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RESEARCH ARTICLE

Clinical presentation, diagnostic findings and management of cerebral ischemic events in patients on treatment with non-vitamin K antagonist oral anticoagulants – A systematic review

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Abstract

Background

Non-vitamin K antagonist oral anticoagulants (NOAC) are equally or potentially superior in terms of effectiveness in the prevention of ischemic stroke and carry a lower associated risk of intracranial hemorrhage compared to Vitamin K antagonists. Nevertheless, ischemic strokes also occur in patients who are being treated with NOAC. In those particular patients, knowledge about the underlying stroke etiology, clinical presentation, acute management, and complication rates is scarce.

Objective

Systematic literature review to provide a comprehensive clinical overview in terms of presentation, laboratory, imaging parameters and outcomes of patients suffering from acute cerebral ischemic events (i.e. TIA and acute ischemic stroke) while on treatment with a NOAC. Only if available, comparison to VKA is presented which was not the primary focus of this analysis.

Data sources

PubMed/MEDLINE, Scopus and EMBASE from January 1, 2006, to November 20, 2018.

Study eligibility criteria

52 studies providing detailed information on a total of 12247 patients were included. We excluded case reports and case series with less than five patients.

Study appraisal and synthesis method

We systematically assessed study quality using a bias tool and pooled consistent data.

Results

Existing data indicates milder stroke severity and smaller infarct size of acute ischemic stroke on treatment with NOAC compared to stroke occurrence on Vitamin K antagonists (VKA). Established risk factors for ischemic events also play a role in stroke while on NOACs, albeit the underlying etiology remains poorly understood. Intravenous thrombolysis and endovascular therapy seem to be safe and effective, but patient selection for recanalization therapies is challenging.

Limitations

Limited quality of published data, duplicate cases, statistical issues of data pooling, possible incomplete retrieval of identified research and reporting bias might have limited our findings.

Conclusions

Acute ischemic events despite treatment with NOAC therapy are insufficiently investigated.

Systematic review registration number

PROSPERO: CRD42018074853.

Introduction

Rationale

The introduction of rivaroxaban in 2008 and the subsequent addition of three more non-vitamin K antagonist oral anticoagulants (NOAC) had an enormous impact on the primary and secondary prevention of acute ischemic stroke (AIS) in the setting of nonvalvular atrial fibrillation (AF). Most guidelines now recommend NOAC over vitamin K antagonists (VKA) with a class I recommendation level [1–4]. The net clinical benefit arises mainly from a reduced risk of intracerebral hemorrhage (ICH) with NOAC treatment, whereas the prevention of AIS or TIA, which are later in this review referred to as acute ischemic events (AIE), is equal or better compared to VKA treatment. Nevertheless, 1–2% of patients per year suffer from an AIE while on NOAC treatment [5]. The knowledge about stroke subtype, vessel occlusion location, pattern of cerebral infarction, complications and therapy strategies in those patients is scarce. Identifying factors that are associated with AIE that occur while on NOAC treatment may improve individualized treatment decisions. Furthermore, it is important to analyze the reasons for NOAC failure in real-life data, because randomized-controlled trials represent a highly selective patient population. For example an additional indication for anticoagulation, chronic non-steroidal anti-inflammatory drug therapy, severe chronic renal insufficiency, anemia, unreliability or short life expectancy (e.g. malignancy) were exclusion criteria in the pivotal phase III trials, but are likely to be present in NOAC real-life patients [6–9].

Objectives

We aimed to provide a comprehensive clinical overview (clinical presentation, laboratory, imaging parameters and outcomes) of AIE in patients on NOAC treatment by performing a systematic review of the current literature. Only if available, comparison to VKA is presented which was not the primary focus of this analysis.

Methods

Protocol and registration

The study protocol has been published prior to performing the study (PROSPERO: CRD42018074853).

