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Review article

# Presentation, therapy and outcome of patients with ischemic stroke under new oral anticoagulants

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ABSTRACT

*Background:* Aim was to describe the clinical spectrum, therapy, and outcome of ischemic strokes under therapy with new oral anticoagulants (NOAC).
*Methods and results:* A literature research was carried out in PubMed. Clinical trials as well as case reports were included. Four large trials comparing NOAC with warfarin reported 469 ischemic strokes but neither co-medication, nor comorbidities, location, clinical spectrum, therapy, nor outcome are reported. Eleven cases with ischemic strokes under dabigatran from the literature are reported. Six patients received thrombolytic therapy, in three of them unaware dabigatran therapy. Two patients received mechanical recanalization. Two patients died, one due to cerebral hemorrhage after thrombolysis, the other after partial recanalization of the basilar artery.
*Conclusions:* Little is known about ischemic strokes under NOAC. To increase the knowledge, the data of 469 ischemic strokes which occurred in NOAC-investigating trials should be analyzed. Furthermore ischemic and bleeding events under NOAC outside clinical trials should be reported. An international registry, independent from the pharmaceutical industry for collecting these informations is desirable.


## 1. Introduction

The embolic risk of atrial fibrillation (AF) can be reduced by vitamin-K-antagonists (VKA) and new oral anticoagulants (NOAC) like dabigatran, rivaroxaban, and apixaban [1–3]. Nevertheless, these drugs cannot completely abolish the risk of stroke or embolism. It has been shown that in VKA-treated AF-patients the strokes are not as severe as in patients without any anticoagulant therapy [4]. The clinical course of patients with stroke occurring under NOAC-therapy is largely unknown and pragmatic approaches have been published for individualized decision making [5,6]. Thus, aim of the present article was to describe and discuss the clinical spectrum, therapy, and outcome of ischemic strokes under NOAC-therapy.

## 2. Methods

A literature research was carried out in PubMed using the terms "stroke", "atrial fibrillation", "embolism" "dabigatran",

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"rivaroxaban", and "apixaban" from 1998 to 2013. Clinical trials as well as case reports in all languages, but no abstracts, were included. Reference lists and older references generated from initial papers were also considered. We included only studies investigating NOAC in patients with atrial fibrillation and excluded studies in patients with venous thromboembolism. Only studies reporting ischemic strokes but not cerebral bleeding were considered.

## 3. Results

### 3.1. Clinical trials

Four clinical trials were identified comparing NOAC with VKA which reported overall 469 ischemic strokes [1–3,7]. The PETRO-trial studied different dosages of dabigatran in 432 patients during 12 weeks. One patient had a stroke under 50 mg bid dabigatran [7]. In the RE-LY trial the rate of ischemic stroke was 1.34%/year with 110 mg bid dabigatran and 0.92%/year with 150 mg bid during a follow-up of 730 days. Overall 270 ischemic strokes occurred under a therapy with dabigatran, 110 mg bid ($n = 159$) or 150 mg bid ($n = 111$) [8]. In the ARISTOTLE-trial, the rate of ischemic stroke was 1.19%/year with either 5 or 2.5 mg bid apixaban during a follow-up of 657 days. Overall ischemic strokes occurred in 149 patients under a therapy with apixaban. It is not indicated how many of the stroke-patients were assigned to apixaban 5 mg or 2.5 mg bid [1]. In the ROCKET-AF trial, the rate of stroke or systemic embolism in the per-protocol population was 1.7%/year with either 15 or 20 mg rivaroxaban during a follow-up of 707 days. Overall ischemic strokes occurred in 149 patients under a therapy with rivaroxaban. It is not indicated how many of the stroke-patients were assigned to rivaroxaban 20 mg or 15 mg/d [3]. From these 4 clinical trials neither the co-medication, comorbidities, location of stroke, clinical manifestations of the stroke, nor therapy or outcome of ischemic strokes are reported. Since there are no studies available comparing one NOAC with the other it is not possible to assess if one of these drugs is safer and more effective than the other. Caution, however, is necessary when interpreting the results of the ARISTOTLE study since 380 patients (2.2%) were lost to follow-up [1]. Despite the large number of randomized patients in ARISTOTLE, the absolute difference between the warfarin- and apixaban-treated patients was only 53 patients regarding stroke/embolism, 63 regarding death and 70 regarding intracranial bleeding. Since the number of patients with missing data was larger than the difference between the treatment groups, doubts arise about the reliability of ARISTOTLE. These problems were less frequent in RE-LY with 0.11% and ROCKET-AF with 0.22% of patients lost to follow-up.

### 3.2. Case reports

Additionally, 11 case reports about ischemic strokes, all occurring under dabigatran were found [9–19]. The clinical characteristics of these 11 patients are listed in Table 1.

Ischemic strokes occurred in five female and six male patients with an age range of 46–89 years. In all of these 11 patients, the ischemic stroke was confirmed by computed tomography; in two patients magnetic resonance imaging was additionally performed. In one of the 11 patients the ischemic stroke occurred after electrical cardioversion [11]. In two other patients the stroke occurred after dabigatran has been discontinued either for three days because of surgery [9], or because of skipping one tablet [18]. Stroke etiology was assessed as cardioembolic in the majority of cases, in one patient, it was due to dissection of the common and internal carotid artery [10].

Indication for anticoagulant therapy was atrial fibrillation in 10 patients, one patient received dabigatran as prophylaxis for venous thromboembolism after orthopedic surgery because of a knee prosthesis [12]. Comorbidities are listed Table 1. One patient suffered simultaneously from gastrointestinal major bleeding due to non-steroidal-anti-inflammatory-drugs-induced colitis and ischemic stroke [19].

The comedication was reported in three patients and comprised acetylsalicylic acid in one [13], digoxin, enalapril, hydrochlorothiazide in the second [16], and levothyroxine, dronedarone, nicorandil, furosemide, pantoprazole, atorvastatin, lornoxicam, zolpidem, macrogol, isosorbide mononitrate, and alprazolam in the third patient [19]. Four of these drugs – levothyroxine, dronedarone, pantoprazole, and atorvastatin are known to affect the p-glycoprotein activity and thus may have changed the pharmakokinetics of dabigatran [20–23].

As expected with dabigatran, routinely performed blood coagulation tests like international normalized ratio (INR) and activated partial thromboplastin time (aPTT) were only slightly abnormal. The lack of typically abnormal coagulation tests associated with neurologic deficits contributed to unawareness about dabigatran-medication when deciding about acute stroke therapy in three cases [12,14,17].

Six patients under dabigatran received thrombolytic therapy for acute ischemic stroke [10–12,14,17,18]. In three of these six patients, the physicians were unaware of the dabigatran therapy [12,14,17]. In awareness of dabigatran, two further patients received mechanical recanalization, one of the basilar artery, the other of the middle cerebral artery [15,16]. The remaining three patients received no specific therapy.

Two patients died. One patient died after thrombolysis due to cerebral hemorrhage who had the shortest interval of only 370 min between the last dabigatran intake and thrombolysis [11]. The other patient died after partial mechanical recanalization of a basilar artery occlusion without recanalisation [16]. The outcome of the nine surviving patients is reported as favorable in eight patients during a follow-up time ranging from 1 to 365 days (Table 1).

For secondary stroke prevention two patients received VKA [10,15], one patient received a combination of VKA and acetylsalicylic acid [13], one patient received dabigatran [14], and in one patient, any antithrombotic therapy was contraindicated due to concomitant gastrointestinal bleeding [19]. In the case reports of three further patients, no information about secondary stroke prevention is given [9,12,17].