Treatment of intracerebral hemorrhage in patients on non-vitamin K oral anticoagulants with tranexamic acid

(TICH-NOAC)

Clinical Study Protocol

A randomized, placebo controlled phase-IIb/III multi-center treatment trial.

Study Type:	Clinical trial with Investigational Medicinal Product (IMP)
Study Categorisation:	Risk category C
Study Registration:	NCT02866838 (clinicaltrials.gov)
Sponsor, Sponsor-Investigator or Principal Coordinating Investigator:	Stroke Center, University Hospital Basel Prof. Dr. med. Philippe Lyrer Stroke Center and Neurology Petersgraben 4 4031 Basel/Switzerland
Investigational Product:	Tranexamic acid (verum) vs. NaCl 0.9% (Placebo)
Protocol Version and Date:	Version 1.4 of April 16th 2020

Signature Page(s)

Study number	NCT02866838
Study Title	Treatment of intracerebral hemorrhage in patients on non-vitamin K oral anticoagulants with tranexamic acid (TICH-NOAC)

The Sponsor-Investigator and trial statistician have approved the protocol version 1.4 dated April 16rh 2020, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Prof. Dr. med. Philippe Lyrer, Sponsor-Representative and Coordinating Investigator

Place/Date	Signature

Prof. Dr. med. Stefan Engelter, Deputy Coordinating Investigator; Local Principal Investigator University Hospital Basel

Place/Date	Signature

Prof. Dr. med. Nils Peters, Deputy Coordinating Investigator and Executive Trial Manager; Local Principal Investigator Klinik Hirslanden Zürich

Place/Date	Signature

PD Dr. med. David Seiffge, Scientific Trial Manager

Place/Date	Signature

Sabine Schaedelin, MSc, Trial Statistician

Place/Date	Signature

Marina Maurer, Trial Coordinator

Place/Date	Signature

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site

Principal investigator

Place/Date	Signature **Prof. Dr. med. Stefan Engelter**

Table of Contents

STUDY SYNOPSIS

Title	**Treatment of intracerebral hemorrhage in patients on non-vitamin K oral anticoagulants with tranexamic acid (TICH-NOAC)**
Sponsor	Stroke Center, Universitätsspital Basel, Basel, Switzerland
Sponsor-Investigator	Prof. Dr. Philippe Lyrer
Steering committee	Prof. Dr. N. Peters, Prof. D. Tskaris, Prof. C. Stippich, Prof. R. Guzman; Prof. Dr. C. Nickel, , Prof. Dr. N. Sprigg, S. Schaedelin MSc, PD Dr. D. Seiffge
Trial registration	NCT02866838
Protocol Version and Date	Version 1.4 of April 16th 2020
CRO	CTU Basel
Background	Novel, non-vitamin K antagonist oral anticoagulants (NOAC) target selected players in the coagulation cascade as the direct thrombin inhibitor dabigatran and the factor Xa-inhibitors apixaban, edoxaban and rivaroxaban. Intracerebral hemorrhage (ICH) is the most feared complication of NOAC treatment (NOAC-ICH). Outcome of NOAC-ICH can be devastating and is a cause of death and disability. There is no proven treatment for NOAC-ICH. Hematoma expansion (HE) is associated with unfavorable outcome. Tranexamic acid (TA) is an anti-fibrinolytic drug that is used in a number of bleeding conditions other than ICH.
Primary Research Hypothesis	Treatment with TA as add-on treatment to best medical treatment for NOAC-ICH reduces HE
Primary Objective	To demonstrate that treatment with TA for NOAC-ICH in addition to best medical treatment reduces rate of HE compared to best medical treatment (includes “antidotes” if available) only
Methods	Randomized controlled, double-blinded multicenter trial
Primary Endpoint	The primary outcome measure will be a surrogate imaging outcome measure – hematoma expansion (HE) – that is defined as the difference between ICH-volume on baseline CT and on follow-up-CT at 24 ± 3 hours.
Secondary Endpoints	1. modified Rankin Scale (mRS) 0–4 at three-months; 2. mRS 0–3 at three-months; 3. Categorical shift in mRS at three-months; 4. Absolute ICH growth volume by 24 ± 3 hours, adjusted for baseline ICH volume; 5. Symptomatic HE defined as HE associated with neurological deterioration of NIHSS >/=4 points or GCS >2 points 6. Death due to any cause by three-months;

	7. major thromboembolic events (myocardial infarction, ischemic stroke, pulmonary embolism) 8. NCH intervention (including craniectomie, EVD, hematoma evacuation) 9. In-hospital mortality
Statistical Hypothesis	TA reduces rate of HE in patients with NOAC-ICH compared to placebo in addition to best medical treatment
Inclusion Criteria	- Acute intracerebral hemorrhage (symptom onset <12h) - Prior treatment with a novel direct oral anticoagulant (apixaban, dabigatran, edoxaban or rivaroxaban; last intake <48hours OR proven NOAC activity by relevant coagulation assays) - Age >18 years, No upper age limit - Informed consent has been received in accordance to local ethics committee requirements
Exclusion Criteria	- Severe pre-morbid disability (modified Rankin scale >4) - Anticoagulation with VKA - Secondary intracerebral hemorrhage (e.g., AVM, tumor, trauma) Note it is not necessary for investigators to exclude underlying structural abnormality prior to enrolment, but where an underlying structural abnormality is already known, these patients should not be recruited. - Glasgow coma scale <5 - pregnancy - Planned neurosurgical hematoma evacuation within 24 hours (before follow-up imaging) - Pulmonary embolism/deep vein thrombosis within the last 2 weeks.
Sample Size	109
Study Centers	Basel (coordinating center), Bern, Luzern, Zürich, Aarau, St. Gallen, Hirslanden
Randomization	1 : 1
Intervention	intravenous tranexamic acid (1g loading dose given as 100 ml infusion over 10 minutes, followed by another 1g in 250 ml infused over 8 hours) or as comparator placebo (normal saline 0.9%) administered by identical regimen.
Study Procedure	The study contains of 5 study visits (Screening-/Randomization visit, Follow-up-visit on day 2, day 7, discharge from primary care hospital and 90 days) and lasts 3 months. Clinical measures (mRS, NIHSS) and adverse events will be obtained at every visit after randomization. On day 2, a follow-up native head CT-scan for determination of hematoma expansion will be performed.
Calculation of Sample Size	Assuming a rate of hematoma expansion of 54% in the placebo group and 27% in the TA group, 109 patients need to be included to yield 80% power to detect a significant absolute difference in the proportion of patients with hematoma enlargement at 24 h at a two-sided statistical significance threshold of P = 0·05.

Relevance of the study	Use of NOAC is frequent and will still increase in the future. Treatment of NOAC-ICH is unsolved. Due to its mode of action, TA is a promising compound to be tested for hemostatic treatment in ICH and may improve clinical outcome. The results of the present trial will show whether TA is beneficial in patients with NOAC-ICH.

STUDY SUMMARY IN LOCAL LANGUAGE

Neue, direkte, nicht Vitamin-K antagonisierende orale Antikoagulantien (NOAC oder DOAC) sind wirksame Medikamente zur Prophylaxe und Behandlung einer Vielzahl von thrombembolischen Erkrankungen wie zum Beispiel der Hirnschlagprophylaxe bei Patienten mit Vorhofflimmern. Die gefürchtetste Komplikation einer NOAC-Behandlung ist eine Hirnblutung (=intracerebral hemorrhage, ICH). Hirnblutungen bei Patienten unter Antikoagulantienbehandlung (alte Antikoagulantien wie Vitamin K-Antagonisten oder NOAC) weisen häufig Nachblutungen (=Hämatomexpansion, HE) in der Frühphase nach dem Ereignis auf, welche ein schlechter prognostischer Faktor sind. Insgesamt ist die Prognose bei Patienten mit Hirnblutungen unter Antikoagulantien schlecht mit einer hohen Sterblichkeit (ca. 20%) sowie einer hohen Rate an Patienten mit dauerhafter neurologischer Behinderung. Seit kurzem existieren sogenannte Antidots gegen NOAC, jedoch gibt es keine evidenz-basierte Behandlung der NOAC-Hirnblutung, welche nachweislich das klinische Outcome verbessen und Nachblutungen verhindern kann.