Eligibility criteria

Eligible studies included all age groups and all ethnic groups with given demographic, clinical, laboratory or imaging information on NOAC patients in the setting of AIE. We included all evaluative methodologies. Since the first NOAC, rivaroxaban, entered the market in 2008, we only considered publications beyond January 1st, 2006 for analysis. We excluded studies with no specific characterization of patients who suffered an AIE while taking NOAC. We excluded case reports and case series with less than five patients.

Information sources

Data for this review was identified via a search on MEDLINE, PubMed, Scopus and Embase and references from relevant articles using the search terms "DOAC" OR "NOAC" OR "anticoagulation", and "ischemic stroke" or "TIA". Only articles published in English, French, Spanish and German between January 1st, 2006 and November 20th, 2018 were included.

Search

This is the detailed search strategy used for PubMed: ("noacs"[All Fields] OR "noac"[All Fields] OR "non-vitamin k oral anticoagulants"[All Fields] OR "non-vka oral anticoagulant"[All Fields] OR "doacs"[All Fields] OR "doac"[All Fields] OR "direct oral anticoagulant"[All Fields] OR "direct oral anticoagulants"[All Fields] OR "factor xa inhibitor"[All Fields] OR "direct thrombin inhibitor"[All Fields] OR "dabigatran"[All Fields] OR "pradaxa"[All Fields] OR "rivaroxaban"[All Fields] OR "xarelto"[All Fields] OR "apixaban"[All Fields] OR "eliquis"[All Fields] OR "edoxaban"[All Fields] OR "lixiana"[All Fields] OR "savaysa"[All Fields]) AND ("ischemic stroke"[All Fields] OR "tia"[All Fields] OR "transient ischemic attack"[All Fields]) AND (("2006/01/01"[PDAT]: "2018/11/20"[PDAT]) AND "humans"[MeSH Terms] AND (German[lang] OR English[lang] OR French[lang] OR Spanish[lang])).

Study selection

Citations were uploaded into the covidence online review tool. Their relevance was assessed against the predetermined inclusion and exclusion criteria by TRM and SF, who independently screened all titles and abstracts. Forward and backward reference searching complemented the database searches. Full-text manuscripts were obtained for all studies entering the review. Any uncertainties about including a specific manuscript in the review were resolved by consensus.

Data collection process

Data was extracted onto an Excel spreadsheet by SF and reviewed by TRM.

Data items

Data items included number of patients, age, sex, race, vascular risk factors, type of NOAC and dose, concomitant medication, clinical features of the AIE such as stroke severity, drug levels, renal function, coagulation parameters, imaging findings, stroke etiology, acute management and outcome parameters (functional outcome, mortality).

Risk of bias in individual and across studies

We compared data items, outcomes, design strengths and weaknesses across the studies. For each study, the risk of bias was thoroughly assessed at the study level using a modified National Heart, Lung, and Blood Institute (NHLBI) bias tool, and this information was incorporated when interpretation of data was given in the synthesis.

Summary measures

The principal summary measures were the clinical characteristics of patients using a NOAC in the setting of AIE.

Synthesis of results

If available and consistent throughout the studies, the pooled mean weighted corresponding to the sample size is presented. Data items given by median and interquartile range were converted assuming gaussian distribution as described earlier [10]. Until stated otherwise, the comparison to VKA patients is provided within each individual study.

Additional analyses

No additional analyses were performed.

Study selection

The database searches and citation tracking yielded 1309 hits, of which 1025 records were screened as potentially relevant after removing duplicates (Fig 1). Reasons for excluding relevant publications were mainly due to the lack of specific data items on individual patients. In total, 52 publications including 12247 patients met the inclusion criteria and were included in the analysis (1 substudy of a randomized interventional trial, 1 prospective non-randomized interventional trial, 1 nested case-control study, 28 non-randomized observational studies; 18 case series, 2 diagnostic studies, 1 substudy of an observational register).

Study characteristics

The extracted data of the included publications is shown in S1 Table.

