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# Fatal Intracranial Hemorrhage Occurring after Oral Anticoagulant Treatment Initiation for Secondary Stroke Prevention in Patients with Atrial Fibrillation

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**Abstract**

Background and Purpose: In this pooled analysis of 7 multicenter cohorts we investigated potential differences in the incidence, characteristics and outcomes between intracranial hemorrhages (ICHs) associated with the use of non-vitamin K oral anticoagulants (NOAC-ICH) or vitamin K antagonists (VKA-ICH) in ischemic stroke (IS) patients after oral anticoagulant treatment initiation for atrial fibrillation (AF).

Methods: We included data from 4.912 eligible AF patients who were admitted in a stroke unit with IS or transient ischemic attack (TIA) and who were treated with either VKAs or NOACs within 3 months post-stroke. Fatal ICH was defined as death occurring during the first 30-days after ICH onset. We additionally performed a meta-analysis of available observational studies reporting 30-day mortality rates from NOAC-ICH or VKA-ICH onset.

Results: During 5970 patient-years of follow-up 71 participants had an ICH, of whom 20 were NOAC-ICH and 51 VKA-ICH. Patients in the two groups had comparable baseline characteristics, except for the higher prevalence of kidney disease in VKA-ICH patients. There was a non-significant higher number of fatal ICH in patients with VKA (11 events per 3,385 patient-years) than in those with NOAC (3 events per 2,623 patient-years; HR=0.32,95%CI:0.09-1.14). Three-month functional outcomes were similar ($p>0.2$) in the two groups. The meta-analysis showed a lower 30-day mortality risk for patients with NOAC-ICH compared to VKA-ICH (RR=0.70,95%CI:0.51-0.95).

Conclusions: NOAC-ICH and VKA-ICH occurring during secondary stroke prevention of AF patients have comparable baseline characteristics and outcomes, except for the risk of fatal ICH within 30 days, which might be greater in VKA-ICH.

## Introduction

Intracranial hemorrhage (ICH) is the most feared complication influencing the decision to start treatment with oral anticoagulation for ischemic stroke (IS) prevention in patients with atrial fibrillation (AF). While vitamin K antagonists (VKA) double the risk for ICH, with an estimated annual risk of 0.3% to 0.6% per year,[1] randomized-controlled clinical trials (RCTs) suggest that non-vitamin K antagonist oral anticoagulants (NOAC) have similar efficacy but with half the incidence of ICH compared to VKAs.[2] However, observational studies have provided so far conflicting results regarding the outcomes of patients with NOAC associated ICH (NOAC-ICH) compared to VKA associated ICH (VKA-ICH).[3-12]

We aimed to investigate potential differences in the incidence, characteristics and outcomes between NOAC-ICH and VKA-ICH occurring in IS patients after oral anticoagulant treatment initiation for AF (secondary stroke prevention).

## Methods

We included pooled data from 7 European and Japanese observational cohort studies, recruiting AF patients who were admitted in a stroke unit with IS or transient ischemic attack (TIA) and who were initiated with either VKAs or NOACs within 3 months post-stroke.[13] We included all patients with oral anticoagulation initiation for AF and with available follow-up data for ICH occurrence and death after anticoagulant initiation. Patients followed-up for less than one month after anticoagulant initiation were excluded from the present analysis. We excluded patients with mechanical heart valves, or rheumatic or severe mitral valve stenosis, or patients started oral anticoagulation later than 3 months after the index event, or patients with missing information on oral anticoagulants initiation date.[13]

We identified patients with incident intracranial hemorrhage (ICH), defined as intracerebral hemorrhage, subarachnoid hemorrhage or subdural hematoma, after anticoagulant

initiation; patients with hemorrhagic transformation of the ischemic infarct were excluded. The cohort of ICH patients was further dichotomized in those patients receiving treatment with VKA and those treated with NOACs. Fatal ICH was defined as death occurring during the first 30-days after ICH onset. We also determined the functional outcome in 3-months, quantified by the modified Rankin Scale (mRS) score, and the proportion of patients with 3-month poor outcome (mRS score more than 3). Finally, we estimated the all-cause mortality during follow-up.

