# Early Initiation of Anticoagulation with Direct Oral Anticoagulants in Patients after Transient Ischemic Attack or Ischemic Stroke

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*Background:* Direct oral anticoagulants (DOACs) are increasingly used for secondary prevention of cardioembolic stroke. While DOACs are associated with a long-term reduced risk of intracranial hemorrhage compared to vitamin K antagonists, pivotal trials avoided the very early period after stroke and few data exist on early initiation of DOAC therapy post stroke. *Methods:* We retrospectively analyzed data from our prospective database of all consecutive transient ischemic attack (TIA) or ischemic stroke patients with atrial fibrillation treated with DOACs during hospital stay. As per our institutional treatment algorithm for patients with cardioembolic ischemia DOACs are started immediately in TIA and minor stroke (group 1), within days 3-5 in patients with infarcts affecting one third or less of the middle cerebral artery, the anterior cerebral artery, or the posterior cerebral artery territories (group 2) as well as in infratentorial stroke (group 3) and after 1-2 weeks in patients with large infarcts (>⅓MCA territory, group 4). We investigated baseline characteristics, time to initiation of DOAC therapy after symptom onset, and hemorrhagic complications. *Results:* In 243 included patients, administration of DOAC was initiated 40.5 hours (interquartile range [IQR] 23.0-65.5) after stroke onset in group 1 (n = 41) and after 76.7 hours (IQR 48.0-134.0), 108.4 hours (IQR 67.3-176.4), and 161.8 hours (IQR 153.9-593.8) in groups 2-4 (n = 170, 28, and 4), respectively. Two cases of asymptomatic intracranial hemorrhage (.8%) and 1 case of symptomatic intracranial hemorrhage (.4%) were observed, both in group 2. *Conclusions:* No severe safety issues were observed in early initiation of DOACs for secondary prevention after acute stroke in our in-patient cohort. **Key Words:** Oral anticoagulation—ischemic stroke—secondary prevention—hemorrhagic transformation—DOAC—atrial fibrillation.


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## Introduction

Patients with atrial fibrillation (AF) and recent transient ischemic attack (TIA) or ischemic stroke are at high risk for recurrent ischemic stroke especially in the early phase after stroke.[1] Oral anticoagulation (OAC) is highly effective to prevent further cardioembolic ischemic events; thus, it is desirable to initiate this treatment as early as possible after an ischemic event.[2] On the other hand, patients with subacute ischemic stroke are at risk for hemorrhagic transformation of the infarct after early anticoagulation. Pivotal trials of DOACs were mainly carried out in primary stroke prevention, and to maximize safety in patients with ischemic stroke, the study drug could not be started within 7, 14, or even 30 days after an ischemic stroke.[3-6] Therefore, safety data regarding early initiation of DOAC therapy in patients with AF after acute ischemic stroke or TIA is sparse. In the present study, we investigated safety of a treatment algorithm for early initiation of DOACs after cerebral ischemia in an in-patient stroke cohort.

## Methods

### *Study Design*

With respect to possible contraindications, DOACs are initiated early as per the following institutional algorithm dividing patients into 4 groups: (1) In patients with TIA and minor stroke (symptoms lasting more than 24 hours without correlates in cerebral imaging) DOACs are started without delay after initial evaluation (group 1); (2) In patients with supratentorial infarcts affecting one third or less of the middle cerebral artery (MCA), the anterior cerebral artery (ACA), or the posterior cerebral artery (PCA) territories (group 2) as well as (3) in patients with infratentorial infarcts (group 3) DOACs are started within 3-5 days; (4) In patients with larger infarcts (>⅓MCA infarction) (group 4) OAC is delayed for 1-2 weeks. We extracted data from our prospective database of consecutive TIA or ischemic stroke patients admitted between September 2011 and December 2013. Patients were included using the following inclusion criteria: (1) AF-associated acute ischemic event and (2) treatment with DOACs during in-patient hospital stay. Patients receiving several different anticoagulation regimens were excluded (n = 29); 2 patients were excluded due to early cessation of DOAC therapy for other reasons than intracranial hemorrhage (ICH). Antiplatelets were administered according to the discretion of the treating physician (e.g., condition after coronary or neurovascular stenting) but are not routinely used in patients with AF as per an institutional protocol. Infarct size was measured based on computed tomography (CT) imaging or magnetic resonance imaging (MRI) as performed in clinical routine. We investigated baseline characteristics, time to initiation of DOAC therapy, coadministration of antiplatelets, and occurrence of asymptomatic intracranial hemorrhage (aICH) or symptomatic intracranial hemorrhage (sICH). Cerebral imaging was performed in case of clinical deterioration (National Institutes of Health Stroke Scale [NIHSS] score ≥4 points) and for other diagnostic reasons according to the discretion of the treating physician. Intracranial hemorrhages were graded according to European Cooperative Acute Stroke Study III (ECASS III) criteria.[7]

### *Statistical Analysis*

Dichotomous variables were presented as number and percentage, and ordinal variables as median and interquartile range (IQR) if the Kolmogorov–Smirnov test showed no normal distribution. Statistical analyses were performed using the IBM SPSS Statistics 21 software package (SPSS Inc., Chicago, IL).

## Results

Overall 401 patients received OAC during in-hospital stay for TIA or acute ischemic stroke. DOACs were administered in 243 of these patients (60.6%) and in 93 of 107 patients (86.9%) with newly detected AF. Demographic and baseline characteristics are given in Table 1. The median NIHSS scores on admission in patient groups are shown in Figure 1. DOAC therapy was initiated 40.5 hours (IQR 23.0-65.5) after stroke onset in group 1 and after 76.7 hours (IQR 48.0-134.0), 108.4 hours (IQR 67.3-176.4), and 161.8 hours (IQR 153.9-593.8) in groups 2-4, respectively. Median time from symptom onset to initiation of DOAC therapy in days is given in Figure 2. Overall, 89.7% of patients received DOACs within 7 days, and 98.4% within the first 14 days. Thirteen CTs and 12 MRIs were performed after the initiation of DOAC therapy; two of the CTs were due to clinical deterioration. Two cases of aICH (.8%, one HI1 and one HI2) and 1 case of sICH (.4%, PH2) were detected, both in group 2 (see Table 2).

## Discussion

In meta-analyses of the randomized trials, DOACs are uniformly associated with an overall reduced risk of ICH; however, early therapy initiation post stroke was precluded by study design in all pivotal trials.[8,9] In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial (apixaban), a minimum of 7 days was needed between an ischemic stroke and study inclusion, whereas in both Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) (dabigatran) 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) (rivaroxaban), 14 days were required.[3-5] In addition, patients with TIA could not be included in the ROCKET-AF trial within 3 days of the event.[4] The Effective Anticoagulation with Factor Xa Next Generation in Atrial