Risk of bias within and across studies

We used 14 quality items to assess bias using a modified NHLBI bias tool [11]. We defined study quality as low when the sum of the positive quality items was less than six and moderate when it was between six and nine. Overall, the risk of bias was considerable across the studies. 20 studies had moderate quality, and 32 studies had low quality. Retrospective design, small sample size, publication bias, selective reporting and the slanted choice of a particular NOAC

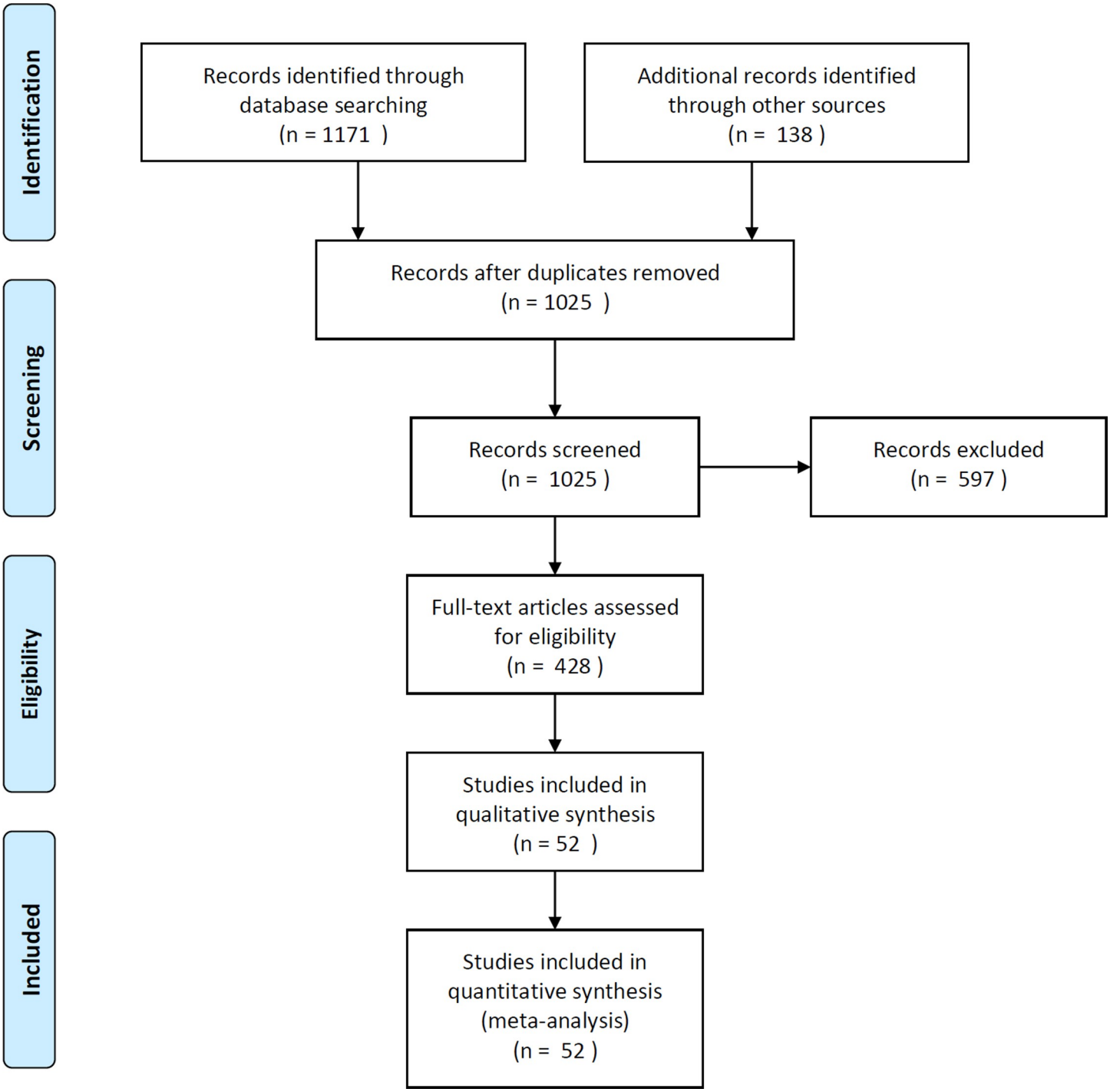

Fig 1. PRISMA flow diagram. Mainly studies were excluded because they only reported incidence rates of ischemic stroke or TIA patients without further clinical information on those patients.

