Recanalization therapies in acute ischemic stroke patients: impact of prior treatment with novel oral anticoagulants on bleeding complications and outcome

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Abstract

We explored the safety of intravenous thrombolysis (IVT) or intra-arterial treatment (IAT) in patients with ischemic stroke on non-vitamin K antagonist oral anticoagulants (NOACs, last intake

Reference


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Recanalization Therapies in Acute Ischemic Stroke Patients
Impact of Prior Treatment With Novel Oral Anticoagulants
on Bleeding Complications and Outcome
A Pilot Study

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Background—We explored the safety of intravenous thrombolysis (IVT) or intra-arterial treatment (IAT) in patients with ischemic stroke on non-vitamin K antagonist oral anticoagulants (NOACs, last intake <48 hours) in comparison with patients (1) taking vitamin K antagonists (VKAs) or (2) without previous anticoagulation (no-OAC).

Methods and Results—This is a multicenter cohort pilot study. Primary outcome measures were (1) occurrence of intracranial hemorrhage (ICH) in 3 categories: any ICH (ICHany), symptomatic ICH according to the criteria of the European Cooperative Acute Stroke Study II (ECASS-II) (sICH ECASS-II) and the National Institute of Neurological Disorders and Stroke (NINDS) thrombolysis trial (sICH NINDS); and (2) death (at 3 months). Cohorts were compared by using propensity score matching. Our NOAC cohort comprised 78 patients treated with IVT/IAT and the comparison groups of 441 VKA patients and 8938 no-OAC patients. The median time from last NOAC intake to IVT/IAT was 13 hours (interquartile range, 8–22 hours). In VKA patients, median pre-IVT/IAT international normalized ratio was 1.3 (interquartile range, 1.1–1.6). ICHany was observed in 18.4% NOAC patients versus 26.8% in VKA patients and 17.4%...
A trial fibrillation is a major risk factor for ischemic stroke.\(^1\) Non-vitamin K antagonist oral anticoagulants (NOACs) are at least as effective as vitamin K antagonists (VKAs) in preventing ischemic stroke in patients with atrial fibrillation (AF), with a better safety profile, especially for intracranial bleeding.\(^2\)\(^-\)\(^4\) NOACs directly target selected players in the coagulation cascade as the direct thrombin inhibitor dabigatran or the factor Xa inhibitors apixaban, rivaroxaban, and edoxaban.\(^5\)\(^,\)\(^6\) Therefore, onset of the anticoagulatory effect of NOACs is quick (peak levels between 2 and 5 hours after intake). Anticoagulative effects of NOACs last only for several hours to a few days, whereas treatment with VKA results in a slow-onset and sustained, long-lasting inhibition of the coagulation cascade.\(^6\)

Conclusions—IVT/IAT in selected patients with ischemic stroke under NOAC treatment has a safety profile similar to both IVT/IAT in patients on subtherapeutic VKA treatment or in those without previous anticoagulation. However, further prospective studies are needed, including the impact of specific coagulation tests. (Circulation. 2015;132:1261-1269. DOI: 10.1161/CIRCULATIONAHA.115.015484.)

Key Words: anticoagulants ⋅ endovascular procedures ⋅ intra-arterial treatment ⋅ intracranial hemorrhages ⋅ ischemic stroke ⋅ non-vitamin K antagonist oral anticoagulants ⋅ thrombolytic therapy ⋅ vitamin K antagonists

Clinical Perspective on p 1269

One percent to 2% of all individuals have AF, a proportion that will increase as populations age and diagnostic procedures improve. Despite the best medical treatment with VKA or NOAC, 1.11% to 3.24% of patients with AF will have an ischemic stroke annually.\(^2\) Furthermore, patients taking VKAs or NOACs for reasons other than AF can develop a stroke. Many of these patients will be evaluated at emergency departments for eligibility for acute recanalization therapies. For patients with ischemic stroke despite VKA, there are both guidelines\(^7\) and registry-based observational data\(^1\) indicating that the use of intravenous thrombolysis (IVT) or intra-arterial treatment (IAT) can be safe under certain conditions.