Tranexamsäure ist ein seit > 20 Jahren bekanntes Medikament, dass in vielen Bereichen der Medizin zur Stillung von Blutungen, zum Beispiel nach Unfällen oder während Operationen, eingesetzt wird. Aktuell wird in einer grossen, multi-nationalen Studie die Wirkung von Tranexamsäure bei Patienten mit spontanen Hirnblutungen (Patienten, die keine Antikoagulantien/NOAC eingenommen haben) erforscht (TICH-2 Studie).

In der vorliegenden Studie möchten wir in einer Studie an mehreren Zentren die Wirkung von Tranexamsäure im Vergleich zu Placebo zusätzlich zur medizinischen Standardbehandlung (welche unter Umständen Antidots beinhalten kann) bei Patienten mit NOAC-Hirnblutungen testen. Das primäre Ziel ist es, die Rate an HE 24 Stunden nach Aufnahme zu reduzieren. Sekundäre Ziele ist eine Reduktion von Tod und neurologischer Behinderung nach 3 Monaten.

ABBREVIATIONS

AE	Adverse Event
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin)*
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
IB	Investigator's Brochure
Ho	Null hypothesis
H1	Alternative hypothesis
HFG	Humanforschungsgesetz (Law on human research)
HMG	Heilmittelgesetz
HRA	Federal Act on Research involving Human Beings
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
ISO	International Organisation for Standardisation
ITT	Intention to treat
KlinV	Verordnung über klinische Versuche in der Humanforschung *(in English: ClinO, in French OClin)*
PI	Principal Investigator
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

STUDY SCHEDULE

Study Periods	Screening	Randomisation /Treatment	Follow-up			
Visit	1	2	3	4	5	6
day	1	1	2	7	Death/ discharge	90
Patient Information and Informed Consent	x					
Demographics	x					
Medical History	x					
In- /Exclusion Criteria	x					
NIHSS	x		x	x		x
Vital Signs (RR, heart rate)	x		x	x		x
Laboratory Tests	x*					
Pregnancy Test#	x					
Randomisation		x				
CT scan	x*	x[1]	x			
Study treatment		x				
mRS	x		x	x	x	x
Secondary outcome variables						x
Concomitant Therapy, Intervention		x	x	x	x	
Adverse Events		x	x	x	x	x

* part of routine work-up (=no study intervention)

if applicable

1 only if no baseline-CT scan performed as part of routine-work up (for example baseline brain imaging is MRI)

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor-Representative, Coordinating Investigator

Prof. Dr. med. Phlippe Lyrer
Stroke Center, University Hospital Basel
Petersgraben 4
4031 Basel

1.2 Deputy Coodinating Investigators

Prof. Dr. med. Stefan Engelter, **Principal Investigator Basel**
Stroke Center and Neurology
Petersgraben 4
4031 Basel
Tel. +41 (0) 61 265 25 25
And
Prof. Dr. med. Nils Peters, **Principal Investigator Hirslanden**
Stroke Center, Klinik Hirslanden
Witellikerstrasse 40
8032 Zürich
Tel. +41 (0) 44 387 21 11

1.3 Statistician ("Biostatistician")

Sabine Schaedelin, PhD
Universitätsspital Basel
Departement Klinische Forschung
Clinical Trial Unit (CTU)
Schanzenstr. 55
4031 Basel
Tel +41 (0)61 556 51 67

1.4 Trial Pharmacist

Dr. rer. nat. Stefanie Deuster
Spital-Pharmazie
Universitätsspital Basel
Rossetti-Bau, Spitalstrasse 26
CH-4031 Basel
Tel: 0041-61-265 25 25

1.5 Monitoring institution

Klaus Ehrlich
Universitätsspital Basel
Departement Klinische Forschung
Clinical Trial Unit (CTU)

Schanzenstr. 55

4031 Basel

Tel +41 (0)61 556 51 67

1.6 Data Safety Monitoring Board

The study will be terminated early in case of major safety concerns. For this purpose, a DSMB (Data-Safety-Monitoring-Board) will be installed. The DSMB will be independent of the sponsor, the CIs and competing interests. It will comprise of two experienced stroke neurologist or neuroradiologists and one statistician. The DSMB will meet after recruitment of 50% and 80% of the patients. It will monitor the frequency of the clinically important safety events. In case of serious safety concerns, the DSMB will alert the chief investigator in order to terminate the study.

1.7 Any other relevant Committee, Person, Organisation, Institution

Day-to-day management of the trial will be the responsibility of the trial executive committee (TEC). The TEC will report to the Trial Steering Committee (TSC). An independent Data Safety Monitoring Board (DSMB, see 1.6) will monitor safety of participants, and will report to the TSC. Trial co-ordination will be through the TEC, in conjunction with the Basel Clinical Trials Unit (CTU).

The Chief Investigators are the data custodian and have overall responsibility for the study and shall oversee all study management.

Trial executive committee (TEC)
The trial executive committee (TEC) will include the Sponsor/Coordinating-Investigator (Prof. Lyrer), the deputy Sponsor-Investigator, the Principal Investigator (Prof. N.Peters) and the Scientific Trial Manager (PD Dr D. Seiffge). This group, based at the Stroke Center at the University Hospital Basel Unit, will meet regularly, once a year.

Prof. Dr. med. Philippe Lyrer (Sponsor-Coordinating Investigator)

Prof. Dr. med. Stefan Engelter (Deputy Coordinating Investigator, Local PI Basel)

Prof. Dr. med. Nils Peters (Deputy Coordinating Investigator, Local PI Hirslanden)

PD Dr. med. David Seiffge (scientific trial management)

Stroke Center and Neurology

Petersgraben 4

4031 Basel

Tel. +41 (0) 61 265 25 25

Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) will provide oversight of the trial. It will meet (in person or by telephone conference) prior to commencement of the trial, and then at regular intervals until completion (at least annually). Specific tasks of the TSC are:

• to approve the trial protocol

• to approve necessary changes to the protocol based on considerations of feasibility

and practicability

• to receive reports from the DSMB

• to resolve problems brought to it by the co-ordinating centre and TEC

• to ensure publication of the trial results

Members of the trial steering committee (additional persons to TEC; representatives from international coordinating centers to be appointed):

Prof. D. Tsakiris (Diagnostic Hematology), Prof. C. Stippich (Neuroradiology) and Prof. R. Guzman

(Neurosurgery), Prof. Dr. C. Nickel (Emergency Departement), Sabine Schädelin, MSc, (trial statistician, CTU Basel), Prof Dr. N. Sprigg (Chief Investigator, TICH-2 Study).

2. ETHICAL AND REGULATORY ASPECTS

Before the study will be conducted, the protocol, the proposed patient information and consent form as well as other study-specific documents will be submitted to the EKNZ as the properly constituted regional Competent Ethics Committee (CEC) and to the competent authorities (e.g. Swissmedic) in agreement with local legal requirements, for formal approval. Any amendment to the protocol must as well be approved (if legally required) by these institutions.

The decision of the CEC and Swissmedic/foreign competent authority concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

This study is registered under NCT02866838 (Clinical trials.gov) and will be registered in the KOFAM registry of the BAG.