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therapy versus VKA therapy contributed to bias. The detailed bias assessment of each individual study using the modified NHLBI bias tool is available in the S2 Table.

Results

Risk factors and reasons for AIE while using a NOAC

In patients starting NOAC therapy, AIE were reported to occur more frequently during the first three months of treatment [12,13] with a declining AIE rate thereafter. Established risk factors such as previous AIE or an elevated CHA2DS2-VASc score were reported to predict AIE while using a NOAC [14–16]. Renal impairment, defined as estimated glomerular filtration rate of less than 60ml/min, was also reported to be a predictor of AIS while on NOAC therapy [17], which fits the borderline impaired pooled renal function parameters in our cohort. Kamal et al. reported an elevated mean body mass index (BMI) in NOAC failure [18]. This is in contrast to Arihiro et al. who found a reduced BMI patients with AIE in NOAC failure [19]. The mean weighted BMI in the pooled cohort was slightly elevated.

Severity and infarction size of AIE. Overall, AIS severity while on a NOAC measured by the National Institutes of Health Stroke Scale (NIHSS score) was mostly mild, and the outcome was favorable compared to AIS severity while on a VKA [13,15,20–27]. The mean weighted NIHSS score on admission in the pooled NOAC cohort was 4.6. In the biggest data set from the *Get with the Guidelines Register*, stroke severity while on a NOAC was equal to stroke severity while on a well-controlled dose of a VKA (NIHSS score 4), but stroke severity while on a NOAC was less severe when the international normalized ratio (INR) was not within the therapeutic range (NIHSS score 6) [28]. Opposing data was reported by Nakase et al., who found a higher NIHSS score in AIS while on a NOAC compared to VKA [29]. In patients qualifying for intravenous thrombolysis (IVT) or endovascular therapy (EVT), NIHSS score values were overall high, but roughly equal with NOAC and VKA pretreatment respectively [30–33].

The ischemic lesion size on magnetic resonance imaging (MRI) was reported to be significantly smaller while on a NOAC versus a VKA [23–25,29]. Also, in comparison to AIS while on acetylsalicylic acid, the size of the infarction on apixaban was smaller while the overall infarct rate was equal [34]. The distal middle cerebral artery territory was reported to be the most location of embolic strokes [18].

Dosing regimen. After propensity-score matching for baseline demographic parameters and co-morbidities, it was found that there was a significantly lower adherence rate than expected among the twice-daily NOAC users. The suboptimal adherence to any dosing regimen was reported to be associated with a 50% increased hazard ratio for AIS [35].

NOAC treatment was frequently found to be interrupted before an AIE [21,36]. Furthermore, subtherapeutic dosing was reported in a relevant proportion of patients as a possible explanation for NOAC failure [15,16,24,37,38]. For example, Sakamoto et al. found an inappropriately lowered dose in about 25% of patients in their cohort [15]. Nevertheless, AIE do occur despite NOAC drug levels being well within the therapeutic range [39].

Etiology. Overall, there are conflicting results regarding stroke subtypes in patients with AIE while on NOAC therapy. Some authors reported that cardioembolic sources, such as intracardiac thrombus or severe congestive heart failure, might present as a frequent reason for AIE under NOAC therapy [13,19–21]. On the other hand, other authors reported a predominantly non-cardioembolic etiology for AIS while on a NOAC, such as microvascular disease [15,40]. Other etiologies for AIS while on NOAC therapy include paraneoplastic coagulation disorders, arterio-arterial embolism [41] and polypharmacy [16].

