Global Coagulation Testing in Acute Care Medicine: Back to Bedside?

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Abstract

Objectives Detailed and decisive information about the patients' coagulation status is important in various emergency situations. Conventional global coagulation testing strategies are often used to provide a quick overview, but several limitations particularly in the trauma setting are well described. With the introduction of direct oral anticoagulations (DOACs), a milestone for several disease entities resulting in overall improved outcomes could be reached, but at the same time providing new diagnostic challenges for the emergency situation.

Design As an alternative to conventional coagulation tests, there is increasing clinical and scientific interest in the use of early whole blood strategies to provide goal-directed coagulation therapies (GDCT) and hemostatic control in critically ill patients. Viscoelastic hemostatic assays (VHAs) were therefore introduced to several clinical applications and may provide as a bedside point-of-care method for faster information on the underlying hemostatic deficiency.

Conclusion The use of VHA-based algorithms to guide hemostatic control in emergency situations now found its way to several international guidelines for patients at risk of bleeding. With this qualitative review, we would like to focus on VHA-based GDCT and review the current evidence for its use, advantages, and challenges in the two different clinical scenarios of trauma and intracerebral bleeding/stroke management.

Keywords
- VHA-based algorithm
- emergency medicine
- global coagulation testing
- trauma-induced coagulopathy
- stroke/intracerebral bleeding

Introduction

Various emergency situations require a fast and targeted evaluation of the patient's coagulative status. Global plasma-based coagulation tests are therefore traditionally used to assess bleeding and thromboembolic risk factors in patients needing urgent medical care. However, these conventional coagulation tests (CCTs) like the prothrombin time (PT) or the activated partial thromboplastin time (aPTT) were developed to examine patients with isolated clotting factor deficiencies or who were being treated with anticoagulant therapy.[1–5] The same applies for other common coagulation

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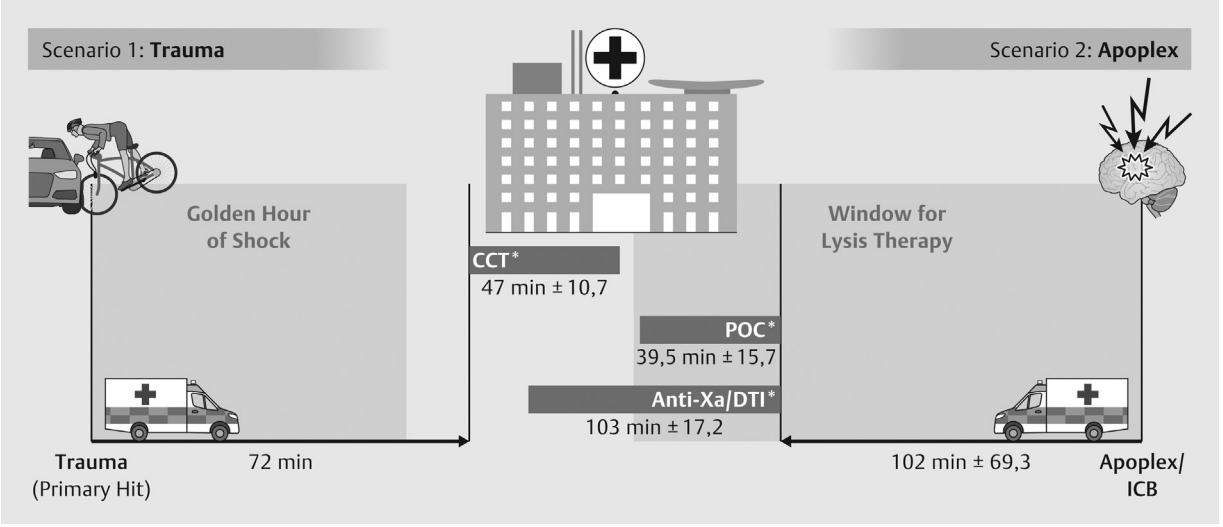