2.2 Categorisation of study

Acccording to Article 19 Categorisation of clinical trials of medicinal products of ClinO, this study is Category C.

2.3 Competent Ethics Committee (CEC)

The responsible investigator at each site will ensures approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the clinical study.

In Switzerland, the trial will be submitted to the “Ethikkomittee Nordwest- und Zentralschweiz” (EKNZ) as leading ethics committee for Switzerland.

Reporting duties and allowed time frame and no changes are made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.4 Competent Authorities (CA)

The Sponsor will obtain approval from the competent authority (e.g. Swissmedic) before the start of the clinical trial.

Reporting duties and allowed time frame to CA including the reporting duties in case of planned or premature study end and the final report are the same as for CEC, except of non-substantial amendments that shall be reported as soon as possible. Amendments are reported according to chapter 2.10.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

This study is funded by the Swiss National Science Foundation (SNF). The investigators report no other disclosures.

2.7 Patient Information and Informed Consent

In the pilot phase, the trial setting is in 6 public Stroke Centers in Switzerland (Aarau, Basel, Bern , Luzern, St. Gallen, Zürich). An extension to additional national or international centers after a pilot phase is intended.

Participants will be recruited from the stroke unit, emergency department or intensive care unit at the participating centers. The local investigator will inform the participant or their legal representative, of all aspects pertaining to participation in the study.

It will be explained to the potential participant or their legal representative that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. If patients are unable to consent themselves (for example due to severe neurological deficits including impaired consciousness or aphasia) they can be included in the study if there is no information available (for example patient decree) providing evidence that the patient does not want to participate in any scientific study. In this case, an independent doctor unrelated to the study will ensure patient's custody. If the patients will be able to provide informed consent themselves at a later time point during the study, a signed informed consent from the patients will be obtained. If it is likely that the patient will not be able to give informed consent throughout the whole study period, a legal representative will be contacted to obtain informed consent as to the patient's presumed will

It will also be explained that they can withdraw at any time. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

The participant will be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study.

The patient information sheet and the consent form will be submitted to the CEC and to the competent authority (as applicable) to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Anonymity of the participants is guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- safety concerns
- on advice of the DSMB

- alterations in accepted clinical practice that make the continuation of a clinical trial unwise

2.10 Protocol amendments

The principal investigators – on behalf of the steering committee - can amend the protocol. Communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, CEC, competent authorities, trial participants, trial registries, journals, regulators) will be assured as to the legal requirements.

Substantial amendments are only implemented after approval of the CEC and CA respectively.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC/CA. Such deviations shall be documented and reported to the sponsor and the CEC/CA as soon as possible.

All Non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Background NOAC

Long-term oral anticoagulation is beneficial for the treatment and prevention of various thromboembolic diseases. For years, Vitamin K-antagonists (VKA), that act as indirect anticoagulants which lower the functional level of different vitamin-K dependent coagulation factors, have been the only option for oral anticoagulation. In contrast, recently developed Non-Vitamin K antagonist oral anticoagulants (NOAC) target selected players in the coagulation cascade as the thrombin inhibitor dabigatran or the factor-Xa inhibitors apixaban, rivaroxaban and edoxaban[1, 2]. Onset of the anticoagulatory effect of NOACs is sudden (peak levels between 2 and 5 hours after intake) and anticoagulation lasts only for several hours to a few days while treatment with VKA results in a sustained, long lasting inhibition of the coagulation cascade[3]. Since 04/2012, NOAC are approved in Switzerland and widely used for prevention of stroke and systemic embolism in atrial fibrillation and prevention and treatment of venous thrombosis and pulmonary embolism. Further indications for stroke prevention in patients with embolic stroke of unknown source (ESUS) are under investigation (NCT02239120 and NCT02313909).

Intracerebral hemorrhage (ICH) is the most feared complication of anticoagulation treatment. There is no proven effective medical or surgical treatment option for ICH related to NOAC treatment (NOAC-ICH). Up to now, data on characteristics, management and outcome of NOAC-ICH is lacking. Nevertheless data on anticoagulation-associated ICH may be derived from patients on VKA that suffer ICH (VKA-ICH). Therefore, in the following, we summarize the current knowledge on VKA-ICH and draw conclusions by analogy to NOAC-ICH, whenever data about NOAC-ICH are not available or insufficient.

Intracerebral hemorrhage and anticoagulation

In VKA-ICH, initial hematoma volume is larger[4] than in patients not taking anticoagulants. In addition, growth of the initial hematoma volume over time - hematoma expansion (HE) - occurs more frequently (45% to 56%[5-7]) than in patients with ICH not associated with the use of anticoagulants (16% to 26%[5, 7]). Consequently, VKA-ICH leads to an increase in unfavourable functional outcome and mortality compared to ICH without prior anticoagulation[4, 7]. ICH related to anticoagulation increased from 5% of all ICH in the 1980s, to 11% in the 1990s, and up to 20% in the early 2000s[8, 9]. Recent data link early aggressive treatment using a combination of prothrombin complex (PCC) and fresh frozen plasma (FFP)[10] and fast INR-reversal within 4 hours and lowering of blood pressure[11] with improved outcome in VKA-ICH.

A reduced rate of intracerebral hemorrhages is reported for all NOAC compared to VKA[12]. Nevertheless, also in patients on NOAC intracerebral hemorrhage (NOAC-ICH) occurs in 0.52 to 0.78% per patient per year[12]. Little is known about management and outcome of patients with NOAC-ICH. Single case reports, one small single center retrospective study (n=5) and data extracted from the larger trials reported on frequent hematoma expansion, and a high case fatality rate[13-19].

Little is known about the HE-rate in NOAC-ICH. The to date largest study[20] found no difference in the HE-rates between NOAC-and VKA-ICH patients. None of the patients in the aforementioned study was treated with TA.

Treatment strategies for anticoagulation-associated ICH

For VKA-ICH, guidelines of the American[21] and the European Stroke Organisation[22] urge acute reversal of anticoagulation by administration of PCC or FFP and vitamin-K. But despite effective reversal (measured by INR normalization), hematoma expansion in VKA-ICH still occurs in 45% of patients and prognosis is poor[6] but fast and aggressive treatment is associated with improved outcome[10, 11]. Thus despite acute reversal of VKA-effect in ICH, there is a need for effective add-on treatments.

In NOAC-ICH, there are only limited data from rodent models[23-25] and no clinical data on treatment options[26].

Antidotes for NOAC

Recently, specific reversal agents for NOACs have been developed[27, 28] and are about to be licensed

for clinical use One study published testing ex vivo effect for a specific antibody against dabigatran – idarucizumab[27]. Further specific antidotes include andexanet alfa, a truncated form of enzymatically inactive factor Xa, which binds and reverses the anticoagulant action of the factor Xa inhibitors (e.g.: rivaroxaban, apixaban and edoxaban) and aripazine, a synthetic small molecule that reverses oral dabigatran, apixaban, rivaroxaban. The published data on idarucizumab and andexanet alpha showed promising pharmacological reversal of the measurable effect of NOACs in peripheral blood samples. One study[28] only included healthy individuals while 2 other studies included a mix of patients taking dabigatran[29] or factor Xa-inhibitors (Apixaban or Rivaroxaban)[30] respectively that suffered from major bleeding or needed urgent surgery. Patients with NOAC-ICH represented only a minority in both studies with 24 respectively 20 patients including in the majority patients with small (<10ml) to medium ICH-volumes. There were no comparison groups in both studies. Only few clinical outcome parameters from this single arm trials were published showing that, mortality was still high of up to 15-20%. None of the above mentioned planned or conducted trials includes clinical endpoints as primary outcome measure.

