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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.

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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 pharmacokinetics 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].

Table 1 – Strokes under dabigatran.

Author	Age/sex	Dose of dab	Diagnostic modalities/ stroke location/stroke severity on admission	Comorbidity	Time between dabigatran intake and stroke	Coagulation tests	Time between dabigatran intake and therapy	Aware of NOAC	Therapy, outcome
[9]	75/f	NI	CT, left middle cerebral artery, NIHSS 8	NI	150 min	NI	NA	Yes	No therapy; NIHSS 2 after 24 h
[10]	46/f ^b	NI	CT, right middle cerebral artery, NIHSS 19	NI	150 min	aPTT 35 s (RI 22–34 s) INR 1.2 (RI 0.8–1.3)	420 min	Yes	t-PA; NIHSS 12 after 24 h, VKA
[11]	62/m	220 mg	CT, left middle cerebral artery, NIHSS 18	Diab	180 min	aPTT 37 s (RI 24–38) INR 1.3 (RI 0.7–1.5)	370 min	Yes	Thrombolysis; lobar hemorrhage, died
[12]	76/f	220 mg	CT, motor aphasia and right homonymous hemianopsia NIHSS 4	Hyp, Diab, knee surgery	780 min	aPTT 30.6 INR 1.0 (RI NI)	900 min	No	t-PA; asymptomatic after 24 h
[13] ^a	62/m	300 mg	CT and MRI, multiple territories, thrombus on the valve prosthesis	Mechanical aortic valve	NI	TT > 80 s (RI 15–20) aPTT 41 s (RI 25–37)	NA	Yes	VKA, ASS; asymptomatic at 12 month follow-up
[14]	73/m	220 mg	CT, right middle cerebral artery, NIHSS 14	Hyp, TIA	420 min	aPTT 38 s (RI 23–32) INR 1.1 (RI 0.7–1.5)	NI	No	72 mg t-PA, after 7 days asymptomatic, dabigatran
[15]	76/f	220 mg	CT, right middle cerebral artery NIHSS 18	NI	30 min	aPTT 33 s (RI 24–38 s) INR 1.3 (RI 0.9–1.2)	285 min	Yes	Mechanical recanalization, VKA; at 3-month modified Rankin scale 1
[16] ^a	78/m	220 mg	CT, basilar artery	Hyp, recent vascular surgery	600 min	aPTT 33 s (RI < 33) INR 2.5 (RI 0.9–1.2) TT 41 s (RI 14–21)	660 min	Yes	Mechanical recanalization, died
[17]	64/m	300 mg	CT, right arm weakness, dysarthria, left frontal infarct, NIHSS 8	CAD	NI	INR 1.1 aPTT 38 s (RI 24–33)	NI	No	t-PA, further therapy and outcome NI
[18]	51/m	300 mg	CT, right middle cerebral artery, NIHSS 6	Stroke	950 min	INR 1.1 (RI 0.9–1.2) aPTT 31 s (RI 23–36) TT 27 s (RI 15–21)	1083 min	Yes	t-PA; at 6-month modified Rankin scale 1; VKA
[19] ^a	89/f	220 mg	CT and MRI, left middle cerebral artery	CAD, Hyp, gastrointestinal bleeding	NI	NI	NA	Yes	No therapy; asymptomatic after 2 weeks

Received dabigatran for prevention of venous thromboembolism after knee operation.

aPTT, activated partial thromboplastin time; CAD, coronary artery disease; Diab, diabetes mellitus; Hyp, hypertension; INR, international normalized ratio; NA, not applicable; NI, not indicated; NIHSS, The National Institutes of Health Stroke Scale; RI, reference interval; t-PA, recombinant tissue plasminogen activator; TT, thrombin time; VKA, vitamin-K-antagonist.

^a Comedication indicated.

^b Participant in the RE-LY trial.

4. Discussion

Although the guidelines of several national and international societies recommend use of NOAC as an alternative to VKA for prevention of stroke or embolism in AF-patients this review shows that our knowledge about ischemic strokes occurring under NOAC is limited to insufficiently reported data from larger studies and a few case reports, all under dabigatran therapy [24,25]. So far, it is unknown if the clinical presentation and outcome differs between ischemic strokes under VKA and NOAC and if there are differences between ischemic strokes occurring under dabigatran, rivaroxaban, and apixaban. It is also unknown if comedication with drugs affecting metabolism and pharmacokinetics of NOAC play a role in the development of ischemic strokes.

The intravenous administration of recombinant tissue plasminogen activator is the only specific treatment that has been approved for acute ischemic stroke with class I recommendation and evidence level A. Its use is contraindicated in patients on VKA with an INR > 1.7 due to the increased bleeding risk [26]. No recommendation exists about thrombolytic therapy in acute stroke patients under NOAC. Clinical decision making in these cases is especially difficult because no laboratory routine tests are available which document the anticoagulant activity. This may lead to the situation that thrombolytic therapy is given, unaware of the NOAC-therapy, as reported in three single cases (Table 1) [12,14,17]. Indications for dabigatran-intake in unconscious or confused patients may be a slightly elevated INR, a prolonged thrombin time, and a slight prolongation of the activated partial thromboplastin time, however, as indicated in Table 1, these findings are not consistent.

The bleeding risk of thrombolysis in NOAC-treated patients is unknown. Although we found only one case of a cerebral hemorrhage after thrombolysis among six dabigatran-treated patients with ischemic strokes who received thrombolytic therapy in the literature, the risk may be underestimated because not all cases are reported and published [11].

5. Conclusion

We conclude that little is known about ischemic strokes under NOAC, and suggest the following activities:

1. *We need the data from the large trials:* The clinical implications and conclusions which can be drawn from the analysis of only 11 case reports occurring under dabigatran are very limited. To increase the knowledge, the ischemic strokes which occurred in NOAC-investigating trials should be analyzed to get more information about the clinical spectrum, concomitant medication, therapy, and outcome of the 469 ischemic events occurring under a therapy of dabigatran, rivaroxaban or apixaban. This task should be performed by independent investigators. Since the data are not published so far it cannot be assessed if the clinical spectrum, therapy and outcome differed between the strokes occurring in the NOAC-investigating trials and in the mentioned 11 case reports.

2. *Practical recommendations:* Unless these data are published we can only infer from case reports that NOAC intake should be suspected in any stroke patient especially if presenting with a history of atrial fibrillation. Laboratory tests indicating potential NOAC intake may be an elevated INR, a prolonged activated partial thromboplastin time or thrombin time. Fatal bleeding occurring in one sixth of the patients who received thrombolysis under dabigatran is an argument against thrombolysis. It remains unknown if patients under NOAC can receive thrombolysis in case of an acute ischemic stroke or not. There are no data about thrombolysis in stroke patients receiving apixaban or rivaroxaban. On the other side, there may be indications for intravenous or endovascular thrombolytic therapy after consideration of all pro- and contra arguments and after informed consent of the patient.
3. *Independent registries might be useful:* It would be desirable to establish an international databank, independent from the pharmaceutical industry, for reporting side effects under NOAC and to provide hospitals and emergency departments with easily available laboratory tests to identify NOAC-use and sufficiency of anticoagulation.

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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