Fig. 1 Turnaround times of first coagulation analysis during primary survey within the two scenarios of Trauma and Apoplex/ICB. **Scenario 1** (left side) displays admission after trauma and average times of first CCT results during shock room management in 2019. As a reference time frame "the golden hour of shock" is given. **Scenario 2** (right side) shows admission after Apoplex/ICB and the difference between first bedside qualitative POC results (DOAC Dipstick, Sysmex, Germany) and turnaround times of standard anti-Xa or direct thrombin inhibition (DTI) tests. All process data are derived from the Cologne-Merheim Medical Centre (CMMC) from 2019.

tests like platelet counts, D-dimers or fibrinogen levels that were subsequently adapted to determine the coagulation status in diverse specific scenarios. Nevertheless, in case of critically ill patients, the clinical benefit was questioned due to little evidence of a correlation between pre-procedure elevated PT or aPTT values and an increased bleeding risk at the time of an invasive diagnostic procedure.[6,7] Conventional global tests are performed at a standardized temperature of 37 °C, which limits the detection of acquired coagulopathies induced by hypothermia or acidosis.[8] Keeping in mind a cell-based model of coagulation, the aPTT and PT tests affect only the initial formation of thrombin in plasma without the presence of platelets or other blood cells. In addition, these tests are also not able to provide any information on clot formation over time or on fibrinolysis and therefore cannot detect hyperfibrinolysis. In addition, even in level-1 facilities that offer highest standards, turnaround times take between 40 and 90 minutes from taking the blood sample to give any result to the clinician.[9] In most scenarios with critically ill patients, this turnaround time may be too long for the decision-making in diagnosis and treatment of emergency situations or it does not reflect the current state of the coagulative status when the results are reported[10,11] (►**Fig. 1**).

As an alternative, there is increasing clinical and scientific interest in the use of early whole blood global coagulation testing to provide goal-directed coagulation therapies (GDCTs) and hemostatic control in critically ill patients. Viscoelastic hemostatic assays (VHAs) were therefore introduced to several clinical applications and may provide faster, more accurate information on the underlying hemostatic deficiency being a bedside point-of-care (POC) method (►**Fig. 2**). These technologies mostly evolved from the original thrombelastometrie (TEG; Haemonetics, Boston, MA) and provide a visual assessment in children and adults including which part of the clotting process is disrupted as well as on the dynamics of clot formation and lysis.[12,13] Several VHA-

Table 1 VHA-based algorithms: one example

	ROTEM	TEG 5000	Treatment options
Fibrinogen	If FIBTEM CA5 <10 mm [If FIBTEM CA5 <9 mm][a]	If FF TEG MA <20 mm	Consider to substitute fibrinogen
Platelets	If (EXTEM CA5) – (FIBTEM CA5) <30mm	If (rTEG MA-FF TEG MA) <45 mm	Consider to give pool of platelets
Plasma	If EXTEM CA5 ≥40 mm and EXTEM CT >80 s	If rTEG MA ≥65 mm and rTEG ACT >120 s	Consider to give additional units of plasma
Tranexamic acid	If EXTEM LI 30 <85%	If rTEG LY30 >10%	Consider to give 1 g of tranexamic acid

Abbreviations: ACT, activated clotting time; VHA, viscoelastic hemostatic assay.
Note: Proposed trigger values for ROTEM and TEG derived from the iTACTIC RCT.
[a]Recommendation from Hagemo et al.[5]

