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STROKE (H.C. DIENER, SECTION EDITOR)

# Patients on NOACs in the Emergency Room

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## Abstract

**Purpose of Review** Despite the increasing use of NOACs, there is still uncertainty on how to treat NOAC patients presenting with neurological emergencies. Initial assessment of coagulation status is challenging but essential in these patients to provide best-possible treatment in case of ischemic or hemorrhagic stroke. Meanwhile, anticoagulation reversal strategies have been suggested; yet, the optimal management is still unestablished. The current review aims to provide up-to-date information on (i) how to identify patients with NOAC intake, (ii) which therapies are feasible in the setting of ischemic and hemorrhagic stroke as well as traumatic intracranial hemorrhage, and (iii) how to proceed with patients requiring emergency lumbar puncture.

**Recent Findings** Despite several expert opinions, there is still an ongoing debate which NOAC patients presenting with ischemic stroke may benefit from recanalizing strategies and whether these treatment approaches can be performed safely. Results from two phase IV trials investigating the efficacy of NOAC-specific reversal agents in case of major bleeding seem promising with regard to hemostatic parameters, but these antidotes have not been verified to clinically benefit patients, and approval by authorities in parts is still pending.

**Summary** Specific reversal agents are on the way and will provide new treatment options in patients with NOAC-related ischemic and hemorrhagic stroke. Up to now, the decision which patients should undergo recanalizing treatment for ischemic stroke, or which specific pharmacological reversal treatment in hemorrhagic stroke should be initiated, has to be made cautiously on an individual basis after assessing hemostatic parameters.

**Keywords** NOAC · Oral anticoagulation · Stroke · Emergency · Reversal · Management

## Introduction

Since their approval, the use of non-vitamin K antagonist oral anticoagulants (NOACs) steadily increased in patients with an indication for oral anticoagulation (OAC) [1•]. Over the last years, prescription rates of NOAC raised to 43–71% in patients with newly diagnosed atrial fibrillation (AF) and replaced vitamin K antagonists (VKA) as the first choice of oral anticoagulants [1•, 2, 3]. Advantages of NOAC over VKA, such as phenprocoumon or warfarin, comprise no need for laboratory monitoring, less drug or food interactions, and most importantly, by a half reduced risk for intracranial bleeding compared to VKA in initial pivotal trials [4, 5].

These findings were replicated in real-world data and may result in a mortality benefit of patients receiving NOAC treatment [6, 7]. Further, NOACs either inhibiting thrombin (dabigatran etexilate, Pradaxa©) or activated factor Xa (rivaroxaban, Xarelto©; apixaban, Eliquis©; edoxaban, Lixiana©) have similar, and at some NOAC dosages, even higher efficacy for prevention of thromboembolism in AF patients [8]. Considering an aging population and a higher prevalence of AF in the elderly (about 10–17% in ≥ 80 years old), the prevalence of patients with NOAC intake will further increase in the next years [9].

As a consequence, the number of patients receiving NOAC therapy admitted to emergency rooms (ER) doubled over the last years [10]. The treatment of these patients is challenging, since there is an ongoing debate about coagulation assessment and safety of treatment procedures in these patients. This review aims to provide up-to-date information in order to clarify the following issues in the management of patients with NOAC intake: (I) how to identify patients with relevant anticoagulatory effects; (II) how to manage NOAC-related complications, notably

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ischemic stroke and intracranial bleedings; and (III) if lumbar puncture as a common diagnostic procedure in the ER can be performed safely in these patients.

## Identification of Relevant NOAC Activity

In all NOAC-treated patients with either urgent need of invasive procedures or initial major bleeding, immediate assessment of coagulation status seems essential in order to minimize the risk of further complications. Both coagulation testing and time since the last intake have been proposed for identification of patients with effective NOAC intake [11••]. Several reports suggested that the parameter "time since last intake" to represent a poor estimator for the degree of anticoagulatory effect. For example, in patients with rivaroxaban intake and ischemic stroke, large variances of trough anti-Xa levels at 24 h after the last intake were observed, ranging from below 20 ng/ml up to 340 ng/ml [12]. Interference with co-medications, relatively short elimination half-lives, and inter-individual variance in pharmacokinetics dependent on patient's age, renal, and hepatic impairment as well as body weight, do not allow sufficient exclusion of NOAC effects in the early time window (< 48 h) without consideration of coagulation tests [13].

