant, arguing for a real effect. Nevertheless, this study has the known limitations of a single-arm multicenter retrospective registry. Most importantly, patient selection for MT was not specified, was center specific, and no medical comparison group was available. We had no information on several predictors that were shown to be associated with sICH after IVT including microbleeds,[52] white matter disease,[53] and glycated hemoglobin A1c.[54] The date of intervention was not known, and patients on DOAC might have been treated somewhat more recently on average due to the change from VKA to DOAC. However, there were no major improvements in stroke care to avoid sICH in this period, and expansion of indications for MT (eg, more distal occlusions) might

have increased the risk of sICH lately. Finally, it remains possible that the choice of VKA over DOAC might represent a surrogate marker of other residual confounding variables not recorded in the registry (renal function, malignancy, frailty, mechanical heart valves, etc) representing the true reason for increased risk for sICH in VKA patients. The studies included in the meta-analysis represent populations with heterogeneous use of IVT and different proportions of IVT use in patients on OAC versus patients not on OAC, as well as different combinations of intraarterial thrombolysis and MT and use of first-generation devices.

Conclusions

EVT patients who have received VKA therapy have an increased risk of sICH, while no excess risk was observable for patients on DOAC therapy, potentially reflecting the benefits of a lower sICH risk of DOAC observed in stroke prevention. In VKA patients undergoing EVT, increased awareness is advisable when clinical deterioration occurs after the procedure. Nevertheless, MT should be performed in most VKA patients with a target large vessel occlusion after a careful risk-benefit evaluation considering the potentially salvageable tissue. Efforts should be made to routinely assess compliance and obtain adequate laboratory diagnosis of the OAC status in patients on VKA and DOAC in emergency situations.

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