Coagulation testing. Routine coagulation tests in patients undergoing NOAC therapy show strong variability and therefore cannot sufficiently predict current anticoagulant effect [42,43]. High plasma levels may remain elevated for more than 12 hours after last intake [43]. Despite this fact, specific coagulation tests are only performed in less than half of acute stroke patients in the emergency setting, even in experienced stroke centers [27,39].

Reperfusion therapies in the acute setting in patients with AIS under NOAC

IVT. In the Get With The Guidelines register, rates of IVT use were much lower in NOAC patients compared to subtherapeutic VKA patients in the (3.3% vs. 11.7%) [28]. Also, Purrucker et al. found NOAC treatment to be a significant barrier to IVT initiation and a cause of an overall lower rate of IVT usage (9/159 patients; 5.7%) in patients on NOAC therapy [44]. Suspected or proven NOAC treatment was reported to be the main reason for not administering IVT in more than half of all patients on their register. Also, an overall time delay to treatment of 35 minutes was reported in NOAC patients compared to VKA patients [30]. In the pooled cohort, the overall rate of IVT in most tertiary stroke centers was low (5.1%) and time from symptom onset to IVT was almost two and a half hours. Seiffge et al. could show, that more than half of patients on rivaroxaban could be candidates for IVT because of low plasma levels on admission [45].

Deciding for or against IVT. In the absence of specific coagulation testing, the time of the last NOAC dose prior to the AIS is of major importance in the decision to administer or withhold IVT, considering also the presence or absence of drug interactions as well as renal and hepatic function. Seiffge et al. reported that about half of their patients with an AIS had their last dose less than 12 hours before hospital admission, whereas the other half had their last dose between 12 and 24 hours before hospital admission [30]. Factor IIa activity assays are the standard of care in dabigatran users with an AIS in deciding for or against IVT. However, if not available, a thrombin time (TT) based protocol (< 38 sec) might be a reasonable alternative [46]. Seiffge et al. showed that a specific factor Xa-activity assay is useful in patients treated with rivaroxaban with an AIE, and that the use of IVT in patients with low levels of factor Xa-activity might be safe. Despite using specific coagulation testing, a a fast door-to-needle time of 37 minutes was feasible [47].

Hemorrhagic complications after IVT. Two studies found no increase in acute-phase hemorrhagic transformation compared to VKA [15,48]. In the largest register dataset available, patients with NOAC pretreatment had the lowest unadjusted rates of life-threatening or serious systemic hemorrhage (0.4%) and of any other IVT complication (6.8%) compared to patients with antiplatelet, VKA or no medical pretreatment. However, data on coagulation parameters, the timing of the last NOAC intake, and whether nonspecific reversal strategies may have been applied were not available [49].

Olivera et al. reported ICH in two of seven patients taking a NOAC and receiving IVT. However, the definition of ICH was not clear [14]. Chen et al. reported severe bleeding events in 2/19 patients receiving IVT in patients taking rivaroxaban with both events occurring in patients with last drug intake <48h before IVT treatment [50]. In contrast, Seiffge et al. found a similar rate of symptomatic ICH using the National Institute of Neurological Disorders and Stroke (NINDS) or European Cooperative Acute Stroke Study II (ECASS-II) definition (sICH) in NOAC patients receiving IVT [30,51,52] and no sICH when the selection of therapy was guided by plasma levels in patients taking rivaroxaban [47]. Suzuki et al. reported no sICH at 24 hours in 71 patients receiving IVT with the study being limited by recall bias and reduced IVT dose [53].

Idarucizumab. In the biggest case series including 55 patients, IVT after dabigatran reversal was feasible with a symptom onset to needle time of 175 minutes [33]. Furthermore, its use was effective with a mean clinical improvement seen in 82% of the patients (6.3 points difference in NIHSS) and a follow-up mRS <2 in 56% of patients. The rate of sICH (3/55, 5.5%) was within the expected range. Other complications included one fatal thrombotic adverse

occurring five days after the Idarucizumab/IVT infusion [54]. However, most authors reported favourable outcome of this approach [55–57].