In the emergency setting, assessment of routine coagulation parameters may be helpful to identify relevant anticoagulatory effects. Changes of thrombin time (TT), prothrombin plastin time, and quick and INR values were reported in patients with NOAC intake but may vary significantly among different NOAC agents and dosages [14–18]. In essence, TT is very sensitive to the thrombin inhibitor dabigatran to such an extent that normal TT values safely exclude relevant anticoagulatory activity in dabigatran patients [19, 20]. Alterations in Quick and INR values are often observed during treatment with factor Xa inhibitors, but are unspecific and, therefore, not suitable to exclude or prove relevant anticoagulant activity [12, 14, 17, 21–23]. Specific coagulation assays should be preferred considering their high sensitivity and specificity for NOAC intake and the collinear correlation with NOAC plasma levels [24]. In specialized laboratories, dilute thrombin time (dTT), Hemoclot thrombin inhibitor assays, and ecarin clotting time (ECT) can be provided without relevant delay (< 30 min) to assess dabigatran effects, whereas agent-calibrated chromogenic anti-Xa assays can guide treatment decisions in patients with factor Xa inhibitors [25•]. But, it has to be considered that diagnostic performance of these tests can differ, notably, between different manufacturers, and specifically in apixaban patients [26•]. Direct determination of NOAC concentrations can be achieved most reliably by use of mass spectrometry, but this approach is not suitable in the clinical care setting [24].

Current guidelines recommend NOAC levels below 30 ng/ml to rule out relevant anticoagulatory effects in NOAC patients [27, 28]. Cut-off values to estimate the rate of hemorrhagic complications in different procedures and diseases are intensively debated and in the following are discussed separately for each disease in the corresponding section. Furthermore, point-of-care devices are currently under investigation and seem to show high specificity for relevant anticoagulatory NOAC levels in a preliminary study, but are not implemented in routine care yet [21, 29]. Expected changes in routine and specific coagulation parameters are summarized in Table 1.

In conclusion, neither last intake nor most routine coagulatory parameters are completely suitable to reliably predict the anticoagulatory effect during NOAC therapy in the early time window. Assessment of specific NOAC levels should be favored in the emergency setting to guide further treatment.

## Ischemic Stroke

OAC therapy was proven to be effective for the prevention of ischemic stroke in AF patients [31]. Since the recommendation of NOAC for patients with AF in 2012 [32], the incidence of ischemic stroke declined from 2.01 to 1.17 per 100 person-years over a 5-year period as a result of increased prescription rates of OAC [33]. This trend was pronounced in elderly patients (≥ 80 years) at high risk for hemorrhagic and ischemic stroke. Especially in patients with impaired renal function, dosing adjustments of NOAC are required to minimize the risk of ischemic and hemorrhagic complications [34]. Observational data reported an increased risk for major hemorrhage in overdosed (hazard ratio, 2.19; 95% CI, 1.07 to 4.46) and a higher rate of ischemic stroke in underdosed NOAC patients (hazard ratio, 4.87; 95% CI, 1.30 to 18.26). In line, sub-analysis of pivotal trials reported an association of low NOAC levels with more frequent occurrence of ischemic stroke [25•]. Further, NOAC intake was reported to be associated with beneficial stroke characteristics, such as lower NIHSS score on admission, less frequent occlusion of intracranial arteries, and lower mortality at least if dosed adequately [35–39].

Patients presenting in ER with ischemic stroke require prompt evaluation of recanalizing strategies, and delay in time to treatment results in significantly increased odds for mortality and functional dependence [40–42]. This time pressure is challenging for stroke physicians, especially in case of NOAC patients with ischemic stroke. Precise assessment of present anticoagulatory effects is time-consuming but seems advisable (at least in factor Xa inhibitor-related ischemic stroke, please see below) in order to reliably identify patients in whom recanalizing strategies can be performed safely [28].

**Table 1** Coagulation testing in NOAC patients

| NOAC agent | Coagulation parameter | Interpretation |
|---|---|---|
| Dabigatran | TT | Very sensitive, allows detection of present effects |
| | dTT | Quantifiable dose-response |
| | ECA | Quantifiable dose-response |
| Factor Xa inhibitors | INR | Small and variable response |
| | aPTT | Small and variable response |
| | Drug-specific chromogenic anti-Xa assay | Quantifiable dose-response |

Adapted from Pollack et al. [30•]. For quantifiable information about NOAC effects, specific coagulation assays are required. We recommend use of dTT or ECA in dabigatran and use of drug-specific anti-Xa levels in factor Xa inhibitor patients

TT indicates thrombin time; dTT, dilute thrombin time; ECA, ecarin-clotting assay; INR, international normalized ratio; aPTT, activated partial thromboplastin time

Unfortunately, randomized controlled trials investigating recanalizing treatment either by intravenous thrombolysis (IVT) or endovascular thrombectomy (EVT) did not include patients at high risk for hemorrhagic complications, such as patients with recent NOAC intake [40, 43••, 44••, 45••, 46••, 47, 48, 49•, 50, 51•, 52••]. Therefore, data regarding acute treatment in NOAC patients with ischemic stroke is limited to observational studies. This uncertainty is reflected by a relatively low proportion of ischemic stroke patients (about 5%) receiving IVT during the first years after NOAC approval in the German-wide RASUNOA registry [23].