However, it remains uncertain how patients with ischemic stroke while taking NOACs should be treated. Current guidelines consider IVT contraindicated and mention the cautious use of IAT.\(^7\) Withholding acute recanalization therapies from all patients with acute stroke under NOAC treatment would deny an effective treatment to a substantial number of patients with stroke.

Theoretical approaches to guide the use of IVT or IAT in patients with stroke taking NOACs have been published.\(^9\)\(^-\)\(^{13}\) Furthermore, a few case reports on the use of IVT in patients taking dabigatran,\(^1\)\(^-\)\(^{12}\) rivaroxaban,\(^1\)\(^-\)\(^{12}\) or apixaban,\(^1\)\(^-\)\(^{12}\) or IAT while taking dabigatran\(^2\) reported favorable clinical outcomes. Conversely, 1 patient with ischemic stroke under dabigatran treatment had a fatal intracranial hemorrhage (ICH) associated with IVT.\(^2\)\(^5\) Thus, currently, there is a lack of systematic outcome and safety data in patients with ischemic stroke under NOAC treatment at the time of IVT or IAT. Standardized data in large cohorts including any comparison group are not available. We therefore orchestrated a multicenter pilot project to investigate the safety of IVT and IAT for acute ischemic stroke in patients taking NOACs. Findings in NOAC patients were compared with (1) patients taking VKA and (2) patients without anticoagulation (no-OAC) before IVT/IAT in an observational cohort study.

Material and Methods

Study Design and Study Population
As a joint initiative of 25 stroke centers (see online-only Data Supplement for study group), we performed an observational collaborative cohort study to investigate: (1) the incidence of ICHs; and (2) functional outcome of patients with ischemic stroke occurring while taking NOACs who were treated with IVT or IAT or both (ie, bridging). IAT included intra-arterial thrombolysis, mechanical revascularization, or both. We introduced 2 comparison groups: first, patients with stroke who underwent IVT and IAT while taking VKA, and, second, patients without anticoagulation at the time of IVT/IAT.

All participating centers applied IVT/IAT according to well-established criteria and guidelines,\(^2\)\(^-\)\(^{20}\) with the exception that, in selected patients, NOAC treatment was not considered an absolute exclusion criterion.

Each center reported on all NOAC patients treated with IVT/IAT during the period for which they had prospectively recorded data on consecutive patients treated with IVT/IAT in local registries or lists since approval of the first NOAC for stroke prevention in AF in their country up to December 31, 2014. Selected centers also provided information on all patients with stroke treated with IVT/IAT (1) while taking VKAs and (2) those without previous anticoagulation (no-OAC) based on local registries. For each contributing center, the number of patients, recruitment periods, and type of data source are summarized in Table I in the online-only Data Supplement.

Data Collection
Data for all patients were collected using a standardized form with predefined variables, as done in previous research.\(^2\)\(^-\)\(^{20}\) Local investigators completed the forms systematically using data from (1) prospectively ascertained in-hospital thrombolysis or stroke registries or (2) from patients’ records and charts in case patients were identified by local patient lists about consecutive IVT/IAT. Completed forms from all centers were sent to the coordinating center in Basel, where analyses of pooled data were performed.

Baseline Data
The following variables were used: age, sex, stroke severity as assessed by the National Institutes of Health Stroke Scale (NIHSS) score before IVT/IAT and at 24 hours, occlusion of main intracranial arteries (assessed by computed tomography angiography or magnetic resonance angiography), blood pressure, time-to-treatment, etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, and the following risk factors applying...
predefined criteria: hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, history of previous ischemic stroke. Previous use of antiplatelets, antihypertensive drugs, and statins was assessed.30 Laboratory measures before IVT/IAT included blood glucose levels, creatinine,27 platelet count, international normalized ratio (INR), activated partial thromboplastin time (aPTT), and calibrated anti–factor Xa assays for rivaroxaban, if available. Current use of VKAs or NOACs was recorded. In patients taking NOACs, agent and daily dosage, reason for use, last intake (in hours before IVT/IAT), and categorized reason for using IVT/IAT treatment were recorded. Functional 3-month outcome was assessed by outpatient visits or telephone interviews by using the modified Rankin Scale (mRS).