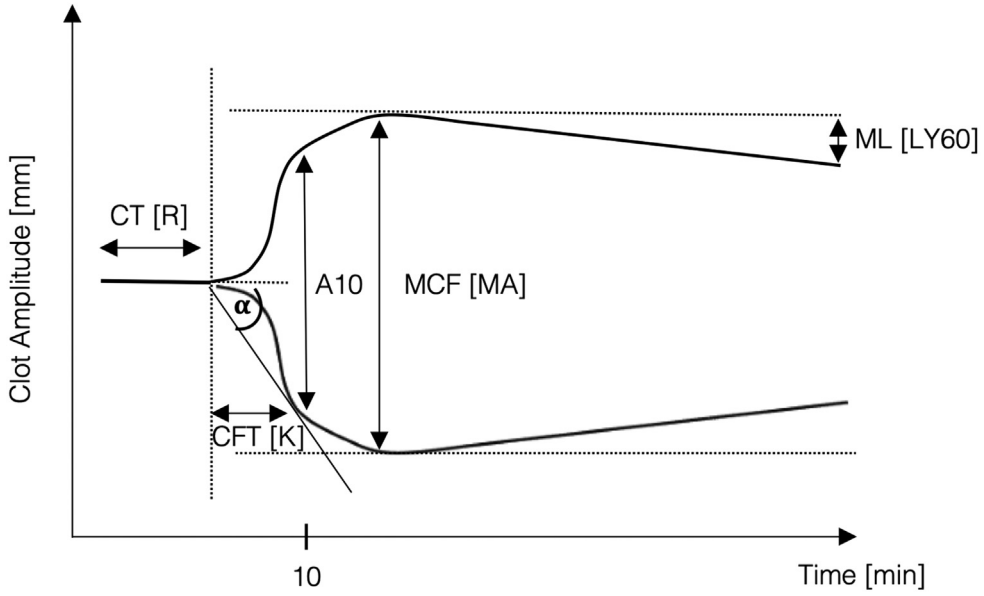

Fig. 2 VHA-based analysis: parameters and clinical significance. Physiologic parameters of ROTEM and TEG. Both systems use equivalent parameters but are labeled differently (TEG labels are presented in square brackets). CT, clotting time; R, reaction time; CFT, clot formation time; K, kinetics; α, the α-angle measures the rate of clot formation by analyzing the angle formed between the end of the CT/[R] point and the 20-mm point on the *y*-axis; MCF, maximum clot firmness; MA, maximum amplitude. MCF/MA represents the maximum clot strength. Maximum lysis (ML) and lysis 60 [LY60] are parameters to show lysis activity. The lysis at 60 minutes [LY60] is a measure of the percent of decrease in amplitude at 60 minutes after achieving MA.

based resuscitation protocols and transfusion algorithms have been developed and introduced to the clinical user to guide resuscitation and transfusion management and were uniformly associated with reduced transfusion requirements.[14–17]

The use of VHA-based algorithms to guide hemostatic control in emergency situations is now recommended in some international guidelines for patients at risk of bleeding[18–21] (►**Table 1**). In the following sections, we will focus on VHA-based GDCT and review the current evidence for its use, advantages, and challenges in two different clinical scenarios.

Scenario 1: Coagulopathy Following Major Trauma: Goal-Directed Coagulation Therapy

Uncontrolled hemorrhage with subsequent hemostatic derangement still represents the most common cause of preventable death following major trauma and is responsible for 25 to 50% of trauma deaths.[22–28] Exsanguination after major injury may be aggravated by an endogenous entity which includes all components of hemostasis that rapidly follows the traumatic impact of tissue injury, hypoperfusion and shock, currently referred to as acute traumatic coagulopathy (ATC).[29–31] Timely detection and aggressive control of ATC have been associated with improved outcomes, but our current understanding of all pathomechanisms that lead to ATC remains still elusive in major parts.[32] From a clinical point of view, identification of advantages resulting from goal-directed strategies that allow quick evaluation of the coagulation status in terms of outcome as well as transfusion-saving effects and not at least a survival benefit is of crucial importance. In addition, there is a large diversity in the clinical management of major bleeding events even among advanced trauma centers.[33] There is still a controversy whether the empiric administration of blood products in predefined and fixed ratios (cf. damage control resuscitation [DCR]) might be superior to global coagulation testing in acute setting of trauma to enable goal-directed strategies.[18] One part of this clinical and scientific controversy might be the methodological problem that the optimal ratio of blood products to be transfused in DCR strategies is still not standardized. In contrast to goal-directed strategies, there is no consent defining the ratio of packed red blood cells (pPBC), plasma (fresh-frozen plasma [FFP] or pathogen-inactivated plasma), and platelets. In addition, there is no universal recommendation backed by large evidence how to include specific factor concentrates (e.g., prothrombin complex concentrates [PCC]) or single coagulation factors products (fibrinogen [FI], FVII), within these algorithms. Keeping that in mind, multiple but mostly retrospective data indicate an overall benefit of goal-directed resuscitation and transfusion strategies using global coagulation testing approaches guided either via VHA[34,35] or CCT monitoring[36,37] over DCR in bleeding trauma patients. Interestingly, these studies suggest that (besides all limitations of CCT-monitored strategies like longer turnaround times compared with bedside VHA and missing information on clot formation dynamics

and lysis) they might be superior to the use of fixed-ratio methods.