## Intravenous Thrombolysis (IVT)

IVT, using recombinant tissue-type plasminogen activator (rt-PA), represents the fundament of recanalizing strategies in ischemic stroke [53]. Of note, another fibrinolytic agent, tenecteplase, was reported to have even higher rates of recanalization without an increase of hemorrhagic complications translating into a net clinical benefit compared to patients treated with rt-PA, but is not considered by current guidelines yet, given the relatively small sample sizes in these trials [44••]. Further, low-dose application of rt-PA (0.6 mg/kg BW) seems to have a beneficial safety profile without impaired efficacy compared to currently recommended rt-PA dose (0.9 mg/kg BW) [45••]. But up to now, none of these approaches was investigated in NOAC patients.

In eligible patients, IVT can be performed safely and results in significantly improved outcomes [41, 42]. Currently, the use of rt-PA is contraindicated for patients with OAC treatment to minimize the risk of iatrogenic symptomatic ICH [54]. This IVT-related complication occurs in nearly 6% of patients and contributes to worse functional outcome and mortality rates up to 50% [55]. In the specific setting of previous VKA use, consensus exists to perform IVT at INR levels ≤ 1.7 [28, 56••]; yet in NOAC, comparable laboratory cut-off values are essentially unestablished.

According to the current recommendations for NOAC patients, only those should undergo IVT who have last NOAC intake 48 h ago, or who have absence of altered coagulation or specific NOAC levels below 30 ng/ml [28, 56••]. However, observational data suggest that patients with NOAC levels above these thresholds may still benefit from IVT and are not at a higher risk for hemorrhagic complications. The observational NOAC in stroke patients (NOACISP) registry comprised 78 NOAC patients (dabigatran 29, rivaroxaban 47, apixaban 2), 441 VKA patients, and 8,938 patients without OAC treated with IVT or EVT [57•]. Sixty-eight (87.2%) patients received the last NOAC dosage within 24 h prior to recanalizing treatment. The decision to use IVT or IAT was mainly based on time since the last intake > 24 h ($n = 10$) or low levels in drug-specific coagulation testing ($n = 23$). All IVT-treated patients had specific anti-factor Xa levels below 100 ng/ml. Rates for any ICH and sICH were 15.7%/4.0% for NOAC and 28.7%/3.6–5.7% for VKA patients post-thrombolysis, respectively. The same working group presented their treatment algorithm to identify rivaroxaban patients suitable for IVT/IAT procedure considering measured anti-factor Xa concentrations (plasma level < 100 ng/ml IVT can be considered, > 100 ng/ml no IVT, no plasma level cut-off for EVT) [58•]. The authors were able to identify one-third of patients, otherwise ineligible for recanalizing strategies according to current AHA guidelines [56••]. None of these patients developed symptomatic intra- or extracranial hemorrhage post-treatment.

In case of ischemic stroke during dabigatran treatment, IVT after reversal with idarucizamb (Praxbind©) may be considered [59]. A recent case series published promising results with clinical improvement observed in over 80% and favorable follow-up outcome (defined as modified Rankin scale score < 2) achieved in 56% of all patients ($n = 55$) [59]. Further, no bleeding complication occurred in patients treated with idarucizumab prior IVT in a German case collection ($n = 19$) resulting in a current expert recommendation supporting

this treatment approach in dabigatran patients [60, 61]. The largest cohort of OAC patients receiving IVT, specifically studying factor Xa inhibitor-related strokes as well, was provided by the "Get with the guidelines" (GWTG) registry [62•]. Overall, 42,887 patients treated with rt-PA within the 4.5-h time window were analyzed consisting of 251 NOAC (dabigatran 87, rivaroxaban 129, apixaban 35), 1500 warfarin, and 41,136 non-OAC patients. Considering the relatively short half-lives of NOAC agents compared to warfarin, the determination of NOAC treatment as intake within the last 7 days seems relatively broadly defined with a high risk of inclusion of non-effectively anticoagulated patients. The authors reported no significant differences among the three groups regarding rates of symptomatic ICH (NOAC 4.8%), any rt-PA complication, in-hospital mortality, or functional outcome at discharge. Treatment at experienced stroke centers and stroke severity were main contributors for the decision to perform IVT in patients despite NOAC intake presenting within the early time window (< 4.5 h) [62•]. Current meta-analysis of available evidence regarding IVT in NOAC patients reported rates of sICH, mortality, and good functional outcome to be 4.3%, 11.3%, and 43.7%, respectively, indicating that IVT may be beneficial in selected patients with NOAC intake without increased risk of bleeding [63, 64•].