We compared all available clinical characteristics [including ICH severity assessed with the National Institutes of Health Stroke Scale (NIHSS)] and the aforementioned outcomes of interest between NOAC-ICH and VKA-ICH patients. All binary variables were presented as percentages, while continuous variables were expressed with their median values, and corresponding interquartile ranges. Statistical comparisons between NOAC-ICH and VKA-ICH patients were performed with the Pearson's $\chi 2$ test and Mann-Whitney test, as appropriate.

The risk of fatal ICH between NOAC- and VKA-treated patients was further assessed in univariable and multivariable Cox regression models, providing the corresponding unadjusted and adjusted HRs. As candidate variables for inclusion in the multivariable cox regression models we used all baseline characteristics, including oral anticoagulant type (NOAC vs. VKA), which were found to yield a p-value lower than 0.1 in the initial univariable cox regression analyses. The resulting multivariable models were finally tested under a two-sided statistical significance hypothesis with a significance level of 0.05. We additionally performed a meta-analysis of available observational studies reporting mortality rates within 30 days from NOAC-ICH or VKA-ICH onset.[3-12]

*Data availability Statement*

Datasets used in the present study will be made available upon formal request to the RAF, RAF-DOAC, CROMIS-2, SAMURAI, NOACISP, Erlangen and Verona registry collaborators.

*Ethics approval*

The NOACISP LONG-TERM registry and the analysis of pooled individual patient data were approved by the ethics committee in Basel, Switzerland (EKNZ 2014-027). Patients provided written consent for participation in NOACISP LONG-TERM. The requirement for additional local ethical approval differed among participating centers and was acquired by the local principal investigator as well as written informed consent by the patient, if necessary. CROMIS-2 was

approved by the National Research Ethics Committee, London Queen Square. Patients with capacity gave informed written consent. When patients could not consent, we obtained written consent from a proxy as defined by relevant local legislation. The SAMURAINVAF registry and the collaboration with the joint initiative were approved by the ethics committee in the National Cerebral and Cardiovascular Center (M23-18-3 and M29-077).

**Results**

From the total 5421 AIS/TIA patients starting treatment with oral anticoagulation within 3 months due to AF, we identified 4912 eligible individuals satisfying our inclusion and exclusion criteria. Patients receiving NOAC treatment had lower prevalence of diabetes mellitus, without any other significant differences in baseline vascular risk factors, when compared with patients receiving VKA treatment. Patients started on NOAC treatment also presented with lower NIHSS scores at their index ischemic event and received more often intravenous thrombolysis compared to patients initiated on VKA treatment (Supplemental Table). During 5970 patient-years of follow-up 71 participants had an incident anticoagulant related ICH [median age: 77, interquartile range (IQR): 70-81; males: 61%; median NIHSS score: 10, IQR: 6-17]. NOAC-ICH (n=20) and VKA-ICH (n=51) patients had comparable baseline characteristics, except for the higher prevalence of kidney disease in VKA-ICH compared to NOAC-ICH patients (0% vs. 26.4%, p=0.027; Table 1).

Although fatal ICH was more common in AIS/TIA patients started on treatment with VKA (11 events per 3,385 patient-years), compared to those started on NOAC treatment (3 events per 2,623 patient-years), this difference did not reach statistical significance (HR=0.32, 95%CI: 0.09-1.14; Figure 1). In multivariable analysis, only ICH neurological severity on admission was independently associated with the risk of fatal ICH (HR=1.12, 95%CI: 1.01-1.25; Table 2). NOAC-ICH patients had comparable rates of fatal ICH (15.0% vs. 21.5%, p=0.531), all-cause mortality (25.0% vs. 31.3%, p=0.597) and poor 3-month outcome (55.5% vs. 55.2%, p=0.983), with similar 3-month mRS scores [4 (2-5) vs. 4 (3-5), p=0.915), to VKA-ICH patients (Table 1).

Pooling data from the current report with similar previous reports[3-12] we documented a significantly lower risk for 30-day mortality in patients with NOAC-ICH, compared to VKA-ICH patients (RR=0.70, 95%CI: 0.51-0.95), with significant heterogeneity across included studies ($I^2$=68%, p for Cochran Q<0.001; Figure 2).