Outcome Measures
Primary outcome measures were the occurrence of ICH in 3 categories, or death within 3 months (ie, mRS of 6, denoted as mRS6). ICH included: (1) any ICH on follow-up imaging including hemorrhagic transformation (ICH+t); (2) symptomatic ICH (sICH) according to the criteria of the European Cooperative Acute Stroke Study II (ECASS-II) trial11 (sICH ECASS-II); and (3) sICH based on the criteria of the National Institute of Neurological Disorders and Stroke (NINDS) thrombolysis trial12 (sICH NINDS).

Secondary outcome measures were: (1) NIHSS at 24 hours; (2) major neurological improvement, defined as an improvement in NIHSS score of 8 points at 24 hours in comparison with the initial NIHSS (or an NIHSS score of 0 at 24 hours) as defined in previous research30; and (3) favorable 3-month outcome (ie, mRS of 0, 1, or 2, denoted as mRS0–2).

Statistical Analyses
We used a bootstrapping procedure that combined propensity score matching with multiple imputation.38 Because of the heterogeneous sample sizes between groups, we used triple group (TriMatch) propensity score matching (PSM) to balance characteristics of patients according to baseline covariates. Propensity scores were estimated from a logistic model and matched against a caliper of 0.25.39 Variables likely to affect outcome or complications were chosen based on previous research.30–38 PSM predictors were age, sex, time-to-treatment, admission NIHSS, systolic and diastolic blood pressure, blood glucose level, creatinine and prior medication with statins, antihypertensive agents, or antiplatelets, as well, and the presence of diabetes mellitus, hypertension, hypercholesterolemia, coronary artery disease, atrial fibrillation, and history of previous ischemic stroke.

Statistical analysis proceeded in 3 steps. First, missing data among the set of PSM predictors were completed by single imputation. Across all variables, 6.2% of data were missing (interquartile range [IQR], 0.6%–9.4%). Min/max of data missing for PSM were <0.1% [age]/0.3% [NIHSS on admission] and 15.9% [creatinine on admission]. Overall differences in the proportion of patients in the NOAC, VKA, and no-OAC groups were estimated and patients in the NOAC, VKA, and no-OAC groups were compared. In patients taking NOACs, agent and daily dosage, reason for use, last intake (in hours before IVT/IAT), and categorized reason for using IVT/IAT treatment were recorded.

Ethics
The study was approved by the ethics committee in Basel, Switzerland. The requirement for additional local ethical approval differed among participating centers and was acquired as necessary.

Results
Study Population
Our patient cohort included 9457 patients with acute ischemic stroke treated with IVT or IAT. The NOAC cohort comprised 78 patients (apixaban n=2, dabigatran n=29, and rivaroxaban n=47). IVT was used in 51 NOAC patients, including 6 who received IVT followed by IAT. IAT only was used in 27 NOAC patients; 25 of these 27 patients underwent purely mechanical thrombectomy. The comparison groups comprised (1) 441 VKA (phenprocoumon or acenocoumarol in all centers except Helsinki/Finland: warfarin) patients and (2) 8938 patients that were not on anticoagulation when they received IVT or IAT (no-OAC; Table 1 in the online-only Data Supplement).

Baseline Characteristics
There were significant differences in baseline characteristics between all cohorts. Baseline characteristics and the recanalization therapies applied are displayed in Table 1 (before PSM) and Table 2 (after PSM).

Last Intake, Coagulation Parameters, and Indication for NOAC Treatment
For NOAC patients, the median time between last intake and IVT/IAT was 13 hours (IQR, 8–22 hours); it was ≤12 hours in 38 patients, 13 to 24 hours in 30 patients, 25 to 48 hours in 7 patients; and unknown (but within ≤48 hours) in 3 patients. Atrial fibrillation was the indication for NOAC use in 69 of 78 (88%) patients. Other indications included prevention (n=2) and treatment (n=3) of deep vein thrombosis and other/unknown recorded (n=4).

In patients receiving rivaroxaban (n=47), the median INR was 1.3 (IQR, 1.1–1.51) and the mean aPTT was 32 (IQR, 27–35) seconds; in patients receiving dabigatran (n=29), median INR was 1.3 (IQR, 1.1–1.5) and mean aPTT was 32 (IQR, 27–35) seconds. The 2 apixaban patients had INRs of 1.18 and 1.16 and aPTTs of 32 and 33 seconds, respectively.