Endovascular therapy (EVT). A target large vessel occlusion was more often observed when NOAC dose was incorrectly low or compliance inadequate [58]. Seiffge et al. reported EVT without IVT in patients with high rivaroxaban plasma levels to be safe and feasible [30,47]. Several authors reported EVT to be safe and feasible with a similar rate of sICH as compared to patients without anticoagulation [59–63].

Outcome. Similar outcomes between AIE on NOAC or on VKA treatment were found [24]. This was also true in patients receiving IVT [30] and EVT [14,59]. Overall, in-hospital mortality was highest in patients not receiving antithrombotic treatment prior to the AIS (9.3%), followed by subtherapeutic warfarin (8.8%), antiplatelet treatment only (8.1%), therapeutic warfarin (6.4%), and NOAC (6.3%) [28].

Management. There are no randomized trials on the therapeutic management after AIE on NOAC. Following the AIE, switching temporarily to low molecular weight heparin was preferred by some authors [14], whereas most authors preferred switching to another NOAC with a different mechanism of action [40] for long-term prophylaxis. However, sometimes restarting the same NOAC was favored—possibly due to the good outcome of AIE on dabigatran and the possibility of antagonizing its effect by idarucizumab [33,54,64]. Also, a change of VKA was reported [14].

Synthesis of results

The pooled data is shown in Table 1. Additionally, in S3 Table we provide the pooled data considering only studies of at least moderate quality, although there were no relevant differences compared to the data of all included studies.

Additional analysis

No additional analysis was performed.

Discussion

Epidemiology

It was expected that about 1% of AIS patients will be on NOAC treatment in the future [65]. With an estimated AIE rate of 1–2% per year in patients taking a NOAC and the increasing number of indications for NOAC use, this rate is likely to increase significantly [66] reaching 6% in 2017 in our tertiary stroke center.

Risk factors and reasons for AIE under NOAC

Information on stroke subtype distribution according to validated classifications such as the Trial of Org 10172 in Acute Stroke Treatment (TOAST) or ASCOD in AIE under NOAC is currently not available [67,68].

Apart from the classical etiologies, there are several potential reasons for an AIE while taking a NOAC, including non-adherence to medication, under-dosage and potential treatment failure of NOAC with thrombus formation despite treatment.

The finding that classical vascular risk factors are associated with AIE under NOAC suggests that large artery disease or small vessel disease may represent a cause of AIE in a relevant percentage of patients [69]. However, incorporation of biomarkers associated with cardioembolic etiology (Cardiac troponin I, N-terminal pro-B-type natriuretic peptide, and D-dimer) enhanced risk assessment for subsequent ischemic events [70]. Surprisingly, the finding that

Table 1. Pooled characteristics of patients suffering acute cerebral ischemic events while taking non-vitamin K antagonist oral anticoagulants (N = 12247).

Characteristic	item positive	item available	%	Weighted mean
Female sex	5594	10898	51.3	
Age (years)		10989		78.6
BMI (kg/m^2)		750		26.3
Medical history				
Atrial fibrillation	11036	11301	97.7	
Hypertension	8614	10450	82.4	
Dyslipidemia/hyperlipidemia	4984	9721	51.3	
Previous ischemic stroke or TIA	4465	10191	43.8	
Coronary heart disease or myocardial infarction	3438	10040	34.2	
Diabetes mellitus	3456	10436	33.1	
Heart failure	2013	9616	20.9	
Smoker	745	9298	8.0	
Peripheral vascular disease	575	8900	6.5	
Carotid stenosis	415	8859	4.7	
Prosthetic heart valve	142	8768	1.6	
NOAC				
Rivaroxaban (total)	1626	3092	52.6	
Dabigatran (total)	1162	3092	37.6	
Apixaban (total)	299	3092	9.7	
Edoxaban (total)	5	3092	0.2	
Twice daily	635	1150	55.2	
Once daily	500	1150	43.5	
Medication				
Antihypertensive	7170	9190	78.0	
Cholesterol lowering drug	5866	9587	61.2	
Diabetes medication	2054	8859	23.2	
Concomitant antiplatelet	333	1668	20.0	
Laboratory				
Serum creatinine (mg/dl)		833		0.95
Renal clearance (ml/min)		897		63.5
apTT (sec)		650		34.5
INR		9756		1.2
Blood glucose (mg/dl)		742		124.2
D-Dimer (ng/ml)		128		964.1
BNP (pg/ml)		128		198.4
Clinical features				
Stroke severity (NIHSS score)		10291		4.6
Treatment				
Any IVT	598	9196	6.5	
Onset of symptoms to IVT (min)		402		141.9
Time since last drug intake to IVT (h)		276		10.2