Discussion

Our study showed that NOAC-ICH and VKA-ICH occurring during secondary stroke prevention of AF patients have comparable baseline characteristics and outcomes, except for the risk of fatal ICH that appears to be greater in VKA-ICH subgroup.

A partial explanation on the higher fatal ICH risk in VKA-ICH patients could be the significantly higher incidence of ICH in patients on VKA treatment compared to patients on NOAC treatment (52 events/3,302 patient-years vs. 22 events/2,549 patient-years, HR=0.42, 95%CI: 0.24–0.71; Supplemental Figure).[13] This notion is in accordance with evidence from randomized-controlled clinical trials suggesting that NOACs halve the risk of fatal ICH compared with VKAs due to the lower incidence of NOAC-ICH compared to VKA-ICH and not due to an inherent risk difference in the fatality between NOAC-ICH and VKA-ICH.[14] Our results did not confirm those from some previous work[15] suggesting poorer functional outcome in VKA-ICH compared to NOAC-ICH patients on admission. However, it should be noted that compared to previously published studies in the present cohort all patients had a history of previous IS or TIA. Thus, the functional outcome resulted from the index ischemic event also contributed to the estimation of the neurological severity on admission for the ICH event.

Despite the strengths of the present study, being the first large, multicenter cohort reporting fatal ICH rates in patients with history of IS/TIA receiving treatment with NOACs or VKAs, some limitations should also be acknowledged. First, as noted above we were not able to separate the neurological severity of ICH event with that accumulated from the previous ischemic event. Second, no neuroimaging data were available and thus we could not compare the ICH volumes or localizations between NOAC-ICH and VKA-ICH patients. Both ICH volume and ICH location are known to be important risk factors for mortality after an ICH. Thus the lack of adjustment for these factors in our analyses poses a significant risk for residual confounding in the reported associations. Third, as no data on blood pressure control, small vessel disease burden, adherence to anticoagulant use and administration of reversal agents is available the potential confounding role of antidote administration or blood pressure reduction between NOAC-ICH and VKA-ICH patients cannot be assessed. Fourth, we need to highlight the potential selection bias with the non-randomised choices for which patients receive NOACs and VKAs (Table 1). Choice of treatment was up to the decision of the treating physician, while reasons for the choice of the type of anticoagulation and the use of a specific agent were not recorded.[13] The percentage of patients receiving concurrent antiplatelet and anticoagulation treatment in included cohorts is higher than those reported in randomized clinical trials.[2] However, it should be noted that we present real-

world evidence and international clinical practices for ischemic stroke prevention for patients with significant vascular risk factors (median $CHA_2DS_2VASC$ score of 5, Supplemental Table). Finally, we should particularly highlight the small number of ICH cases presumably resulting in limited statistical power to detect any significant difference in the outcomes after ICH between NOAC-ICH and VKA-ICH patients, and the potential overlap of individual patient data including in more than one cohorts in the meta-analysis.

As evident from the pooled analysis (Figure 2) our cohort was potentially underpowered to detect significant differences in the risk of fatal ICH or other outcomes of interest. An adequately powered multicenter cohort study with comprehensive neuroimaging evaluation is therefore required to provide definitive answers on the potential association of VKA (compared to NOAC) use for secondary stroke prevention with higher risk of fatal anticoagulant-related ICH. Secondary analysis from ongoing RCTs investigating early versus late initiation of direct oral anticoagulant treatment in patients with recent atrial fibrillation-related ischaemic stroke may also provide information further information, as they are expected to enroll altogether more than 10,000 patients.[16]

**Conflict of Interest**

None

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**Table 1.** Baseline characteristics and outcomes of patients with intracranial hemorrhage associated to the use of non-vitamin K oral anticoagulants or the use of vitamin K antagonists.