In the VKA group, the median INR was 1.3 (IQR, 1.1–1.58). In 308 VKA patients (69.8%), the INR was ≤1.7. In 80 patients (18.1%), no INR was recorded. Among the 53 VKA patients (12%) with INR >1.7 (median, 2.0 [IQR, 1.9–2.35]), 37 were treated with IVT, whereas 16 had IAT (median INR, 2.15 [IQR, 2.0–2.87]).
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September 29, 2015

The reported decision to use IVT/IAT in NOAC patients was based on the time since last intake >24 hours (n=10), low levels in drug-specific coagulation assays (n=23), normal values in routine coagulation assays (n=10), or on other/unknown reasons (n=35). The latter included patients in which the use of NOAC was not known before IVT/AT treatment but discovered thereafter.

Outcome Measures
Outcome measure statistics are displayed in Table 3 (before PSM) and Table 4 (after PSM).

Primary Outcome Measures
ICHany was observed in 14 of 76 (18.4%) NOAC patients in comparison with 105 of 394 (26.6%) VKA patients, and 1332 of 7677 (17.4%) patients in the no-OAC group (P=0.30). sICH NINDS occurred in 2 of 76 (2.6%) NOAC patients in comparison with 7 of 415 (1.7%) VKA patients, and 417 of 8281 (5.0%) no-OAC patients (P=0.48). sICH NINDS was reported for 3 of 76 (3.9%) NOAC patients, 40 of 432 (9.3%) VKA patients, and 616 of 8539 (7.2%) no-OAC patients (P=0.56). At 3 months, 17 of 74 (23.0%) NOAC patients had died in comparison with 113 of 420 (26.9%) VKA patients and 1172 of 8414 (13.9%) no-OAC patients (P=0.44).

Secondary Outcome Measures
A favorable 3-month outcome occurred in 30 of 74 (40.5%) NOAC patients in comparison with 166 of 420 (39.5%) VKA patients and 4736 of 8414 (56.3%) no-OAC patients. Here, we find the only significant overall difference of frequencies in our data (P=0.037). The pattern of frequencies suggests a more favorable 3-month outcome for no-OAC patients than for the VKA and the NOAC patients. Pairwise comparisons, however, remain insignificant in all cases (all P>0.05). Major neurological improvement occurred similarly often in all 3 groups.
IVT Only
IVT only was used in 51 NOAC and 390 VKA patients. ICHany occurred in 8 (15.7%) patients on NOAC and 54 (28.7%) patients on VKA. sICH ECASS-II and sICH NINDS occurred in 2 (4.0%) patients on NOAC each, in comparison with 7 (3.6%) and 11 (5.7%) patients on VKA.

IVT/IAT and Calibrated Anti–Factor Xa Assays
In 21 patients taking rivaroxaban, the decision to administer IVT was based on calibrated anti–factor Xa assays with a mean level of 21 ng/mL (IQR, 8–23 ng/mL). In all these patients anti–factor Xa levels were <100 ng/mL. Each of the 3 patients with anti–factor Xa levels of >100 ng/mL (range, 146–246 ng/mL) had IAT only. None of these patients experienced a sICH.

NOAC and VKA_{INR>1.7} or VKA_{INR≤1.7}
Outcome measures for the subgroup analysis comparing patients on NOAC and VKA_{INR>1.7} or VKA_{INR≤1.7} are summarized in Table 5.

Discussion
This observational multicenter pilot study yielded the following key findings: first, in selected patients with ischemic stroke who are on NOAC treatment (last intake ≤48 hours), IVT/IAT was feasible and not associated with an excessive risk of ICH in comparison with patients on VKA or without oral anticoagulation. Second, in comparison with VKA patients, NOAC patients had numerically fewer intracranial hemorrhages, lower death rates, and a better functional outcome. However, none of these differences reached statistical significance.

Overall, our study highlights that, at least in experienced stroke centers, IVT/IAT application in carefully selected patients with ischemic stroke under NOAC treatment did not raise any suggestion of safety concerns.