## Endovascular Thrombectomy (EVT)

In eligible stroke patients with a large vessel occlusion, EVT with or without additional IVT represents an effective and safe procedure [65••]. Current meta-analysis of 9 studies including 3,885 patients reported no safety issues in VKA patients undergoing EVT. In particular, comparable rates of symptomatic ICH, mortality, and recanalization were reported among patients with and without OAC [66]. A similar safety profile of EVT is suggested in patients with recent NOAC intake, but data regarding this procedure is limited to observational studies of NOAC patients [67]. In the RASUNOA registry, 28 EVT patients had NOAC intake, about one-fifth received additional IVT [66]. Reported rates for ICH were 46% and 4% for symptomatic ICH without negative impact on functional outcomes [68, 69]. Successful recanalization (TICI 2b/3) was achieved in 59% of all patients. The NOACISP registry comprised 27 NOAC patients receiving EVT, but no analysis of efficacy or bleeding endpoints was performed for this subgroup [57•]. In the absence of reported safety issues, eligible ischemic stroke patients with a large vessel occlusion should undergo EVT regardless of NOAC intake in accordance with current recommendations by the European Stroke Organization [28]. The author's recommendations for recanalizing treatment of NOAC patients presenting with ischemic stroke are summarized in Fig. 1.

## NOAC-Related Intracerebral Hemorrhage

The high prescription rates of NOACs and an aging population will result in increased rate of patients presenting with NOAC-related intracerebral hemorrhage (ICH) in the emergency room in the next years (approximately 21,000 cases per year in Europe) [70•]. ICH represents the most severe complication of NOAC treatment and is associated with significant morbidity and mortality rates up to 50% after 30 days [71–73]. Early general management includes prompt cessation of NOAC therapy [11••] and administration of active charcoal to impede further NOAC absorption in patients with the last intake within 4 h [74]. Alongside, acute blood pressure control and reversal of anticoagulatory effects (please see section "reversal treatment" below) are strongly recommended [75, 76]. The importance of blood pressure management was stressed by a recent meta-analysis reporting lower rates of hematoma enlargement (HE) in spontaneous ICH patients achieving systolic blood pressure levels below 140 mmHg [77•]. In line, systolic blood pressure levels below < 160 mmHg within 4 h after admission were significantly associated with lower rates of HE in NOAC-related ICH patients (risk ratio, 0.598; 95% CI, 0.365–0.978) [78•]. Hence, basic blood pressure management should not differ between non-OAC or NOAC patients [75, 76].

Bleeding characteristics in NOAC-related ICH were reported to be similar to those in VKA-related ICH in several observational studies [78•, 79•, 80, 81]. Especially, initial hematoma volume and occurrence of hematoma enlargement (HE) did not differ among NOAC- and VKA-related patients in those studies. The rate of HE in follow-up imaging at 24 h varied between 33 and 38% without significant differences among different NOAC agents [78•, 79, 81]. In line, there were no differences regarding mortality and functional outcome among NOAC and VKA patients [79, 82•]. In the German-wide RETRACE II registry, the mortality rate of NOAC-related ICH was 30% at 3 months with only one-third of patients achieving a good functional outcome, defined as modified Rankin score between 0 and 3 [78•].

On the other hand, a recent analysis of the GWTG registry (15,036 patients with warfarin vs. 4,918 patients with NOAC intake within the last 7 days) reported lower rates of mortality in NOAC compared to VKA-ICH patients [83•]. However, this study did not account for baseline hematoma characteristics [83•], and the last intake of NOAC agent was used as the definition of NOAC-related ICH, leaving room for controversy whether or not all included patients indeed were therapeutically anticoagulated at the onset of ICH. Regarding HE observational data suggested that specific coagulation testing may help to identify patients at high risk for HE [78•, 79, 80, 82•, 84]. In a sub-analysis of patients with factor Xa inhibitor intake, agent-specific anti-Xa levels greater than 118 ng/ml