BMI: body mass index, apTT: activated Partial Thromboplastin Time, INR: international normalized ratio, BNP: brain natriuretic peptide, NIHSS: National Institute of Health Stroke Severity, IVT: intravenous thrombolysis.

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previous AIS predicts treatment failure is in contrast to a subgroup analysis of the ROCKE-T-AF trial [71]. Future research should address the question whether impaired renal function

is an independent predictor of AIE in patients taking NOAC or only if inadequate dosing is prescribed. Importantly, it was shown, that excellent renal function was a risk factor of AIE, at least in patients receiving Edoxaban [72].

Recurrent AIE is reported to occur more frequently in the first three months after NOAC therapy initiation, which behooves caregivers and patients to be especially attentive to the signs of an AIE. The elevated risk in the first weeks after the event at the same time of NOAC initiation might explain this observation. However, it might also be possible that the increased incidence in the first three months may be because NOACs may induce the mobilization of preexisting thrombi. Comparison of NOAC initiation for primary and secondary prophylaxis could clarify this phenomenon. Insufficient drug levels due to varying drug interactions have been analyzed [73], but their relevance in the real-world setting remains unclear.

Furthermore, early termination in up to one of three NOAC patients within the first year of treatment has been reported [74,75]. In this setting, mild cognitive dysfunction was not a risk factor for non-adherence [76].

Severity and infarction size of AIE

The severity of an AIS while on a NOAC seems to be at least equal compared to VKA pretreatment. This finding is confirmed by another study that showed an equally reduced frequency of severe strokes in patients on therapeutic doses of a VKA as well as patients on NOAC therapy [77]. There is insufficient data on AIS size, although preliminary data, which showed smaller infarct volumes on MRI, was reassuring [25].

Dosing regimen

Once daily dosing seems to be associated with a slightly better adherence [78]; although its effect in clinical practice is unclear because worse pharmacokinetics could easily balance this benefit [79]. Because body weight and renal function might be altered in the acute event setting, NOAC doses should be reviewed after about three weeks [38]. Treatment discontinuation in about a quarter of patients at one year demands care models increasing the delivery of continuous therapy [80].

Laboratory parameters

Abnormal routine coagulation tests may provide a hint that a patient presenting with an AIE might take a NOAC, but they do not reflect the actual coagulation status. Specific tests for the activity of a particular NOAC should be used routinely, because they aid in the decision to administer or withhold IVT. Prospective studies with consistent data are warranted to define reliable recommended cut-off values for each NOAC.

Reperfusion therapies in the acute setting in patients with AIS under NOAC

IVT. There are no randomized trials concerning IVT in the setting of an AIS under a NOAC. Seiffge et al. estimated that IVT could be used in more than half of patients with prior rivaroxaban treatment with about 28% of patients denied by current guidelines [30,45,81]. Recent analyses concluded that IVT is probably effective and safe in select AIS patients undergoing NOAC treatment [81–84]. However, optimal patient selection is dependent on coagulation parameters that have not yet been sufficiently evaluated, and the variable selection criteria used in available studies do not allow for a consensus [39,42,85,86]. Prospective, randomized

studies are crucial for the creation of valid guidelines for this situation comparable to the INR cutoff in VKA patients.