Combined use of antidots with tranexamic acid

In one ex vivo study investigating the effect of PCC compared to idarucizumab on coagulation parameters in an animal model of traumatic systemic bleeding with a prior intake of dabigatran, additional treatment with tranexamic acid was beneficial in both treatment regimens – PCC and idarucizumab[27].

Current European Stroke Organisation guidelines[22] published 2014 for the treatment of NOAC-ICH are based on theoretical considerations and expert opinions[31]. Due to the lack of evidence-based-data there is no recommendation for a specific treatment of NOAC-ICH.

Hematoma expansion – a surrogate marker for unfavourable outcome

Outcome after intracerebral hemorrhage is closely related to whether brain bleeding expands after onset, so called hematoma expansion (HE), and is associated with a poor outcome[32]. Especially, in the presence of oral anticoagulation hematoma volume is usually large and HE occurs frequently[4]. Observational studies report rates of HE ranging from 36% in patients with primary ICH (e.g. without prior treatment with anticoagulants) to 45-56% in patients on vitamin K-antagonists (VKA)[5-7]. In patients with ICH not-associated with anticoagulation, extravasation of contrast medium within the hematoma – the spot-sign – is a radiological biomarker to identify patients with a higher rate of HE of up to 61%[33]. There are no reports on the significance of the spot-sign in NOAC-ICH. HE is used as primary outcome measure in trials for ICH in spot-sign positive patients and treatment with tranexamic acid (NCT01702636, which excluded patients with NOACS)[34] or recombinant factor VIIa (NCT00810888) and as a secondary outcome measure in other trials in ICH.

Tranexamic acid

Tranexamic acid (TA) is an anti-fibrinolytic drug that can be administered intravenously or orally and is used in a number of bleeding conditions to reduce bleeding[35]. In a recent trial (CRASH-2) in 20,000 patients with major bleeding following trauma, TA significantly reduced mortality with no increase in vascular occlusive events[36]. Treatment was most effective when given rapidly; delayed administration was associated with lack of efficacy and potential harm. In a subgroup analysis of patients with traumatic intracerebral hemorrhage, TA showed a non-significant trend to reduced mortality and death of dependency[37]. However, patients in CRASH-2 were younger and had less co-morbidities than those with spontaneous intracerebral hemorrhage. A single-center randomized pilot-trial showed feasibility of rapid administration of TA in patients with intracerebral hemorrhage[38]. Since 2012, an investigator-initiated phase III trial (TICH-II) investigates whether TA is safe and reduces death and dependency after hyperacute (within 8 hours of onset) primary ICH (i.e. no prior treatment with anticoagulants)[39]. Patients with NOAC-ICH are excluded from this trial. In an animal model of traumatic systemic NOAC-bleeding, TA was given in addition to treatment with the specific antibody idarucizumab or PCC and was beneficial in both treatment regimes[27]. We therefore hypothesize that TA might be a beneficial treatment in NOAC-ICH.

3.2 Investigational Product

3.2.1 Description and Manufacture

Intravenous tranexamic acid (Cyklokapron, 100mg/ml 5ml ampoules, Pfizer Manufacturing Authorisation: PL 00057/0952) or matched placebo of intravenous Sodium Chloride 0.9% 5ml ampoules (Hameln, Manufacturing Authorisation: 1502 / 0006R). Tranexamic acid 100mg/ml 5ml ampoules are a licensed product and the summary of the product characteristics is available for investigator.

3.2.2 Blinding and unblinding procedure

The tailoring and randomisation of the study medication will be performed by the Hospital Pharmacy of the USB according to GMP. Each study medication package consists of either experimental or comparator using licensed and labelled products packed in an outer box which is blinded. The packed and therefore blinded study medication will be provided to the study team after randomization. An unblinded study nurse will prepare the study medication and administer it to the patient. The used vials are packed again in the outer box and sealed. In case of unblinding, the box with the used vials can be opened and assignment is visible.

3.2.3 Trial treatments

The treatments to be used in this trial are outlined below in Table 1:

Drug	***Dose***	***Administration***	***Route of Administration***	***Use***
Tranexamic acid (Cyklokapron)	2000 mg	Loading dose of 1000 mg in 100 ml normal saline over 10 minutes followed by 1000 mg in 250 ml normal saline as a continuous infusion over 8 hours	Intravenous	Experimental
Normal Saline	0,9 %	Loading dose of 10 ml in 100 ml normal saline over 10 minutes followed by 10 ml in 250 ml normal saline as a continuous infusion over 8 hours	Intravenous	Comparator

Table 1: Trial treatments

3.2.4 Packaging, Labelling and Supply (re-supply)

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of the study medication in accordance with the protocol and any applicable laws and regulations.

Product descriptions

Product name	***Potency***	***Dosage Form***
Tranexamic acid (Cyklokapron)	1000 mg / 10 ml	Solution for infusion
NaCl 0,9% Mini-Plasco Fresenius	0,9%	Solution for infusion

Study medication will be packed in an outer box and labelled in accordance with regulatory requirements. Labels for the infusion bags will also be packed in the outer box.

Receipt and dispensing of study medication must be recorded at the study site. Study medication must

not be used for any purpose other than that stated in the protocol.

3.2.5 Storage Conditions

Study medication must be stored in a secure, limited-access location under the storage conditions specified on the label

3.2.6 Known Side Effects

Gastrointestinal disorders (nausea, vomiting, diarrhoea) may occur but disappear when the dosage is reduced. Hypotension has occasionally been reported after rapid intravenous infusion. Rare instances of colour vision disturbances have been reported following long-term use. Rare cases of thromboembolic events have been reported. Rare cases of allergic skin reactions have also been reported (see Appendix A). Tranexamic acid will counteract the thrombolytic effect of fibrinolytic preparations but these would be contra-indicated in patients with haemorrhagic stroke.

3.3 Explanation for choice of comparator (or placebo)

The comparator of the IMP is placebo in addition to best medical treatment in a Stroke Center according to local SOPs following national and international guidelines. The trial steering committee encourages all investigators to evaluate the use of idaruzicumab for patients suffering ICH under dabigatran or andexanet alpha for patients suffering ICH under treatment with a factor Xa-inhibitor (edoxaban, rivaroxaban or edoxaban) if available. This approach guaranties that NOAC-ICH-patients participating on TICH-NOAC will have the chance to benefit from a potentially beneficial agent on top of state-of-the-art treatment, available for all participants.

3.4 Risks / Benefits

Benefit
Patients participating in TICH-NOAC may directly benefit from a potentially beneficial treatment (tranexamic acid) in addition to standard medical state-of-the-art treatment. This benefit can consist in a reduced rate of hematoma expansion and an improved clinical outcome.

Risks:
Patients may experience an increased risk for thromboembolic complications including ischemic stroke or deep venous thrombosis due to treatment with tranexamic acid although this risk was not elevated compared to placebo in prior trials involving tranexamic acid[36].

Trial Procedures
Patients suffering intracerebral haemorrhage under a prior treatment with a NOAC will be included in this study shortly after admission to a participating center and after informed consent has been obtained (see page 17). After inclusion, patients will receive two intravenous infusions containing either tranexamic acid or placebo (a bolus containing of 100ml over 10 minutes followed by a 8 hours infusions of 250ml). 24 hours after admission, a single run non-contrast CT head scan will be performed (day 2). Patients will be followed up in-hospital until day 7/discharge with a final outpatient follow-up at 90 days. If patients are unable to come for the follow-up visit to the study center, a telephone interview with the patient or care giver will be performed.