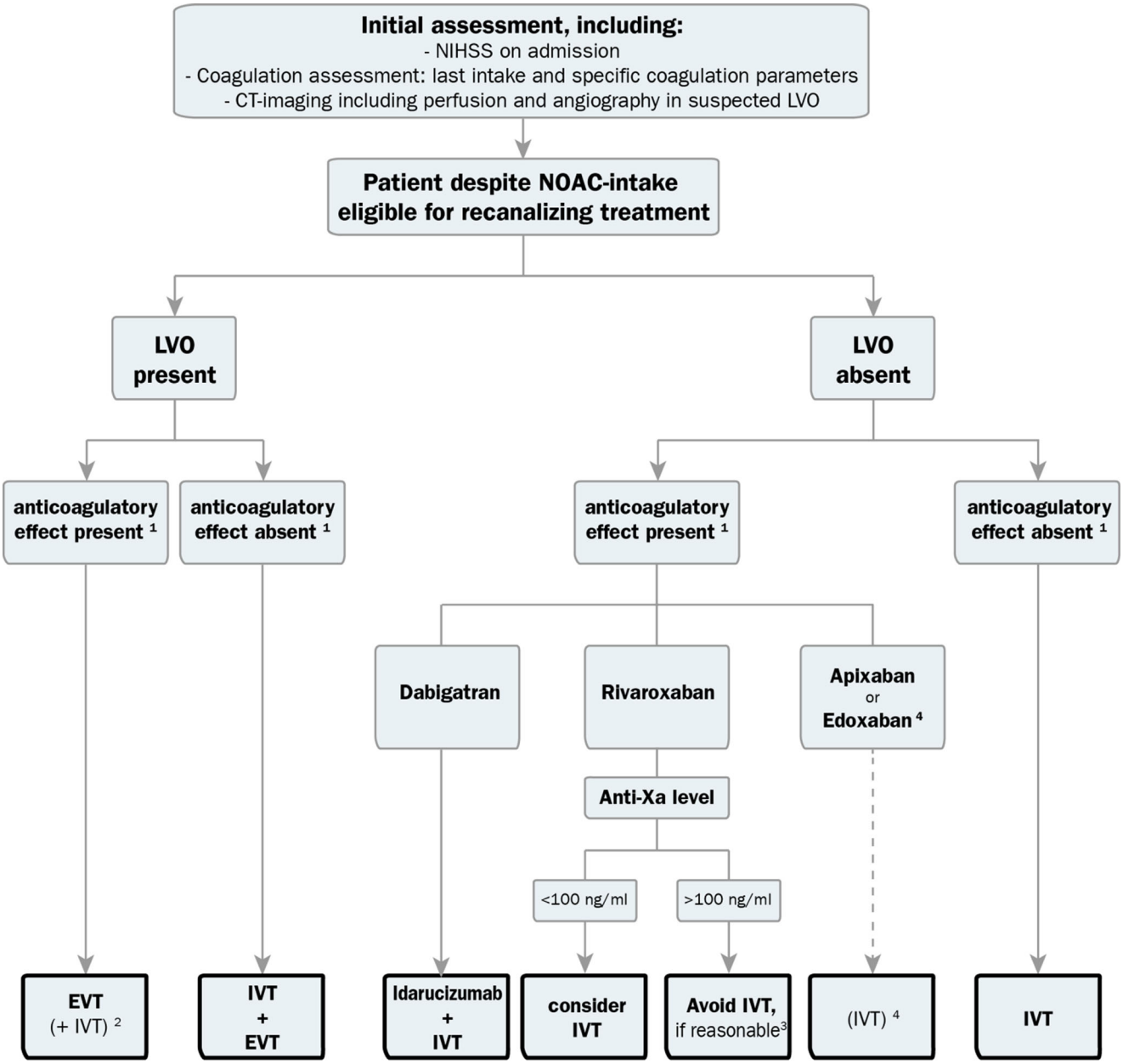


**Fig. 1** Treatment approach in NOAC patients presenting with ischemic stroke based on the authors' recommendation.[1]Anticoagulatory effect present defined as NOAC level > 30 ng/ml or, if unavailable, last intake within the last 48 h. [2]IVT can be considered in rivaroxaban patients if drug-specific anti-Xa level is below 100 ng/ml or in dabigatran patients after reversal by administration of idarucizumab. [3]No data regarding safety. If IVT is necessary in individual patients, low-dose application of rt-PA (0.6 mg/kg BW) may lower the risk of IVT-related hemorrhagic complications. [4]Too low evidence to give formal recommendations for apixaban and edoxaban. At our hospital, IVT is performed/considered/avoided in patients with anti-Xa levels < 50 ng/ml/50–100 ng/ml/> 100 ng/ml. IVT decisions in patients with anti-Xa levels 50–100 ng/ml should be cautiously made on an individual basis considering NIHSS and time window since stroke onset. Low-dose application of rt-PA (0.6 mg/kg BW) may be feasible to lower the risk of IVT-related hemorrhagic complications. LVO indicates large vessel occlusion; IVT, intravenous thrombolysis (rt-PA at 0.9 mg/kg BW); EVT, endovascular thrombectomy

on admission were associated with a threefold increased risk of HE (risk ratio, 3.375; 95% CI, 1.245–9.115). Thus, it seems likely that hematoma characteristics may be influenced by specific NOAC drug levels, similar to INR levels in VKA-ICH, and that baseline ICH volumes probably do not differ among both sufficiently anticoagulated patients with VKA- versus NOAC-related ICH.