| | **NOAC (n=20)** | **VKA (n=51)** | **p-value** |
|---|---|---|---|
| Baseline characteristics | | | |
| Age (years, median, IQR) | 78 (76-83) | 76 (70-81) | 0.268 |
| Males (%) | 60.0% | 62.7% | 0.830 |
| Ischemic stroke as baseline event (%) | 94.4% | 100% | 0.132 |
| NIHSS index event (median, IQR) | 7 (2-13) | 6 (3-11) | 0.846 |
| Endovascular treatment (%) | 0% | 0% | - |
| NOAC type (%) | Apixaban: 15.0%<br>Dabigatran: 20.0%<br>Rivaroxaban: 55.0%<br>Unspecified: 10.0% | - | - |
| Ischemic event to anticoagulation initiation (days, median, IQR) | 8 (4-14) | 7 (1-17) | 0.808 |
| Antiplatelets (%) | 25.0% | 38.8% | 0.317 |
| Statins (%) | 28.0% | 30.4% | 0.925 |
| Diabetes (%) | 20.0% | 41.1% | 0.093 |
| Hypertension (%) | 75.0% | 84.3% | 0.361 |
| Hyperlipidemia (%) | 41.7% | 40.8% | 0.957 |
| Kidney failure (%) | 0% | 26.4% | 0.027 |
| Current smoking (%) | 10.5% | 17.6% | 0.466 |
| $CHADS_2VASC$ score (median, IQR) | 5 (4-5) | 5 (4-6) | 0.305 |
| HAS-BLED (median, IQR) | 3 (2-4) | 3 (2-4) | 0.355 |
| NIHSS score of the ICH event (median, IQR) | 8 (5-17) | 11 (7-18) | 0.601 |
| Event type | | | 0.603 |
| | 95.2% | 92.0% | |

| | | | |
|---|---|---|---|
| - Intracerebral hemorrhage<br>- Subarachnoid hemorrhage<br>- Subdural hematoma | 0%<br>4.8% | 6.0%<br>2.0% | |
| Outcomes | | | |
| Fatal ICH* | 15.0% | 21.5% | 0.531 |
| All-cause Mortality | 25.0% | 31.3% | 0.597 |
| 3-month mRS (median, IQR) | 4 (2-5) | 4 (3-5) | 0.915 |
| Poor outcome (%)** | 55.5% | 55.2% | 0.983 |

*defined as mortality within 30 days from intracranial haemorrhage onset

**defined as mRS> 3 at 3-months

NOAC: non-vitamin K oral anticoagulants, VKA: vitamin K oral anticoagulants, NIHSS: National Institutes of Health Stroke Scale, IQR: interquartile range, ICH: intracranial hemorrhage, mRS: modified Rankin Scale

**Table 2.** Univariable and multivariable cox regression analyses on the risk of fatal intracranial hemorrhage in patients with history of ischemic stroke or transient ischemic attack treated with non-vitamin K oral anticoagulants or vitamin K antagonists.