Details of radiation materials and dose
The doses from CT scans will vary between sites with different models of equipment and between different sizes of patient.
A CT of the brain will give an average of 1.5mSv but this could be up to a maximum of 5mSv. So a typical dose from CT due to research exposures would be 1.5mSv, but could be as high as 5mSv.
A 1.5mSv dose would be roughly equivalent to 8 months of exposure to natural background radiation to a member of the public resident in Switzerland. A 5mSv dose is roughly equivalent to 2¼ years of background received by a member of the public resident in Switzerland.
A follow-up CT-scan is often performed also in clinical routine, in order to search for either (i) HE or (i) complications such as intraventricular expansion or hydrocephalus which is important for management

and prognosis. Thus participation in TICH-NOAC must not necessary mean an exposition to additional radiation. Contrast agents are not involved in the study CT-scan at follow-up.

Risk Assessment (induction of fatal cancer)
Based on a risk coefficient for developing fatal radiation induced cancer (all ages) of 5%/Sv (ICRP), this would lead to a risk of radiation exposure incurred as part of the trial similar to the annual risk of dying from an accident in the home. This is classed as an intermediate risk and the required benefit should be aimed directly at diagnosis, cure or prevention of disease.

4. STUDY OBJECTIVES

4.1 Overall Objective

To demonstrate that treatment with TA for NOAC-ICH is beneficial. The results of this trial will determine whether TA should be used for the treatment of NOAC-ICH.

4.2 Primary Objective

The primary objective is to show that treatment with TA in patients with NOAC-ICH reduces the rate of HE as a surrogate marker for unfavourable outcome.

4.3 Secondary Objectives

Secondary objectives of this trial are to show that treatment with TA for NOAC-ICH increases the proportion of patients having a favourable clinical outcome and to show that TA influences hematoma expansion in different definitions.

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary outcome measure is hematoma expansion (HE). In line with prior research[33], HE is defined as an increase of 33% relative or 6ml absolute growth between ICH-volume on baseline CT and on follow-up-CT at 24 ± 3 hours.

5.2 Secondary Outcomes

Secondary outcome measures are

(I) modified Rankin Scale (mRS) 0–4 at three-months;
(II) mRS 0–3 at three-months;
(III) Categorical shift in mRS at three-months;
(IV) Absolute ICH growth volume by 24 ± 3 hours, adjusted for baseline ICH volume;
(V) Symptomatic HE defined as HE and neurological deterioration of NIHSS >4 points or GCS >2 points
(VI) Death due to any cause by three-months;
(VII) major thromboembolic events (myocardial infarction, ischemic stroke, pulmonary embolism – safety endpoints)
(VIII) NCH intervention (including craniectomie, EVD, hematoma evacuation)
(IX) In-hospital mortality

6. STUDY DESIGN

6.1 General study design and justification of design

This trial is a randomized, controlled, double-blinded, placebo-controlled phase IIb/III trial investigating whether tranexamic acid is beneficial for the treatment of NOAC-ICH. Up to now, no evidence proven treatment for NOAC-ICH exists. The trial will be performed in 7 Swiss Stroke Centers recruiting 109 patients. Extension to international centers is intended.

6.2 Methods of minimising bias

Patients recruited in this trial will be randomly allocated 1:1 to receive either tranexamic acid (TA) or placebo. Evaluation of the primary outcome parameter (HE) will be done by 3 independent raters blinded to study treatment.

6.2.1 Randomisation

Patients will be randomly allocated to TA or placebo in a 1:1 ratio. Randomisation will be performed by central computer over the Internet using the eCRF. The investigators will record patient details via a secure web interface before randomisation takes place. Investigators may also contact the Trial Coordinating Centre via the 24-hours help-line.

The randomisation procedure will include a standard minimisation algorithm which will ensure that the treatment groups are balanced for key prognostic factors, such as sex, age, NIHSS score on admission and use of specific antidote treatment. To avoid predictable alternation of treatment allocation, and thus potential loss of allocation concealment, patients will be allocated with a probability of 0.80 to the treatment group that would minimise the difference between the groups on the key prognostic factors.

7. STUDY POPULATION

Consecutive patients admitted to one of the participating stroke centers are enrolled according to the following inclusion and exclusion criteria:

7.1 Eligibility criteria

Inclusion criteria:

- Acute intracerebral haemorrhage
- Prior treatment with a non-vitamin K antagonist oral anticoagulant (NOAC: apixaban, dabigatran, edoxaban or rivaroxaban; last intake <48hours OR proven* NOAC activity by relevant coagulation assays))
- Time of onset <12 hours (or in patients with unknown time of symptom onset, the time patient was last known to be well divided by 2)
- Age >18 years, No upper age limit
- Informed consent has been received in accordance to local ethics committee requirements

*proven NOAC activity is defined as measurable NOAC plasma levels with a suitable specific coagulation test (calibrated anti-factor Xa activity, escarin clotting time) if available.

Exclusion criteria:

- Severe pre-morbid disability (modified Rankin scale >4)
- Anticoagulation with VKA
- Secondary intracerebral hemorrhage (e.g., AVM, tumor) Note it is not necessary for investigators to exclude underlying structural abnormality prior to enrolment, but where an underlying structural abnormality is already known, these patients should not be recruited.
- Glasgow coma scale <5
- pregnancy
- Planned neurosurgical hematoma evacuation within 24 hours (before follow-up imaging)
- Recent pulmonary embolism/deep vein thrombosis within the last 2 weeks

7.2 Recruitment and screening

Patients will be recruited at the participating centers from the acute stroke unit or emergency department. Patients will be approached from a member of the patient's usual care team (which may include investigators). Local investigators or their nominee will inform the participant or their legal representative, of all aspects pertaining to participation in the study. It will be explained to the potential participant or their legal representative that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate. If patients are unable to consent themselves (for example due to severe neurological deficits including impaired consciousness or aphasia) they can be included in the study if there is no information available (for example patient decree) providing evidence that the patient does not want to participate in any scientific study. In this case, an independent doctor unrelated to the study will ensure patient's custody. If the patients will be able to provide informed consent themselves at a later time point during the study, a signed informed consent from the patients will be obtained. If it is likely that the patient will not be able to give informed consent throughout the whole study period, a legal representative will be contacted to obtain informed consent as to the patient's presumed will.

7.3 Assignment to study groups

Patients will be randomly assign 1:1 one to receive either Tranexamic acid or placebo by a web-based randomization tool.

7.4 Criteria for withdrawal / discontinuation of participants

Participation in the trial is voluntary and patients are free to withdraw from the trial at any stage without

giving a reason. Study medication may be stopped at any time by the investigators or any treating clinician if deemed in the patient's best interest. Treatment (with tranexamic acid/placebo) will be given on top of 'best medical care'. Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis. Enrolled participants who withdraw before randomisation can be replaced (though keeping their trial ID), but participants who withdraw after randomisation will not be replaced.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products (treatment)

IMP means intravenous tranexamic acid (1g loading dose given as 100 ml infusion over 10 minutes, followed by another 1g in 250 ml infused over 8 hours) or as comparator placebo (normal saline 0.9%) administered by identical regimen.

8.1.1 Experimental Intervention (treatment)

IMP means intravenous tranexamic acid (1g loading dose given in 100 ml infusion over 10 minutes, followed by another 1g in 250 ml infused over 8 hours)

8.1.2 Control Intervention (comparator treatment)

Control intervention means intravenous saline 0.9% (10ml NaCl 0.9% in 100 ml given as loading dose infusion over 10 minutes, followed by another 250 ml NACL 0.9% infused over 8 hours)

8.1.3 Packaging, Labelling and Supply (re-supply)

The web-based system operates as follows: Participating centres will be allocated a batch of trial treatment. The container numbers for these batches are tracked by the web-based system to the participating site and once receipt has been confirmed they are released for use in the trial. When the supplies at the participating centre reach a pre-determined level then a re-order is triggered and a further supply of trial treatment is sent to the corresponding participating site.