## Reversal Treatment

Unless relevant NOAC intake can be ruled out by either medical history or laboratory testing, in line with current ESO recommendations, all patients with suspected NOAC-related ICH should receive reversal therapy as soon as possible [28]. In the initial absence of specific reversal agents in the first years after

NOAC approval, administration of prothrombin complex concentrations (PCC) was recommended in case of NOAC-related bleeding [85]. This treatment approach was mainly based on experimental studies in animal models and healthy volunteers [85, 86]. Up to now, clinical studies investigating the efficacy of PCC in NOAC-related hemorrhage do not seem promising. Majeed et al. reported outcomes of 84 patients who received PCC for management of major bleeding. Of the included 59 patients with intracranial hemorrhage, ineffective hemostasis according to International Society of Thrombosis and Hemostasis was recorded in 16 (27.1%) patients despite PCC treatment (median dose, 2,000 IU). Also, in NOAC-related ICH, observational studies, so far, provided no evidence for benefits of PCC treatment neither on occurrence of HE nor functional outcome: Purrucker et al. reported that HE rates among 35 patients receiving PCC were similar to patients without PCC treatment (PCC 43% vs. no PCC 29%) [79]. Further, in the RETRACE II study comprising 146 patients gerner et al observed observed no association of PCC administration (using dosages recommended during the study period, i.e., PCC 25 IU/kg body weight) with a lower risk of HE or clinical outcomes [78•]. Nonetheless, current International Guidelines recommend administration of 50 IU/kg PCC; yet, this approach has so far not been verified with respect to safety and efficacy by clinical studies [11••, 78•, 87•].

### Specific Reversal in Dabigatran-Related ICH

In 2015, the first specific reversal agent for NOAC-related major hemorrhage was approved by the FDA. Idarucizumab (Praxbind©) is a humanized antibody fragment binding the oral thrombin inhibitor dabigatran. It is administered as two 50 ml iv bolus infusions, each containing 2.5 g idarucizumab, no more than 15 min apart [88]. The efficacy on hemostasis and coagulation parameters was investigated in the REVERSE AD trial consisting of 503 patients with dabigatran intake and need for reversal due to major hemorrhage ($n = 301$) or urgent procedure ($n = 202$) [89••]. Median time since last intake was 15.6 h and more than 90% had elevated ECT in initial coagulation testing. Administration of idarucizumab led to reversal of dabigatran effects reflected by measured concentrations post-treatment below 20 ng/ml in nearly all patients. Unbound dabigatran concentrations remained below 20 ng/ml for 24 h in the majority of patients (77%) suggesting prolonged restoration of hemostasis. In patients undergoing procedures, normal periprocedural hemostasis was attested in 93.4%, but hemostasis was not assessed in those 98 patients with intracranial hemorrhage (of those 53 with ICH) [89••]. Adverse effects consisted of thrombotic events (6.3–7.4% at 90 days) and detection of antibodies against idarucizumab (5.6%). In addition, clinical data on its use in daily care appear promising, but limited to case series. Kermer et al. observed HE in only 2 of 12 (17%) patients treated with idarucizumab [60]. In essence, the achieved hemostasis after idarucizumab treatment in dabigatran ICH is convincing and administration strongly recommended, although reports on clear clinical benefits, e.g., reduced HE rates or improved outcomes, are still pending.

### Specific Reversal in Factor Xa Inhibitor-Related ICH

Andexanet alfa (Ondexxya© in the European Union, but currently not available; in the USA available as Andexxa©) is a recombinant modified version of the human activated factor X without coagulatory activity and acts as a decoy protein for factor Xa inhibitors [90]. It was approved by the FDA last year (2018) as a specific reversal agent for rivaroxaban and apixaban related serious bleeding, based on positive results from two placebo-controlled phase III trials in healthy volunteers (Annexa-A and Annexa-R) [91].