To decide whether goal-directed resuscitation and transfusion strategies might be beneficial in terms of survival after major trauma, there are first results from military and civilian settings to find monitored strategies to be superior to fixed ratio–based approaches. In 2020, Lammers et al described in a retrospective data analysis including 3,320 patients after combat trauma improved mortality implications within the VHA-guided resuscitation group compared with a 1:1:1 (pPBC:FFP:platelets) DCR strategy. Largest mortality benefits were seen in those patients who underwent massive volume transfusion (10.2 vs. 20.9%, $p = 0.002$), those with a GCS less than 8 on admission (11.9 vs. 30.9%, $p = 0.019$), those with severe abdominal or pelvis injuries (9.3 vs. 23.9%, $p < 0.001$), and those who were hypotensive (17.3 vs. 30.9%, $p = 0.042$).[38] These findings might suggest that most injured and physiologically deranged patients might experience the most benefit from a goal-directed targeted approach. A Cochrane review from 2016 on the use of VHA testing in different clinical scenarios to monitor hemostatic treatment compared with standard care in bleeding patients included 17 studies and 1,493 participants and demonstrated that VHA-based strategies reduce mortality (7.4 vs. 3.9%, 95% confidence interval: 0.28–0.95) and the overall utilization of blood products.[39] There are additional benefits reported attributed to early global goal-directed hemostatic resuscitation via VHA strategies including a faster decision process by using functional clotting parameters (e.g., FIBTEM A5),[40] more efficient processes due to targeted initiation of therapies to correct plasmatic deficiencies,[41,42] and cost savings.[13,34,43]

Considering all described limitations of CCT global tests one might expect that VHA methods should be highly recommended to guide goal-directed strategies, but there are contradicting data. On the one hand the recent European multicenter iTACTIC randomized control trial (RCT) revealed no difference in the overall outcomes between VHA- and CCT-augmented major hemorrhage protocols. This RCT included 396 trauma patients, 201 patients were located to the VHA-guided group, and 195 patients to the CCT-guided group. Primary outcome was the proportion of patients who were alive and free of massive transfusion 24 hours after admission ($\geq$10 RBC transfusions).

On the other hand, there is consistent evidence for a time- and transfusion-saving effect resulting in an overall survival benefit with VHA-guided algorithms. In 2019, Gratz et al demonstrated in a feasibility trial after implementation of a VHA-guided model for hemostatic management in four different emergency departments over Europe a faster decision-making process and a more targeted coagulation therapy in patients suffering from traumatic brain injury (TBI).[44] Early goal-directed hemostatic resuscitation was further explored in a single-center, prospective randomized-controlled trial in the United States that tested whether a massive transfusion protocol (MTP) goal directed by VHA (TEG; Haemonetics) could improve survival compared with an MTP guided by CCT.[45] In total, 111 patients were included in the intent-to-treat analysis (TEG: $n = 56$, CCT: $n = 55$). Survival in the VHA group was significantly higher than the CCT group (log-rank $p = 0.032$, Wilcoxon $p = 0.027$); there were 20 deaths in the CCT group (36.4%) compared with 11 in the TEG group (19.6%; $p = 0.049$). Most deaths occurred within the first 6 hours after admission to the emergency department (21.8% CCT group vs. 7.1% TEG group, $p = 0.032$). CCT patients required a similar number of RBC units as the VHA patients (CCA: 5.0 [2–11], TEG: 4.5 [2–8], $p = 0.317$), but more plasma (CCA: 2.0 [0–4], TEG: 0.0 [0–3], $p = 0.022$) and more platelet units (CCA: 0.0 [0–1], TEG: 0.0 [0–0], $p = 0.041$) during the first 2 hours of resuscitation. This was the first prospective randomized trial to demonstrate that a goal-directed, VHA-guided MTP to resuscitate severely injured patients improves survival compared with an MTP guided by CCT and utilizes less plasma and platelet transfusions during the early phase of resuscitation. Consistently, subsequent studies in TBI patients or on perioperative management of various surgical procedures seem to confirm this effect.[46,47]

In conclusion, data demonstrate a survival and transfusion-saving benefit from goal-directed resuscitation strategies and should therefore, in accordance with current guideline recommendations, be strongly recommended.[18] But there is still limited evidence based on prospective data to support the use of VHA compared with CCT and to prove an advantage for patient-centered outcomes after trauma.