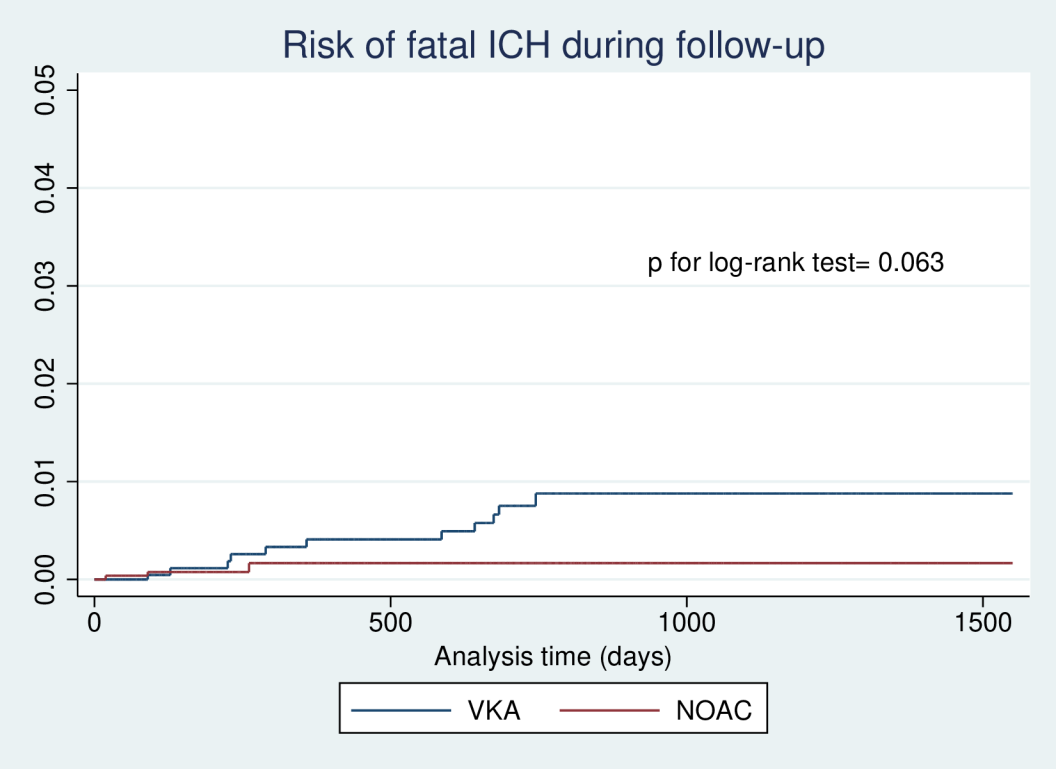
| | **Univariable analysis** | | **Multivariable analysis** | |
|---|---|---|---|---|
| | **HR (95%CI)** | **p-value** | **HR (95%CI)** | **p-value** |
| Age | 1.00 (0.94, 1.07) | 0.934 | - | - |
| Males | 1.00 (0.34, 2.88) | >0.999 | - | - |
| Ischemic Stroke | - | - | - | - |
| NIHSS index event | 0.99 (0.91, 1.08) | 0.866 | - | - |
| Intravenous thrombolysis | 1.22 (0.34, 4.39) | 0.757 | - | - |
| EVT | - | - | - | - |
| NOAC | 0.32 (0.09, 1.14) | 0.078 | 0.45 (0.06, 3.54) | 0.448 |
| Event to anticoagulation initiation | 0.99 (0.93, 1.05) | 0.732 | - | - |
| Antiplatelets | 1.11 (0.35, 3.50) | 0.859 | - | - |
| Statins | 2.16 (0.36, 12.96) | 0.398 | - | - |
| Diabetes | 3.14 (1.10, 8.97) | 0.032 | 0.42 (0.03, 6.40) | 0.533 |
| Hypertension | 1.48 (0.41, 5.31) | 0.548 | - | - |
| Hyperlipidemia | 5.52 (1.54, 19.80) | 0.009 | 0.96 (0.15, 6.36) | 0.973 |
| Kidney failure | - | - | - | - |
| Current smoking | 0.47 (0.06, 3.56) | 0.468 | - | - |
| $CHADS_2VASC$ | 1.35 (0.91, 1.98) | 0.132 | - | - |
| HAS-BLED | 1.34 (0.79, 2.29) | 0.271 | - | - |
| NIHSS ICH | 1.08 (1.01, 1.17) | 0.031 | 1.12 (1.01, 1.25) | 0.043 |

HR: hazard ratio, 95%CI: 95% confidence intervals, NIHSS: National Institutes of Health Stroke Scale, EVT: endovascular treatment, NOAC: non-vitamin K oral anticoagulant, ICH: intracranial hemorrhage

**Figure legends**

**Figure 1.** Kaplan-Meier plots on the risk of fatal intracranial haemorrhage in patients with history of ischemic stroke or transient ischemic attack receiving treatment with non-vitamin K oral anticoagulants or vitamin K oral anticoagulants.

**Figure 2.** Forest plot of available cohort studies reporting on the risk of fatal intracranial hemorrhage within 30 days from onset in patients using non-vitamin K oral anticoagulants or vitamin K antagonists.

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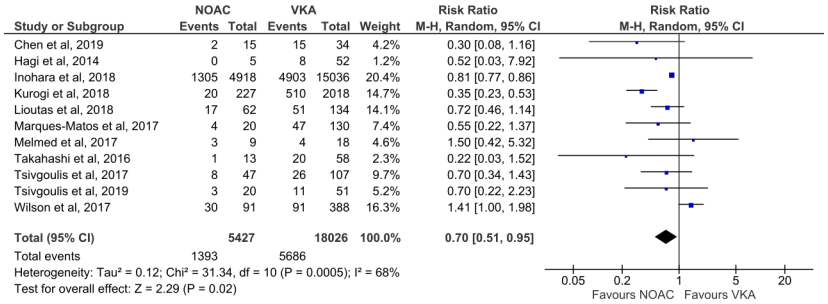


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