The percentage of sICH ECASS-II (2.6%) or sICH NINDS (3.9%) in our NOAC cohort was comparable to sICH rates in a recent multicenter observational study (4.7%)41 or in ECASS-3 (5.3%).42 This finding might not be necessarily reassuring, because the upper limit of the 95%CI (ie, 6.13% for
sICH ECASS-II and 8.2% for ICH NINDS, respectively) indicates that the sICH risk might still be higher than reported in literature for patients without anticoagulation. Based on the observation that the ICH risk in all categories was numerically lower in NOAC than in VKA patients, this scenario seems unlikely, taking into account that IVT/IAT in VKA patients has been reported safe under certain conditions.8,9 Reasons for the relative safety of IVT/IAT under NOAC may include the lower baseline risk of ICH of NOACs in patients with stroke.3

The decision to use IVT was based on rivaroxaban concentration levels in the calibrated anti–factor Xa assay in 22 of our patients and 2 recent single cases.19,21 All 24 IVT-treated patients had levels of the calibrated anti–factor Xa assay <100ng/mL. None had sICH but 1 of 24 had an asymptomatic ICH. This threshold, recommended previously based on theoretical and pharmacological considerations and data,11 may indeed serve as a clinically useful tool to select patients. However, because of the small sample size, further research about the clinical meaning of NOAC-concentration thresholds is needed.

Our analysis had the following strengths: (1) We report on a multicenter cohort; (2) data ascertainment was undertaken systematically and included 2 comparison groups; and (3) safety issues, and functional outcome, as well, were addressed.

### Table 3. Primary and Secondary Outcome Measures Before Matching

<table>
<thead>
<tr>
<th></th>
<th>Novel Oral Anticoagulants</th>
<th>Vitamin K Antagonists</th>
<th>no-OAC</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
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<tr>
<td>ICHany</td>
<td>14 of 76 (18.4%)</td>
<td>105 of 394 (26.6%)</td>
<td>1332 of 7677 (17.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sICHECASS-II</td>
<td>2 of 76 (2.6%)</td>
<td>27 of 415 (6.5%)</td>
<td>417 of 8281 (6.0%)</td>
<td>.25*</td>
</tr>
<tr>
<td>sICHNINDS</td>
<td>3 of 76 (3.9%)</td>
<td>40 of 432 (9.3%)</td>
<td>616 of 8539 (7.2%)</td>
<td>.15</td>
</tr>
<tr>
<td>Death at 3 mo (mRS0)</td>
<td>17 of 74 (23.0%)</td>
<td>113 of 420 (26.9%)</td>
<td>1172 of 8414 (13.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS at 24 h, median (IQR)</td>
<td>9 (2–14)</td>
<td>8 (3–16)</td>
<td>5 (2–13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major neurological improvement*</td>
<td>24 of 77 (31.2%)</td>
<td>128 of 405 (31.6%)</td>
<td>1958 of 6834 (28.7%)</td>
<td>.40</td>
</tr>
<tr>
<td>Favorable clinical outcome at 3 mo (mRS0)</td>
<td>30 of 74 (40.5%)</td>
<td>166 of 420 (39.5%)</td>
<td>4736 of 8414 (56.3%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ECASS-II indicates European Cooperative Acute Stroke Study II; ICH, intracranial haemorrhage; ICHany, any intracranial hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; no-OAC, without previous anticoagulation; sICH, symptomatic intracranial hemorrhage sICHECASS-II, any ICH with neurological deterioration, as indicated by an NIHSS score that was higher by ≥4 points than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death; and sICHNINDS, any ICH on follow-up imaging with any decline in neurological status.

* Major neurological improvement – improvement in NIHSS score of 8 points at 24 h compared to initial NIHSS (or NIHSS score of 0 at 24 h).