In the Annexa-4 trial (352 patients with major bleeding), administration of andexanet alfa (iv bolus of 400 mg or 800 mg followed by a 2-h infusion of 480 or 960 mg) led to a drop of factor Xa activity 149.7 ng/ml at baseline to 11.1 ng/ml post-treatment [92••]. Four hours after the end of infusion, anti-Xa levels raised again to levels 32–42% below the baseline value indicating a rebound effect and, therefore, an increased risk of delayed hemorrhagic enlargement. Efficacy sub-analysis of patients with intracranial hemorrhage ($n = 168$) revealed that HE after 12 h—defined as volume growth greater than 35%—was present in 20% of patients. Of 71 patients with atraumatic ICH, 22.5% had HE in the follow-up imaging at 12 h (presented at the International Stroke Conference 2019, Honolulu, HI, USA). Thrombotic events occurred in 10% of treated patients within 30 days. Compared to idarucizumab, pharmacodynamics of andexanet alfa seems like a disadvantage as hemostasis lasts only short (1–2 h) with significant rebound effects thereafter [92••]. In addition, handling of andexanet appears not as straightforward requiring different dosages as a bolus (400 vs. 800 mg) depending on dose and time point of the last intake of the specific factor Xa inhibitor, followed by continuous infusions (again with different dosages) for another 2 h to counterbalancing of rebound effects [93]. Similar to idarucizumab, also for andexanet alfa, clear clinical benefits (reduced rates of hemorrhage growth or improved clinical outcomes) need to be verified [89••, 92••].

So far, andexanet alfa is only approved in the USA with high costs for treatment (ranging between USD24,000 and USD48,000). The European Medicines Agency (EMA) has agreed to consider Ondexxya for fast-track approval provided results of ongoing trials (ClinicalTrials.gov number: NCT03661528). Although andexanet alfa may be purchased using international pharmacies, costs to import andexanet for treatment are extremely expensive.

### Other Treatments in NOAC-ICH

A universal antidote (ciraparantag; PER977) is currently under development and supposed to reverse anticoagulatory effects of thrombin and factor Xa inhibitors as well as unfractioned and low molecular weight heparin [94•]. As published, data on the efficacy of ciraparantag is limited and its approval seems unlikely in the near future [95]. So far, alternative hemostatic treatments, such as administration of fresh frozen plasma, activated PCC or tranexamic acid, have not been investigated sufficiently and, therefore, cannot be recommended on a general basis [75, 87•, 96•].

In conclusion, in accordance with current guidelines, we recommend administration of specific reversal agents (idarucizumab or andexanet alfa) in patients with NOAC-related hemorrhage, and, if antidotes are not available, PCC should be used at dosages of 50 IU/kg body weight (see Table 2). Prospective studies are required to investigate optimal reversal strategies and their translation into clinical endpoints (NCT03661528; NCT02866838; NCT02533960).

## Traumatic Intracranial Hemorrhage and Subarachnoid Hemorrhage

Traumatic brain injury (TBI) is one major cause of mortality in Europe accounting for 37% of all injury-related deaths [97•]. In pivotal trials of NOAC in AF patients, rates of traumatic intracranial hemorrhage, consisting of ICH, subdural hematoma (SDH), epidural hematoma (EDH), or subarachnoid hemorrhage (SAH) were similar or even lower compared to warfarin [72, 84]. Reported mortality rates did not differ among patients with either NOAC or warfarin intake [72, 84, 98]. Current clinical data regarding this topic are controversial and scarce. Beynon et al. reported similar rates of neurosurgical intervention (65%), intracranial re-hemorrhage (18%), and mortality at 30 days (26–27%) among 65 NOAC and 63 VKA patients presenting with acute SDH [99]. In a propensity score-matched analysis of 70 NOAC and 140 warfarin patients presenting with TBI, authors observed higher rates of hematoma progression and mortality not favor of NOAC patients. But after focusing on those patients with severe TBI (Glasgow coma scale < 8) only, no difference regarding the abovementioned outcomes among NOAC and warfarin patients were observed [100]. Contrary, another study reported higher rates of reversal therapy and mortality in VKA compared to NOAC patients in this setting (33 NOAC, 32 VKA) [101].

For patients presenting with atraumatic SAH (aSAH), information is even more limited. In the pivotal trials of dabigatran, rivaroxaban, and apixaban, only 19 NOAC patients were recorded with aSAH [71, 72, 98]. Incidence and mortality rates seem lower compared to warfarin, but significant differences were not detected as a result of the low sample size. Clinical evidence is restricted to case reports which do not add valuable information for SAH management [102]. In our opinion, the increased risk for hemorrhagic complications during effective NOAC treatment may endorse an earlier treatment of ruptured aneurysms (within 24 h) compared to the recommended time window of 72 h in non-coagulated patients with aneurysmal SAH [103].