Scenario 2: Coagulation Testing in Intracerebral Hemorrhage/Stroke Management

Ischemic stroke is still one of the leading causes of morbidity and mortality in industrialized countries. Fortunately, because of numerous adjustments to the existing guidelines for secondary prophylaxis, the recurrence rate after a cerebrovascular ischemic event has been almost halved over the past few decades.[48] One of the milestones along the way was the introduction of direct oral anticoagulants (DOACs) for stroke prophylaxis in nonvalvular atrial fibrillation (AF). Although these substances are very effective, 1 to 2% of patients treated this way suffer an ischemic stroke every year.[49] Stroke may occur despite good intake compliance, but DOAC plasma concentration may correlate both with stroke severity (as is the case with international normalized ratio (INR) in patients on vitamin K antagonist) and large vessel occlusion.[50] Case series and observational studies reveal that an adequate DOAC dose at ischemic stroke onset is associated with milder severity and more favorable outcome compared with non-anticoagulated stroke patients with AF.[49,51]

However, this new situation also raises new questions, especially in case of emergency situations. Up to 13% of patients with an acute stroke have now been pretreated with oral anticoagulants, the largest group with a DOAC.[52] Of these, around 28% are candidates for intravenous thrombolytic (IVT) therapy based on clinical and temporal criteria.[53] As an expression of the resulting uncertainty, the lysis rate in such patients in a multicenter German registry study was only 6%, compared with an overall national rate of 70%.[54]

Routine coagulation tests (PT, aPTT, activated clotting time) do not provide an accurate assessment of DOAC anticoagulant effects and cannot be used to accurately gauge anticoagulant activity. Anti-Xa inhibitors show some degree of correlation with aPTT and PT/INR; however, results are hampered by overall poor correlations, significant reagent-dependent sensitivities, and variability within assays.[55] Studies in patients with acute stroke show similar results with normal aPTT and INR in 11 to 44% of patients with peak DOAC drug levels.[56] A normal thrombin time can exclude the presence of clinically relevant concentrations of DTIs or unfractionated heparin, but not low-molecular-weight heparin since factor X is not involved in the assay.[57]

Mass spectrometry measurements are considered the gold standard for drug-specific assays for DOAC measurement, but due to poor availability and long turnaround times (►Fig. 1) it is unsuitable for emergency situations. Besides mass spectrometry, only Ecarin clotting time/diluted thrombin time (for dabigatran) and calibrated anti-Xa assays (for Xa inhibitors) show linear correlations to serum levels in a dose-dependent fashion but the same availability issue.[55] POC methods appear mandatory, but there is not enough information to consider the use of thromboelastography or rotational thromboelastometry (ROTEM) for adequately assessing DOAC activity.[58] There are a few data that indicate that VHA techniques might be useful for detecting rivaroxaban peak plasma levels qualitatively.[59] In case of rivaroxaban and apixaban, Adelmann et al showed in 2014 that apixaban and rivaroxaban activity correlates with low tissue factor in ROTEM clotting time in vitro.[60] Urine tests may be useful for detecting exposure to DOACs, but levels do not correlate well with actual plasma concentrations and may be used only as qualitative detection method.[58,61]