### Table 4. Primary and Secondary Outcome Measures After Propensity Score Matching

<table>
<thead>
<tr>
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<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ICHany</td>
<td>13 of 62 (20.8%)</td>
<td>85 of 300 (28.4%)</td>
<td>44 of 184 (23.8%)</td>
<td>0.30</td>
</tr>
<tr>
<td>sICHECASS-II</td>
<td>2 of 62 (3.2%)</td>
<td>21 of 338 (6.1%)</td>
<td>14 of 207 (6.6%)</td>
<td>0.48*</td>
</tr>
<tr>
<td>sICHNINDS</td>
<td>3 of 62 (4.8%)</td>
<td>30 of 338 (8.9%)</td>
<td>19 of 203 (9.6%)</td>
<td>0.56*</td>
</tr>
<tr>
<td>Death at 3 mo (mRS0)</td>
<td>16 of 60 (26.1%)</td>
<td>76 of 324 (23.6%)</td>
<td>43 of 204 (20.9%)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS at 24 h, median (IQR)</td>
<td>10 (2–15)</td>
<td>8 (3–16)</td>
<td>8 (3–17)</td>
<td>0.45</td>
</tr>
<tr>
<td>Major neurological improvement†</td>
<td>20 of 62 (31.4%)</td>
<td>98 of 317 (30.8%)</td>
<td>41 of 154 (26.3%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Favorable clinical outcome at 3 mo (mRS0)</td>
<td>23 of 60 (39%)</td>
<td>138 of 324 (42.7%)</td>
<td>88 of 204 (43.2%)</td>
<td>0.03†</td>
</tr>
</tbody>
</table>

ECASS-II indicates European Cooperative Acute Stroke Study II; ICH, intracranial haemorrhage; ICHany, any intracranial hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; no-OAC, without previous anticoagulation; sICH, symptomatic intracranial hemorrhage sICHECASS-II, any ICH with neurological deterioration, as indicated by an NIHSS score that was higher by ≥4 points than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death; and sICHNINDS, any ICH on follow-up imaging with any decline in neurological status.

*χ² approximation unstable (small group sizes).
†Major neurological improvement – improvement in NIHSS score of 8 points at 24 h compared to initial NIHSS (or NIHSS score of 0 at 24 h).
‡All pairwise comparison: P>0.05.
Nevertheless, several limitations should be noted: First, this is a retrospective study. Second, there was heterogeneity between centers with regard to the criteria applied for the decision to use or avoid IVT/IAT in individual patients, and whether IVT or IAT was preferred. Third, NOAC patients differed from the VKA and the no-OAC patients in several baseline characteristics. Despite application of PSM as an effort to minimize confounding effects, unmeasured characteristics might have differed between these patients and confounded our results. Fourth, a comparison group of patients with stroke despite NOAC treatment not treated with IVT/IAT was not available. Thus, the bleeding risk in patients with ischemic stroke taking NOACs treated with IVT/IAT versus those without IVT/IAT could not be studied. Fifth, despite being the largest cohort available so far, the total numbers of patients taking NOACs or VKAs are still relatively small. Thus, subgroup analyses were performed descriptively. Accordingly, we stress the exploratory character of our study and urge a cautious interpretation of our findings.

The safety of IVT in patients on VKA and an INR ≤1.7 has been established based on large cohorts.\(^5\)\(^5\) The knowledge about IVT in NOAC patients is limited and based on case reports.\(^1^4\)\(^-^1^8\),\(^2^0\),\(^2^1\),\(^2^4\) Data from animal models showed no excessive risk of ICH after IVT in rodents with a prior treatment with rivaroxaban,\(^4^5\),\(^4^4\) dabigatran,\(^4^5\),\(^4^6\) and apixaban\(^4^4\) in comparison with VKA. Currently, the use of IVT for acute ischemic stroke in patients with a recent (<48 hours) intake of a NOAC is regarded off-label.\(^7\) A recent survey among US vascular neurologists showed a lack of consensus regarding the management of patients with ischemic stroke on dabigatran.\(^4^7\) The guidelines of the American Heart Association/American Stroke Association state that IVT might be considered “if [if] sensitive laboratory tests such as aPTT, INR, platelet count, and ECT, TT, or appropriate direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for ≥2 days (assuming normal renal metabolizing function).”\(^7\) NOACs have only limited influence on standard coagulation assays.\(^4^8\) Practical approaches for the use of IVT/IAT in patients with stroke taking NOACs have been proposed.\(^1^0\),\(^1^1\) A recently developed and prospectively assessed approach for patients with stroke despite dabigatran by using aPTT and thrombin time reported on 2 patients receiving IVT within 8 months of recruitment. Neither had ICH.\(^4^9\)