8.1.4 Storage Conditions, dispense and return

The packs will be stored at room temperature and protected from excessive heat and freezing in a restricted access area. Stability data exists which demonstrates that Tranexamic Acid is stable at temperatures between -20°C and 50°C. Temperature monitoring will not be required. The IMP will be clearly labelled for clinical trial use only. Each pack will be a numbered box containing either tranexamic acid or placebo according to a computer-defined sequence.

The local site investigator is responsible for ensuring trial treatment accountability, including reconciliation of trial treatment and maintenance of trial treatment records, throughout the course of the study in accordance with local regulatory requirements. Responsibility can be delegated to the site pharmacy clinical trials staff.

Following randomisation the participant will be allocated a treatment pack number. Specifically authorised personnel will retrieve the appropriate pack number and complete the participant name, date of randomisation and participant number. Pack number allocation will be checked and countersigned by the research staff and the nursing staff administering the treatment. The treatment will be prescribed on the participant's treatment chart as trial medication. The nurse administrating the study treatment is unblinded, which represents a potential bias. Nevertheless, all personal will receive order not to communicate to anybody the treatment and whether it contains tranexamic acid or placebo. Nursing staff administrating the treatment is not involved in the evaluation of any outcome parameters.

Dispensing will be recorded on the appropriate trial specific accountability forms. Trial treatment must not be used for any other purpose than the present study. Returned trial treatment that has been dispensed to a participant must not be re-dispensed to a different participant. Any unused drug will be returned to pharmacy.

8.2 Compliance with study intervention

Compliance with study intervention will be monitored by checking prescription drug charts. The pharmacist will maintain records of the dispensing of the drug and the research nurse will record administration of the drug to the patient. Dispensing details will be recorded on each participant's CRF. Unused and partially used supplies will be returned to pharmacy. This will be recorded in the pharmacy study log.

9. STUDY ASSESSMENTS

Participants will be assessed before treatment (day 1), after treatment (day 2), after 7 days, at death/discharge and 90 days. See flow chart for more details.

Patients will be assessed clinically at baseline in line with local clinical practice prior to inclusion (day 1), end of treatment (day 2), on day 7 and at discharge/death (in hospital – if death/discharge occurs before day 7 visit, both visits are performed simultaneously). Follow up at day 90 (+/- 14 days) will be via a clinical outpatient visit or – if the patients' functional status does not allow outpatient visit – by a structured telephone interview with the patient, next-to-kin or other care-giver.
Brain imaging (CT head scan) will be performed as part of routine clinical management prior to enrolment (all acute stroke patients have a CT head scan performed on admission to hospital). For the purpose of the study the CT head scan will be repeated after treatment, day 2, (tranexamic acid/placebo) to assess haematoma expansion. A day 2 CT scan for patients with intracerebral haemorrhage is part of standard care in many stroke centers. In this case, routine day 2 CT scan can be used for trial purpose and no additional CT scan is required. If a patient received MRI scan on admission as first neuroimaging, the patient will undergo a baseline CT scan after inclusion in the trial to assure that hematoma expansion can be measured correctly and is comparable throughout all patients included in the study.

9.1 Study flow chart(s) / table of study procedures and assessments

Study Periods	Screening	Randomisation /Treatment	Follow-up			
Visit	1	2	3	4	5	6
day	1	1	2	7 (+/- 24h)	Death/ discharge	90 (+/- 14 days)
Patient Information and Informed Consent	x					
Demographics	x					
Medical History	x					
In- /Exclusion Criteria	x					
NIHSS	x		x	x		x
Vital Signs (RR, heart rate)	x		x	x		x
Laboratory Tests	x*					
Pregnancy Test#	x					
Randomisation		x				
CT scan	x*	x[1]	x			
Study treatment		x				
mRS	x		x	x	x	x
Secondary outcome variables						x
Concomitant Therapy, Intervention		x	x	x	x	
Adverse Events		x	x	x	x	x

NIHSS: National Institute of Health Stroke Severity Scale; mRS: modified Rankin Scale Score; CT: computer tomography

* routine CT scan/laboratory test

in woman of childbearing age

1only if no baseline-CT scan performed as part of routine-work up (for example baseline brain imaging

is MRI)

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

Evaluation of hematoma volume and hematoma expansion will be based on 2 CT scans. All participants at one center will be evaluated with identical imaging protocols at baseline and follow-up. The first CT scan is part of clinical routine. The follow-up scan on day 2 will be part of the study protocol (if not performed in routine clinical care). If a patient received MRI scan on admission as first neuroimaging, the patient will undergo a baseline CT scan after inclusion in the trial to assure that hematoma expansion can be measured correctly and is comparable throughout all patients included in the study.

In line with prior research[33], hematoma expansion (HE) is defined as an increase of 33% relative or 6ml absolute growth between ICH-volume on baseline CT and on follow-up-CT at 24 ± 3 hours.
All images will be evaluated independently by a rater blinded to treatment and outcome (experienced stroke neurologist/neuroradiologst) at the imaging core lab in Basel.

Any intraventricular hemorrhage (IVH) components will not be included in ICH volumes. In addition, presence or absence of the spot-sign[33] on baseline CT-scan will be assessed in the core lab.

Semi-automatic segmentation by region growing will be performed using the Aquarius software (Version 4.4.8) by Terarecon. The target region (hematoma) will be selected manually and region growing in full resolution and medium connectivity will be done automatically (region growing is spherical from seed point with regard to houndsfield units connected to seed point). Finally, segmentation and identified hematoma in three planes will be controlled manually. Target volumetry will be calculated automatically of the segmented area by the software and will result in a volume given in cm3.

9.2.2 Assessment of secondary outcomes

The following secondary outcome measures are assessed at day 90 and day 365 visit: (I) modified Rankin Scale (mRS) 0–4; (II) mRS 0–3; (III) Categorical shift in mRS; (IV) Death due to any cause.

The following secondary outcome measures are assessed based on the day 2 CT-scan: (V) Absolute ICH growth volume by 24 ± 3 hours, adjusted for baseline ICH volume; (VI) Symptomatic HE defined as HE and neurological deterioration of NIHSS >4 points or GCS >2 points

9.2.3 Assessment of safety outcomes

Throughout the study, information on the following safety outcome events will be collected at each visit: major thromboembolic events (myocardial infarction, ischemic stroke, pulmonary embolism)

9.2.3.1 Adverse events

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.

An AE does include a / an:

1. Exacerbation of a pre-existing illness.
2. Increase in frequency or intensity of a pre-existing episodic event or condition.
3. Condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.
4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

An AE does not include a / an:

1. Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.
2. Pre-existing disease or conditions present or detected at the start of the study that did not worsen.
3. Situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. Disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.
5. Overdose of concurrent medication without any signs or symptoms.

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the IMP or placebo that results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalisation or prolongation of existing hospitalisation
4. A disability / incapacity
5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious. Serious adverse events are common in haemorrhagic stroke, for a full list of expected SAE that are not subject to expedited reporting, investigators should refer to Appendix A.

As the IMP is administered once and has a short half-life, serious adverse events occurring within the first 7 days will be assessed for seriousness, expectedness and causality. In addition fatal SAEs and safety outcome events (VTE, recurrent stroke, TIA, MI, PAD and seizures) will be reported until day 90.

9.2.4 Causality and reporting

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation. This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Drug Reaction. With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Participants will be asked to contact the study site immediately in the event of any serious adverse event. All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. The Chief Investigator (delegated the sponsor's responsibilities) shall be informed immediately (within 24 hours) of any serious adverse events, occurring within the first 7 days and shall determine seriousness and causality in conjunction with any treating medical practitioners. Reporting of SAE to the competent EC will be done in accordance with Swiss laws.