EVT. EVT also seems to be safe and effective in large vessel occlusion (LVO) in patients undergoing NOAC therapy, but further trials are needed to confirm general safety [60,87]. Either on its own or in combination with, recanalization strategies are available for about one out of three patients with an AIS undergoing therapy with a NOAC [47].

NOAC reversal agents. Initial reports on successful and safe IVT after idarucizumab administration are promising, but limited experience does not allow for a final statement on the safety of IVT after antagonization [33,84]. Additionally, it is not clear whether idarucizumab/IVT should be administered in every dabigatran patient with an AIS or only if direct EVT is not possible. No data is presently available for the recently approved reversal agent for factor Xa inhibitors, andexanet alfa.

ICH. The incidence of ICH after an AIS with or without IVT/EVT seems to be low, but systematic prospective trials are lacking. Furthermore, heterogeneous definitions of a symptomatic ICH impair the comparability of study results.

Management. Since guidelines on the management of an AIE under NOAC therapy are lacking, and the underlying etiology is heterogeneous, it seems to be most important to search for potentially treatable sources of stroke, such as symptomatic atherosclerotic stenosis, paraneoplastic syndrome, vasculitis or endocarditis. Moreover, a measurement of NOAC activity on admission may help to identify instances of compliance-related AIE and to guide individualized dosing of NOACs in the future.

When none of the listed etiologies are found, it is controversial, but many clinicians switch to another NOAC substance [88].

Summary of evidence

AIE in patients using a NOAC are becoming a more frequent event. Contributing risk factors as well as the etiology remain poorly understood. Stroke severity seems to be favourable or at least equal to an AIS that occurs while on a VKA. Standardized management protocols for diagnostic work-up and management are necessary to provide optimal and rapid stroke care. IVT and EVT seem to be safe and effective, but patient selection for these therapies is challenging.

Limitations

Our analysis has several limitations that limit the generalization of findings. Those include the overall low quality of published data, statistical pooling procedures, incomplete retrieval of identified research, reporting bias, and the small number of reports of patients suffering from an AIE while using Apixaban and Edoxaban. Furthermore, we only report characteristics of patients suffering AIE while taking NOAC, but we had no information on patients on NOAC not suffering AIE which limits the explanatory power of the findings.

Conclusions

There is an unmet need for prospective trials on the diagnostic workup and treatment of an AIE under NOAC therapy. High volume registers of patients suffering from an AIE while undergoing NOAC therapy are already being created and will hopefully soon contribute to the management of AIE under NOAC therapy. (RASUNOA prime, ClinicalTrials: NCT02533960; NOACISP; ClinicalTrials: NCT02353585, ARAMIS Register, ClinicalTrials: NCT02478177).

Studies included. [12–16,18–24,26–29,31,34,37,40–42,44,46,47,49,54–56,58,59,64,77,78,83,89–101].

Supporting information

S1 Table. Extracted data of included studies. Extracted items are shown.
(XLSX)

S2 Table. Bias assessment tool. For each study, the risk of bias was thoroughly assessed at the study level using a modified National Heart, Lung, and Blood Institute (NHLBI) bias tool recommended for non-randomized observational studies.
(XLSX)

S3 Table. Pooled characteristics of patients suffering acute cerebral ischemic events according to study quality. Data is presented of all included patiens suffering acute cerebral ischemic events while taking non-vitamin K oral anticoagulants (N = 12247) and only considering studies of at least moderate quality (n = 10840).
(DOCX)

S4 Table. Prisma checklist. Checklist of systematic reviews according to the PRISMA guidelines.
(DOC)

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Conceptualization: Thomas Raphael Meinel, Marcel Arnold, Simon Jung.

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Writing – review & editing: Thomas Raphael Meinel, Marcel Arnold, Sarah Kendroud, Urs Fischer, Johannes Kaesmacher, Mirjam Rachel Heldner, Simon Jung.

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