Twenty-seven of our NOAC patients were treated with IAT only; 25 of those had pure mechanical thrombectomy. sICH was absent in all patients and also in a case report of mechanical thrombectomy under NOAC.\(^2^4\) Despite the small numbers, the absence of sICH suggests, that in patients with abnormal hemostasis and NOAC treatment, mechanical recanalization strategies might be more appropriate. However, it remains to be shown, whether sICH rates are indeed lower when NOAC patients with acute stroke are treated with mechanical IAT than with IVT. For patients with abnormal hemostasis\(^3^0\),\(^3^5\) and treatment with IAT, sICH rates were 7.1%\(^3^6\) and 11.4%,\(^5^1\) which were numerically higher than those observed in our NOAC cohort treated with IVT.

In conclusion, our data suggest that IVT/IAT treatment in patients with an ischemic stroke despite NOAC is feasible and probably not associated with an excessive risk for ICH. However, this assumption requires that patients (1) are treated in experienced stroke centers and (2) are carefully selected based on time from last intake of the oral anticoagulant and the findings of specific coagulation tests. Nevertheless, our observations must be considered with caution before generalizing them to standard practice. More research is needed, which should include a systematic assessment of the clinical meaning of coagulation tests and drug doses with regard to safety and effectiveness measures. We recently set up a prospective multicenter registry to systematically investigate the management of patients experiencing an acute ischemic stroke or intracranial hemorrhage while taking NOACs (NOACISPACUTE, clinicaltrials.gov: NCT02353585).

### Sources of Funding

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Disclosures

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References

Seifge et al. Recanalization in Stroke Patients on NOAC


Clinical Perspectives
Non-vitamin K antagonist oral anticoagulants (NOACs) changed clinical practice and are now frequently used for stroke prevention in patients with atrial fibrillation. Despite their efficacy, patients with atrial fibrillation taking NOACs might experience an ischemic stroke. Clinical physicians are faced with the dilemma to evaluate patients on NOACs who present with ischemic stroke in stroke centers and to balance the risk of bleeding complications against benefits of recanalization therapies like intravenous thrombolysis (IVT) and intra-arterial treatment (IAT, including mechanical thrombectomy). This multicenter observational pilot study is the first to report on a cohort of patients with a previous recent (within the last 48 hours) intake of a NOAC treated with IVT/IAT for ischemic stroke and compares bleeding complications and outcome with a large data set of patients who were either on Vitamin K antagonists or without anticoagulation before IVT/IAT. In this study, in selected patients with ischemic stroke under NOAC treatment, IVT/IAT had a safety profile similar to both IVT/IAT in patients on subtherapeutic Vitamin K antagonist treatment or in those without previous anticoagulation. The present study suggests that IVT/IAT in patients with a previous intake of a NOAC might be safe and that specific clotting tests (eg, calibrated anti-factor Xa assays or hemoclot test) might be helpful to guide or support treatment decisions. Nevertheless, treatment with IVT/IAT in patients with a previous intake of a NOAC should be based on individual treatment decisions balancing the risks and benefits. It should be discussed with patients and next-of-kin. However, more data are needed and results from ongoing research studies are warranted (for example, NOACISP-ACUTE, clinicaltrials.gov: NCT02353585).
Recanalization Therapies in Acute Ischemic Stroke Patients: Impact of Prior Treatment With Novel Oral Anticoagulants on Bleeding Complications and Outcome


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SUPPLEMENTAL MATERIAL

Novel oral anticoagulants in stroke patients (NOACISP) Study Group*

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*countries in alphabetic order
Supplemental Table 1. Participating centers, number of contributed patients receiving acute recanalization therapies and data source.

<table>
<thead>
<tr>
<th>Center</th>
<th>Recanalization therapies in patents on NOAC</th>
<th>Recanalization therapies in patients on VKA</th>
<th>Recanalization therapies in patients without anticoagulation</th>
<th>Data source (registry or patient list*)</th>
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*Definition:*

"Registry": In-hospital thrombolysis registry or stroke-registry of all consecutive patients receiving IVT/IAT with prospective ascertainment of all relevant data (at least vast majority).

"List": Lists of all consecutive stroke patients receiving IVT/IAT. Several individual patient data were derived from charts and/or records

# recruitment period 04/2012-12/2013