International multicentre trial protocol to assess the efficacy and safety of tenecteplase during cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest: The Thrombolysis in Cardiac Arrest (TROICA) Study


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Abstract

Prehospital cardiac arrest has been associated with a very poor prognosis. Acute myocardial infarction and massive pulmonary embolism are the underlying causes of out-of-hospital cardiac arrest in 50–70% of patients. Although fibrinolysis is an effective treatment strategy for both myocardial infarction and pulmonary embolism, clinical experience for this therapy performed during resuscitation has been limited owing to the anticipated risk of severe bleeding complications. The TROICA study is planned as one of the largest randomized, double-blind, placebo-controlled trials to assess the efficacy and safety of prehospital thrombolytic therapy in cardiac arrest of presumed cardiac origin. Approximately 1000 patients with cardiac arrest will be randomized at approximately 60 international study centres to receive either a weight-adjusted dose of tenecteplase or placebo after the first dose of a vasopressor. Patients can be included if they are at least 18 years, presenting with a witnessed cardiac arrest of presumed cardiac origin, and if either basic life support had started within 10 min of onset and had been performed up to 10 min or advanced life support is started within 10 min of onset of cardiac arrest. Primary endpoint of the study is the 30-day survival rate, and the coprimary endpoint is hospital admission. Secondary endpoints are the return of spontaneous circulation (ROSC), survival after 24 h, survival to hospital discharge, and neurological performance. Safety endpoints include major bleeding complications and symptomatic intracranial haemorrhage.

Keywords Cardiopulmonary resuscitation, clinical study, myocardial infarction, prehospital, pulmonary embolism, randomized, thrombolysis.

Introduction

Clinical and experimental background

The prognosis of patients suffering out-of-hospital cardiac arrest is generally poor and has not improved substantially [1–4]. For example, except for administration of mild therapeutic hypothermia in selected patients after cardiac arrest, no specific treatment option has been shown to improve neurological outcome in these patients [5]. In approximately 50% to greater than 70% of patients requiring resuscitation after out-of-hospital cardiac arrest, the event is caused either by acute myocardial infarction or by massive pulmonary embolism and, thus, intravascular thrombosis [6,7]. Although thrombolytic therapy is an effective treatment strategy for both of these disease entities [8,9], it has been relatively contraindicated owing to the anticipated high risk of severe bleeding complications associated with cardiopulmonary resuscitation (CPR) procedures [10,11]. Numerous clinical case reports and small case series have suggested that fibrinolysis during CPR can contribute to haemodynamic stabilization and long-term survival in patients suffering cardiac arrest following suspected acute myocardial infarction or massive pulmonary embolism [12]. Moreover, an unusual proportion of patients in these reports survived prolonged periods of cardiac arrest and CPR without any or only minor neurological deficits [4,13]. This may be owing to the fact that, after cardiac arrest, reperfusion is associated with a marked and disseminated intravascular activation of blood coagulation without adequate activation of endogenous fibrinolysis and, thus, with intravascular clotting and fibrin formation [14–16]. Therefore, besides representing a causal therapeutic approach in acute myocardial infarction and pulmonary embolism, fibrinolysis during CPR may result in a general improvement in microcirculatory flow throughout the entire organism, including cerebral reperfusion [17].