Since specific treatment approaches in TBI and aSAH in patients with NOAC intake are not established yet and International Guidelines do not address this issue in their

**Table 2** Recommendation of reversal agents in NOAC patients with life-threatening hemorrhage

| NOAC agent | Hemostatic reversal recommendation | |
|---|---|---|
| | Preferred agent | Alternative unspecific agents |
| Thrombin inhibitor (dabigatran) | Idarucizumab<br>iv administration of 5 g<br>(2 vials with 2.5 g/50 ml each)<br>- Two consecutive infusions<br>or<br>- Bolus injection one after another | PCC or activated PCC (FEIBA)<br>PCC 50 IU/kg body weight<br>- iv infusion over 15 min<br>FEIBA 50 IU/kg body weight<br>- iv infusion (2 IU/kg body weight per min) |
| Factor Xa inhibitor<br>(rivaroxaban, apixaban, edoxaban) | Andexanet alfa<br>High dose:<br>- Initial iv bolus 800 mg (target rate 30 mg/min)<br>- Follow-on iv infusion: 8 mg/min for up to 120 min<br>Low dose:<br>- Initial iv bolus 400 mg (target rate 30 mg/min)<br>- Follow-on iv infusion: 4 mg/min for up to 120 min | PCC or activated PCC (FEIBA)<br>PCC 50 IU/kg body weight<br>- iv infusion over 15 min<br>FEIBA 50 IU/kg body weight<br>- iv infusion (2 IU/kg body weight per min) |

Summary over current recommendations for reversal agents in life-threatening bleeding situations, adapted from Steiner et al. [70•]. Dosing of andexanet alfa depends on last intake of factor Xa inhibitor and type of factor Xa inhibitor (see FDA recommendation for further details): in case of last intake ≥ 8 h or last-dose rivaroxaban ≤ 10 mg/apixaban ≤ 5 mg - 400 mg i.v. bolus and 480 mg i.v. as infusion over 2 h; otherwise, 800 mg i.v. bolus and 960 mg i.v. as infusion over 2 h. Currently, andexanet alfa is not approved for edoxaban patients.

current versions, we recommend the same reversal management as described above for ICH patients [70•, 75, 87•, 103, 104•].

## Lumbar Puncture

Evaluation of cerebrospinal fluid (CSF) is often essential in the emergency room to exclude infection of the central nervous system or bleeding into the subarachnoid space [105•, 106•]. Generally, lumbar puncture (LP) is a safe procedure, and rates of major complications requiring further treatment are very low, e.g., only 0.01% of patients developing spinal or epidural hematoma [105•, 107]. However, as bleeding may occur into spaces not accessible to manual compression, current recommendations classify LP as a high-risk procedure in NOAC patients [11••]. Non-emergent diagnostic LP should be postponed until normal hemostatic function is restored, usually after interruption of NOACs for five half-lives dependent on renal function (3 days in factor Xa inhibitors and 4–5 days in dabigatran) [11••, 108].

If acute CSF assessment is needed to guide treatment in life-threatening diseases, specific coagulation assessment may add valuable information to estimate the risk for hemorrhagic complications in patients with NOAC intake. Cut-off values of these tests have not been established yet; therefore, only patients with absent anticoagulatory effects of NOAC may receive LP safely. In case of apparent NOAC effects, a cautious evaluation of the risk/benefit ratio of LP shall be made in every single patient and use of specific reversal agents may be considered. NOAC therapy can be restarted after 6 h post-uncomplicated LP without an increase of bleeding complications [109]. In the specific setting that LP is mandatory for diagnosis, however, it cannot be performed because of relevant anticoagulatory NOAC effects; we recommend to initiate disease-specific treatment as if LP would have confirmed CNS disease, i.e., antibiotics in presumed bacterial meningitis, or extended imaging to rule out/confirm SAH, and to perform LP as soon as possible after normalizing of coagulation.

## Conclusions

Management of NOAC patients presenting in the ER is challenging and mainly requires immediate coagulation assessment to guide diagnostic work-up and treatment decisions in patients with ischemic or hemorrhagic intracranial complications. In eligible patients with ischemic stroke, EVT can be performed safely regardless of NOAC intake. Furthermore, observational data suggest that more patients may undergo and benefit from IVT. In case of NOAC-related ICH, prompt reversal treatment—using idarucizumab in dabigatran-related ICH—is mandatory to minimize risks of hematoma enlargement and to improve clinical outcomes. In patients with factor Xa inhibitor-related ICH, preferably andexanet alfa should be administered, and in countries without approval, patients should be either randomized into ongoing trials evaluating andexanet alfa or receive PCC according to guideline recommendations.

## Compliance with Ethical Standards

**Conflict of Interest** Hagen B. Huttner reports personal fees outside the submitted work from Boehringer Ingelheim (dabigatran, idarucizumab), Daiichi Sankyo (edoxaban), and CSL Behring (Beriplex—PCC). He also reports grants from Medtronic, Novartis, and UCB Pharma, outside the submitted work. Stefan T. Gerner declares no potential conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
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