The ESO guidelines published in 2021 postulate insufficient data to make evidence-based recommendations on how to proceed if a DOAC was taken within the last 48 hours before an acute ischemic stroke. As an expert consensus, anti-Xa activity less than 0.5 U/mL (for factor Xa inhibitors) or a thrombin time less than 60 seconds (for dabigatran) is mentioned as prerequisites for IVT therapy.[62] The 2019 AHA/ASA guidelines recommend IVT in patients on medication with a direct thrombin or factor Xa inhibitor only if the substances have not been taken within the last 48 hours (assuming normal renal function) or aPTT, INR, platelet count, Ecarin clotting time, thrombin time, and "appropriate direct factor Xa activity tests" are normal.[63] For rivaroxaban, there were additional factors described resulting in a higher-than-expected DOAC plasma concentration. In their study of real-life patients, impaired kidney function (glomerular filtration rate <60 mL/min) and co-medication with amiodarone were independently associated with higher residual rivaroxaban plasma concentrations and longer needed standard intervals of RXA discontinuation before elective surgery.[64]

Until a few years ago, the recent intake of a DOAC or the detection of relevant serum levels was considered an absolute contraindication for intravenous thrombolysis. This has fundamentally changed with the current ESO guideline. If dabigatran was taken within 48 hours before the event, antagonism using idarucizumab in combination with subsequent IVT is now advocated in the sense of an expert consensus.[62] Idarucizumab is formally approved by the EMA (European Medicines Agency, https://www.ema.europa.eu/en) not only for life-threatening or uncontrollable bleeding but also when emergency surgery/urgent interventions require rapid reversal of the anticoagulant effect of dabigatran; from this, at least indirectly, approval before planned IVT therapy can be derived. In a retrospective review of 80 IVTs after administration of idarucizumab, 78% experienced a notable clinical improvement of a median of 7 points on the National Institutes of Health Stroke Scale. Relevant bleeding complications did not occur.[65] Also regarding this development, POC testing of DOAC levels in the emergency room is becoming increasingly important.

Andexanet alfa, an antidote for the anti-Xa inhibitors rivaroxaban and apixaban, has been available since 2019. In contrast to idarucizumab, it has been approved by the EMA only for the treatment of clinically relevant bleeding, not before planned surgery. The hypothetical administration prior to planned IVT thus represents off-label use. More important in everyday clinical practice, however, is the fact that the substance must be administered for a further 2 hours after the initial bolus administration, which makes it seem rather unsuitable for time-critical stroke treatment. There is only one recent case report describing the use of andexanet alfa prior to thrombolysis in a patient with ischemic stroke and recent intake of apixaban without bleeding or thrombotic complications.[66]

Besides ischemia as the most common cause, spontaneous intracerebral bleeding (ICB) accounts for 8 to 15% of strokes in Europe and the United States. In some patients, secondary hematoma expansion occurs after the initial diagnosis, associated with poor clinical outcome.[67] Therefore, early prediction of later hematoma growth can help identify a group of patients who would benefit from a more aggressive therapeutic approach. On the one hand, there are various patterns in the initial computed tomographic imaging, such as an irregular hematoma boundary or CT angiographic evidence of active bleeding at the time of the examination (the so-called spot sign; ►Fig. 3).[68,69] On the other hand, any preexisting oral anticoagulation is associated with an increased risk of secondary hematoma growth; 15 to 25% of all intracranial hemorrhages (ICH; also including subarachnoid, epidural, and subdural hemorrhage) are related to DOAC.[70,71] RCTs indicate an ICB incidence of 0.13 to 0.37% per year in AF patients on DOAC treatment, while the incidence of ICH is 0.23 to 0.55% per year.[72–76] In the meantime, several retrospective database analyses with large numbers of cases have shown a better outcome in ICH with preexisting anticoagulation with a DOAC compared with vitamin K–dependent anticoagulants.[77–79]

The availability of the specific antidotes idarucizumab and andexanet alfa has not yet found its way into international guidelines. The national guideline of the German Society of Neurology states that administration of the respective antidote can be considered in patients with ICB on dabigatran or