10. SAFETY

During hospitalisation in the participating center until day 7, all adverse events (AE) and all serious adverse events (SAEs) are collected, fully investigated and documented in source documents and case report forms (CRF). After discharge from the participating hospital and/or day 7 (what occurs first), only study outcome events (death, ischemic vascular events) are collected as SAE until end of study. Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed.

10.1.1 Reporting of SAEs

All SAEs must be reported immediately and within a maximum of 24 hours to the Sponsor-Investigator of the study. The Sponsor-Investigator will re-evaluate the SAE and return the form to the site.

SAEs resulting in death are reported to the local Ethics Committee (via local Investigator) within 7 days. The other in the trial involved Ethics Committees receive SAEs resulting in death in Switzerland via Sponsor-Investigator within 7 days using the BASEC account.

Exemptions from expedited reporting may be possible if the SAE is either a clear result of the underlying disease or well-known and described in the currently approved product information.

10.1.2 Reporting of SUSARs

A SUSAR needs to be reported to the local Ethics Committee (via Sponsor-Investigator in Switzerland using BASEC) and to Swissmedic (via Sponsor-Investigator) within 7 days, if the event is fatal, or within 15 days (all other events).

The Sponsor-Investigator will inform all Investigators participating in the clinical study of the occurrence of a SUSAR. All in the trial involved Ethics Committees will be informed about SUSARs in Switzerland via Sponsor-Investigator according to the same timelines.

11. STATISTICAL METHODS

A detailed Statistical Analysis Plan will be drawn up before breaking the randomisation code.

11.1 Hypothesis

The null hypothesis (H0) is that tranexamic acid does not alter HE in participants with acute NOAC-ICH. The alternative hypothesis (HA) is that HE differs between those participants randomised to tranexamic acid versus placebo.

11.2 Determination of Sample Size

There exists no retrospective or prospective study reporting rates of HE in NOAC-ICH. Based on the largest available studies investigating HE in anticoagulation-related ICH ranging from 54-56% in VKA-ICH we estimate a 54% rate of HE in placebo NOAC-ICH patients.

As there are no previous trial data on the effect of TA in NOAC-ICH, we base our sample size estimate on feasible recruitment rates and use an adaptive sample size procedure as done in prior research. Estimating a rate of 27% of HE in NOAC-ICH patients receiving TA, we provisionally plan our sample size at 109 patients. This yields 80% power to detect a significant absolute difference in the proportion of patients with hematoma enlargement at 24 h at a two-sided statistical significance threshold of P = 0·05.

Justified by lack of previous efficacy data, adaptive increase in sample size is planned. An interims analysis of the primary endpoint is performed using data from the first 82 patients. As described in Mehta &Pocock the sample size is increased if and only if the results of the interim analysis are 'promising' (i.e. power is in the predefined 'promising' range). In the interims analysis conditional power is evaluated and if it falls within the prespecified 'promising' range between 0.33 - 0.8, the sample size will be increased to increase the conditional power to 0.8 level, but at most to the predetermined upper limit of 218 patients. With a sample size of 218 patients, the trial should detect with 80% power an incidence rate in relevant hematoma expansion under TA of 35 % assumed a drop-out rate of 5 % and an incidence rate of 54 % under placebo. If the estimated sample size exceeds 218, continuation of the trial will be discussed with the CIs and the steering committee. The final decision to increase the sample size or stop the trial prematurely will be taken by the CIs and the steering committee.

11.3 Statistical criteria of termination of trial

The DSMC will recommend to the TSC that the trial be stopped if there is proof beyond reasonable doubt (with a 99% CI) of overall benefit with the active treatment or if there is a lower level of evidence suggesting overall hazard. Evidence of hazard will include effect on the primary outcome (HE) and analysis of safety endpoints, as specified in the protocol (death, VTE, ischaemic events, seizures, serious adverse events).

11.4 Planned Analyses

Analysis will by intention-to-treat; Missing outcome data will be inputed assuming worst possible outcome.

The primary outcome (HE) is be compared between treatment and control arms adjusted for baseline volume using binary logistic regression. Although both baseline covariate adjusted and unadjusted results will be reported, baseline covariate adjusted analysis is prespecified as the primary outcome analysis for this trial.

As secondary outcome analyses, the proportions of mRS 0–4, mRS 0–3, and mortality outcomes will be compared between active and placebo arms of the trial adjusted for baseline volume using a binary logistic regression model. Analysis of the categorical shift in mRS will also be undertaken on the full range of the mRS using the Cochran–Mantel–Haenszel shift test and proportional odds logistic regression, subject to the validity of shift analysis model assumptions. Other secondary outcome analyses will be carried out according to standard statistical principles for comparison of parametric or nonparametric distributions as appropriate.

Exploratory analysis will be run on the primary and secondary outcomes, with adjustments for baseline

variables such as age, Glasgow coma scale (GCS), presence of IVH, and ICH location, and in the following subgroups: onset-to-treatment time (<six vs. >six-hours), baseline ICH volume (<30 vs. >30 ml), anatomical location (deep, lobar, or cerebellar), IVH (absent vs. present), GCS (>12 vs. 8–12), and age (<70 vs. >70), presence of spot-sign. These analyses will be hypothesis generating, as the trial is not powered for them.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

All patients will be assigned a unique code number. The patient data will be linked to this number, and the patients' names or other personal identifiers will not be included in the database. The patient database will be kept on a separate, secure computer. The code will be stored on another, secure computer, and will be deleted 15 years after the results of the trial have been published. The trial's procedures for data protection will conform to the Swiss applicable regulatory requirements, and to the conditions set by the Swiss Data Inspectorate.

12.1.1 Case Report Forms

Patients' data will be collected using a web-based electronic case report form located at the Clinical Trial Unit in Basel. Case report forms will be filled in by local investigators.

12.1.2 Specification of source documents

Source data must be available at the site to document the existence of the study participants. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

12.1.3 Record keeping / archiving

All study data must be archived for a minimum of 10 years after study termination or premature termination of the clinical trial.

12.2 Monitoring

During the course of the trial the Data Safety and Monitoring Board (DSMB) will after recruitment of 50% and 80% of the trial population perform an review of SAEs, in all patients; in case of concerns, unblinding will be requested. If, in their view, there is credible evidence of harm, or overwhelming evidence of efficacy, the committee will advise the CIs. Unless this happens, the CIs and the Steering Committee will remain ignorant of all interim results.

The DSMB will also be responsible for monitoring the overall conduct of the trial, and may formulate recommendations relating to the selection, recruitment, or retention of participants, or their management, or to improving their adherence to protocol-specified regimens, and the procedures for data management and quality control.

12.3 Audits and Inspections

The study documentation and the source data/documents are accessible to auditors/inspectors (also CEC and CA) and questions are answered during inspections. All involved parties must keep the participant data strictly confidential.

12.4 Confidentiality, Data Protection

Direct access to source documents will be permitted for purposes of monitoring, audits and inspections.

13. PUBLICATION AND DISSEMINATION POLICY

The trial will be published in accordance with the CONSORT guidelines and will be presented by a writing committee on behalf of the investigators. All participating centres and collaborators will be acknowledged in the main publication. The primary results and results of any substudies will be presented at international meetings and in public media.

14. FUNDING AND SUPPORT

This study is funded by a grant from the Swiss National Science Foundation (grant no: 32003B_163378)

15. INSURANCE

Insurance will be provided by the Sponsor. A copy of the certificate is filed in each investigator site file and the trial master file.