In a prospective clinical trial, patients undergoing CPR after out-of-hospital cardiac arrest of cardiac origin were treated with a bolus of 5000 U of heparin and a 50-mg injection over 2 min of tissue-type plasminogen activator (rt-PA) after 15 min of unsuccessful CPR. This intervention was repeated if return of spontaneous circulation was not achieved within the following 30 min. In the rt-PA group (n = 40) return of spontaneous circulation (ROSC) was achieved in 68%, and 58% of patients were admitted to a cardiac intensive care unit, as compared with 44% (P = 0.026) and 30% (P = 0.009) of controls (n = 50), respectively. At 24 h after cardiac arrest 35% of rt-PA-treated patients (vs. 22% of controls; P = 0.171) were still alive, and 15% of rt-PA-treated patients (vs. 8% of controls) were discharged alive from the hospital. Thus, following initially unsuccessful out-of-hospital CPR, thrombolytic therapy combined with heparin seemed to be safe and to improve patient survival. Similar data have been published by an Austrian group, which retrospectively reported on 108 patients treated with fibrinolysis during out-of-hospital CPR [18]. Return of spontaneous circulation occurred more often in patients treated with rt-PA (70.4 vs. 51.0% in controls; P = 0.001). Fifty-two patients from the fibrinolysis group survived the first 24 h (48.1 vs. 32.9% in controls; P = 0.003), while 27 (25.9%) survived to discharge. In a prospective uncontrolled multicentre in-hospital observational trial, Kleiner and colleagues showed that empirical fibrinolysis using tenecteplase in 30 patients with cardiac arrest was associated with ROSC, hospital discharge, and good neurological function [19]. Recently, a randomized, double-blind placebo-controlled in-hospital trial on fibrinolysis during CPR showed that treatment of 35 patients who had been resuscitated unsuccessfully in a prehospital setting with tenecteplase was associated with ROSC (42% vs. 6% in the placebo group) [20]. In contrast to these clinical studies, a randomized study comparing fibrinolysis during CPR vs. standard treatment in 233 patients presenting with prehospital cardiac arrest and pulseless electrical activity did not show a benefit of thrombolytic therapy [21]. However, selection of a group of patients with an exceptionally poor prognosis, late administration of thrombolytic treatment and a control group without any survivor allowed no conclusive interpretation of fibrinolysis during CPR by these data [22].

Safety of thrombolytic therapy during resuscitation has been a major concern [10,11]. However, recently available data do not suggest a markedly increased incidence of major bleeding complications following fibrinolysis during CPR. In their retrospective study, Lederer and colleagues performed an autopsy in a subgroup of patients having received either thrombolytic (n = 45) or standard treatment (n = 46). The incidence of major bleeding complications did not differ between both groups [18]. A systematic review focusing on all available case reports and clinical studies on fibrinolysis during and shortly after CPR did not suggest an increase in bleeding complications if thrombolytic therapy was combined with CPR [23]. Fibrinolysis for treatment of acute myocardial infarction (MI) or massive pulmonary embolism (PE) carries a risk of 1.9–3.0% for severe and potentially fatal haemorrhage. Studies on fibrinolysis during CPR have shown an incidence of 2.0–12.1% of severe bleeding complications depending on whether thrombolytic treatment was applied in hospital or in the field [23]. Most of the severe bleeding complications can be treated effectively either by a transfusion of blood or by surgical intervention. However, data from a large, randomized multicentre study are needed to answer definitively the question of safety and efficacy of this new treatment option.

Therefore, a randomized, controlled clinical outcome trial focusing on the concept of fibrinolysis during CPR is considered ethical and necessary. The TROICA study is performed under the aegis of the European Resuscitation Council (ERC).

Study design

The TROICA study is a prospective, randomized, double-blind, placebo-controlled, international, multicentre, parallel-group trial evaluating the efficacy and safety of tenecteplase during CPR as compared with standard treatment in
patients suffering from out-of-hospital cardiac arrest of presumed cardiac origin.

Study objectives and endpoints

The primary objective of the study is to assess whether administration of tenecteplase during advanced life support CPR (ALS-CPR) improves survival after out-of-hospital cardiac arrest. The primary endpoint of this study is the 30-day survival rate. The coprimary endpoint of this study is survival to hospital admission. The secondary objective of the study is to assess the safety of administration of tenecteplase during ALS-CPR.

Secondary endpoints of this study are:

- ROSC;
- 24-h survival;
- survival to hospital discharge or at day 30, whichever comes first; and
- distribution of neurological and overall outcome scores [occurrence of Cerebral Performance Categories (CPC) 1–5 and Overall Performance Categories (OPC) 1–5] at hospital discharge or at day 30, whichever comes first.

Safety criteria include:

- symptomatic intracranial haemorrhage;
- major bleeds up to hospital discharge or day 30, whichever comes first.

Study population

Approximately 1000 patients will be randomized (1:1) at approximately 60 study centres located in Europe. Randomization is performed immediately after insertion of an IV line is established. The study drug (tenecteplase or placebo) should be administered, as a single intravenous (IV) bolus, immediately after the first vasopressor application during the ALS-CPR procedure. All cardiac arrest data will be reported uniformly according to the Utstein style [24].