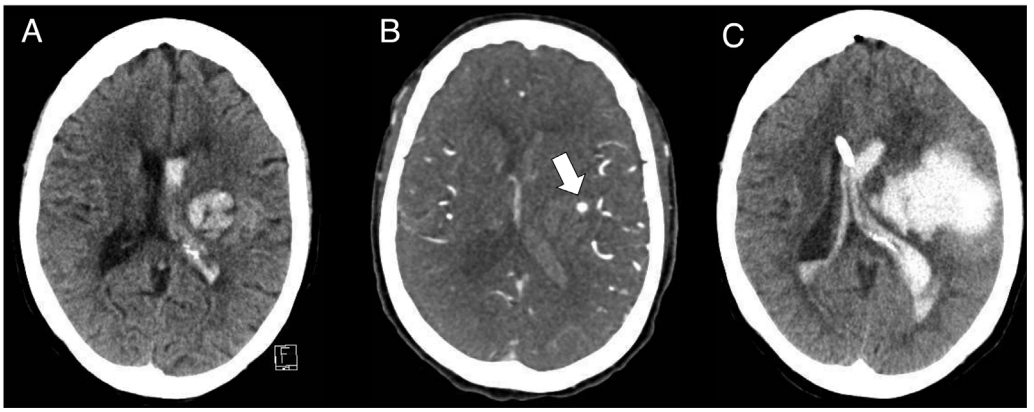

Fig. 3 Early CT signs of active bleeding: the spot sign. (**A** and **B**) The initial CT scans of irregular intracranial bleeding on admission to hospital. The point-like extravasate of contrast agent ("spot-sign"; marked with an arrow in **B**) indicates the active bleeding at the time of the examination. (**C**) Progression 6 hours after admission. (CT images were provided by Dr. med. Jörg Poggenborg, Head of the Department Neuroradiology, Cologne-Merheim Medical Centre.)

the anti-Xa inhibitors rivaroxaban and apixaban. Since andexanet alfa has not yet been approved for the substance edoxaban, the intravenous administration of PCC (PPSB 50 U/kg, IV) is recommended in this case.[62] In view of the relevant rates of consecutive thromboembolic complications and the high treatment costs, a rapid assessment of the coagulation situation using bedside POC methods in the emergency department would also be desirable for this patient population.

In conclusion, in view of the low ischemia tolerance of brain tissue, the decisive factor in the acute treatment of ischemic stroke is to reopen the closed vessel as quickly as possible to save less perfused but still vital tissue (the so-called penumbra). In view of DOAC anticoagulation strategies, the availability of specific antidote agents, and the limited time frame, a bedside POC global coagulation assessment is of particular importance. For the neurologist in the emergency department, clearly

Table 2 Main parameters of selected VHA technologies combined with their informative value on the main clot formation event. Interpretation aids are given. It needs to be emphasized that parameters and technologies are selected and others are on the market.

	ROTEM	TEG 5000	ClotPro	Interpretation aid
Clot initiation	CT	R	CT	Time to clot formation; short CT/R values represent a hypercoagulable state; prolonged CT/R values are seen in hypocoagulability or the presence of anticoagulant agents
	INTEM CT	Kaolin	IN test CT	Similar to aPTT; tests clotting factor activation through the intrinsic pathway
	EXTEM CT	ACT	Ex test CT	Similar to INR; tests clotting factor activation through the extrinsic pathway
Clot kinetics	CFT	K	CFT	CFT/K measures the contribution of fibrinogen to the clot stiffness
	α -Angle	α -Angle	α -Angle	The α -angle displays fibrin kinetics including fibrin turnover and cross-linking
	FIBTEM	–	FIB test	Tests fibrinogen contribution to clot stability after blocking of platelet activation via cytochalasin D; sensitive to lysis
Clot propagation	EXTEM MCF	MA (rTEG)	Ex test MCF	Reflects clot stiffness and contribution of platelets and fibrinogen
Clot stability	ML	–	–	All lysis indices display hyperfibrinolysis by increased clot lysis
	LI 30 or 60	LY 30 or 60	CLI 30 or 60	
	APTEM	–	AP test	
			TPA test	
FXa antagonists	–	–	RVV	Acts as a qualitative/semiquantitative test for FXa inhibitors
Dabigatran	–	–	ECA test	Acts as a qualitative/semiquantitative test for dabigatran

formulated recommendations are essential to be able to select the group of DOAC-treated patients in whom IVT can be performed without a significant increase in complications.

Conflict of Interest

The authors declare that they have no conflict of interest.

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