16. REFERENCES

1. Alberts MJ, Eikelboom JW, Hankey GJ. Antithrombotic therapy for stroke prevention in non-valvular atrial fibrillation. *Lancet Neurol*. 2012;11:1066-1081
2. Weitz JI. New oral anticoagulants: A view from the laboratory. *American journal of hematology*. 2012;87 Suppl 1:S133-136
3. Eriksson BI, Quinlan DJ, Eikelboom JW. Novel oral factor xa and thrombin inhibitors in the management of thromboembolism. *Annual review of medicine*. 2011;62:41-57
4. Flaherty ML, Tao H, Haverbusch M, Sekar P, Kleindorfer D, Kissela B, et al. Warfarin use leads to larger intracerebral hematomas. *Neurology*. 2008;71:1084-1089
5. Cucchiara B, Messe S, Sansing L, Kasner S, Lyden P. Hematoma growth in oral anticoagulant related intracerebral hemorrhage. *Stroke*. 2008;39:2993-2996
6. Dowlatshahi D, Butcher KS, Asdaghi N, Nahirniak S, Bernbaum ML, Giulivi A, et al. Poor prognosis in warfarin-associated intracranial hemorrhage despite anticoagulation reversal. *Stroke*. 2012;43:1812-1817
7. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. *Neurology*. 2004;63:1059-1064
8. Bejot Y, Cordonnier C, Durier J, Aboa-Eboule C, Rouaud O, Giroud M. Intracerebral haemorrhage profiles are changing: Results from the dijon population-based study. *Brain : a journal of neurology*. 2013;136:658-664
9. Lovelock CE, Molyneux AJ, Rothwell PM. Change in incidence and aetiology of intracerebral haemorrhage in oxfordshire, uk, between 1981 and 2006: A population-based study. *Lancet Neurol*. 2007;6:487-493
10. Parry-Jones AR, Di Napoli M, Goldstein JN, Schreuder FH, Tetri S, Tatlisumak T, et al. Reversal strategies for vitamin k antagonists in acute intracerebral hemorrhage. *Annals of neurology*. 2015;78:54-62
11. Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres M, Sobesky J, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA : the journal of the American Medical Association*. 2015;313:824-836
12. Chatterjee S, Sardar P, Biondi-Zoccai G, Kumbhani DJ. New oral anticoagulants and the risk of intracranial hemorrhage: Traditional and bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation. *JAMA neurology*. 2013;70:1486-1490
13. Faust AC, Peterson EJ. Management of dabigatran-associated intracerebral and intraventricular hemorrhage: A case report. *The Journal of emergency medicine*. 2014;46:525-529
14. Hagii J, Tomita H, Metoki N, Saito S, Shiroto H, Hitomi H, et al. Characteristics of intracerebral hemorrhage during rivaroxaban treatment: Comparison with those during warfarin. *Stroke*. 2014;45:2805-2807
15. Hankey GJ, Stevens SR, Piccini JP, Lokhnygina Y, Mahaffey KW, Halperin JL, et al. Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: The rivaroxaban once daily, oral, direct factor xa inhibition compared with vitamin k antagonism for prevention of stroke and embolism trial in atrial fibrillation. *Stroke*. 2014;45:1304-1312
16. Hart RG, Diener HC, Yang S, Connolly SJ, Wallentin L, Reilly PA, et al. Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: The re-ly trial. *Stroke*. 2012
17. Kasliwal MK, Panos NG, Munoz LF, Moftakhar R, Lopes DK, Byrne RW. Outcome following intracranial hemorrhage associated with novel oral anticoagulants. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia*. 2015;22:212-215
18. Simonsen CZ, Steiner T, Tietze A, Damgaard D. Dabigatran-related intracerebral hemorrhage resulting in hematoma expansion. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. 2014;23:e133-134
19. Wassef SN, Abel TJ, Grossbach A, Viljoen SV, Jackson AW, Howard MA, 3rd, et al. Traumatic

intracranial hemorrhage in patients taking dabigatran: Report of 3 cases and review of the literature. *Neurosurgery*. 2013;73:E368-373; discussion E373-364

20. Wilson D, Seiffge DJ, Traenka C, Basir G, Purrucker JC, Rizos T, et al. Outcome of intracerebral hemorrhage associated with different oral anticoagulants. *Neurology*. 2017
21. Morgenstern LB, Hemphill JC, 3rd, Anderson C, Becker K, Broderick JP, Connolly ES, Jr., et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2010;41:2108-2129
22. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, et al. European stroke organisation (eso) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke*. 2014
23. Lauer A, Cianchetti FA, Van Cott EM, Schlunk F, Schulz E, Pfeilschifter W, et al. Anticoagulation with the oral direct thrombin inhibitor dabigatran does not enlarge hematoma volume in experimental intracerebral hemorrhage. *Circulation*. 2011;124:1654-1662
24. Zhou W, Schwarting S, Illanes S, Liesz A, Middelhoff M, Zorn M, et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. *Stroke*. 2011;42:3594-3599
25. Zhou W, Zorn M, Nawroth P, Butehorn U, Perzborn E, Heitmeier S, et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with rivaroxaban. *Stroke*. 2013;44:771-778
26. Lauer A, Pfeilschifter W, Schaffer CB, Lo EH, Foerch C. Intracerebral haemorrhage associated with antithrombotic treatment: Translational insights from experimental studies. *Lancet Neurol*. 2013;12:394-405
27. Honickel M, Treutler S, van Ryn J, Tillmann S, Rossaint R, Grottke O. Reversal of dabigatran anticoagulation ex vivo: Porcine study comparing prothrombin complex concentrates and idarucizumab. *Thromb Haemost*. 2015;113
28. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet alfa for the reversal of factor xa inhibitor activity. *N Engl J Med*. 2015
29. Pollack CV, Jr., Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373:511-520
30. Connolly SJ, Milling TJ, Jr., Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al. Andexanet alfa for acute major bleeding associated with factor xa inhibitors. *N Engl J Med*. 2016
31. Steiner T, Bohm M, Dichgans M, Diener HC, Ell C, Endres M, et al. Recommendations for the emergency management of complications associated with the new direct oral anticoagulants (doacs), apixaban, dabigatran and rivaroxaban. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2013;102:399-412
32. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28:1-5
33. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, Molina CA, Blas YS, Dzialowski I, et al. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the ct-angiography spot sign (predict): A prospective observational study. *Lancet Neurol*. 2012;11:307-314
34. Meretoja A, Churilov L, Campbell BC, Aviv RI, Yassi N, Barras C, et al. The spot sign and tranexamic acid on preventing ich growth - australasia trial (stop-aust): Protocol of a phase ii randomized, placebo-controlled, double-blind, multicenter trial. *Int J Stroke*. 2014;9:519-524
35. Dunn CJ, Goa KL. Tranexamic acid: A review of its use in surgery and other indications. *Drugs*. 1999;57:1005-1032
36. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (crash-2): A randomised, placebo-controlled trial. *Lancet*. 2010;376:23-32
37. Effect of tranexamic acid in traumatic brain injury: A nested randomised, placebo controlled trial (crash-2 intracranial bleeding study). *BMJ (Clinical research ed.)*. 2011;343:d3795
38. Sprigg N, Renton CJ, Dineen RA, Kwong Y, Bath PM. Tranexamic acid for spontaneous intracerebral hemorrhage: A randomized controlled pilot trial (isrctn50867461). *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. 2014

39. Sprigg N, Robson K, Bath P, Dineen R, Roberts I, Robinson T, et al. Intravenous tranexamic acid for hyperacute primary intracerebral hemorrhage: Protocol for a randomized, placebo-controlled trial. *Int J Stroke*. 2016