Patients fulfilling the inclusion and exclusion criteria and presenting with non-ventricular fibrillation/non-ventricular tachycardia (non-VF/VT) as initial rhythm during CPR will be randomized immediately after the insertion of an IV line. Patients with ventricular fibrillation/pulseless ventricular tachycardia (VF/VT) will only be randomized if VF/VT persists after three initial consecutive electric shocks, and after the insertion of an IV line.

Patients, indicated for prehospital CPR procedures must fulfil the following inclusion criteria:

- age at least 18 years (known or estimated; no upper limit);
- out-of-hospital cardiac arrest of presumed cardiac origin; and
- witnessed (by eye and/or ear) cardiac arrest; and
- acceptable enrolment times:
  1 CPR must have been started within a maximum of 10 min of the estimated time of collapse – otherwise the patient cannot be randomized.

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2 Thereafter, the total time for CPR [which includes both basic life support (BLS) and (ALS)] up to the moment of the study drug administration must not exceed 10 min, but in all cases the study drug must be administered with the least possible delay compatible with protocol requirements. Thus, no case can have study drug administered later than 20 min after collapse – but in most cases the delay should be much less.

Subjects who meet any of the following criteria will be excluded from randomization into the study:

- in-hospital cardiac arrest;
- cardiac arrest of presumed noncardiac origin (e.g. drug overdose, carbon monoxide poisoning, drowning, hypothermia, exsanguination, electrocution, asphyxia, hypoxia, trauma, cerebrovascular accident);
- obvious significant internal bleeding;
- known neurological impairment;
- known coagulation disorder;
- known pregnancy;
- known current participation in any other clinical study;
- known hypersensitivity to study medication;
- institutionalized subjects (e.g. prisoner); and
- any other condition that the investigator feels would place the patient at increased risk if the investigational therapy is initiated.

Treatments

Treatments to be compared

Fibrinolysis group. Tenecteplase, as a single weight-adjusted IV bolus (< 60 kg: 30 mg; ≥ 60 to < 70 kg: 35 mg; ≥ 70 to < 80 kg: 40 mg; ≥ 80 to < 90 kg: 45 mg; ≥ 90 kg: 50 mg), immediately after first vasopressor dosage during standardized ALS-CPR procedures according to the international CPR Guidelines.

Standard treatment group. Placebo, as a single IV bolus over 5–10 s, immediately after the first vasopressor dosage during standardized ALS-CPR procedures according to the international CPR Guidelines.

Concomitant therapy

Aspirin can be used at the discretion of the investigator (e.g. 150–250 mg IV). Heparin is not allowed during CPR. Following ROSC, heparin use is discouraged until hospital admission unless considered mandatory for the underlying disease. After the interventional procedure the use of anti-coagulation is at the discretion of the investigator according to clinical need and local practice. For monitoring of treatment with unfractionated heparin during the interventional procedure, activated clotting time (ACT) is preferably used (target range: 300–350 s). In case activated partial
thromboplastin time (aPTT) is used, the local nomogram will apply. All study centres should have percutaneous coronary intervention (PCI) available as an alternative therapy for achieving reperfusion. If PCI is performed within 12 h of randomization, glycoprotein (GP) IIb/IIIa antagonists should not be used as pre-catheter laboratory therapy or during the PCI procedure. If PCI is performed later than 12 h of randomization, usage of GP IIb/IIIa antagonists is at the investigator’s discretion. The use of clopidogrel or ticlopidine is not allowed before hospital admission. Thereafter, usage is at the discretion of the investigator.

Any other medication (e.g. emergency agents such as adrenaline or vasopressin, or other agents such as beta blockers, nitrates, calcium-channel blockers and angiotensin-converting enzyme inhibitors) can be used at the discretion of the investigator.

In case of severe bleeding complications, administration of an antifibrinolytic drug may be considered.

Investigational plan

Study procedures

The study is divided in three different distinct periods:

- enrolment/pre-hospital period;
- in-hospital period (post-CPR); and
- follow-up period.

Enrolment/Pre-hospital period

This is the period between randomization of the patient and admission to the hospital. All patients must receive CPR for at least 30 min, if indicated (i.e. if ROSC is not achieved), following study drug administration. According to the international guidelines on CPR, the treatment of patients with non-VF/VT differs from the treatment of patients with VF/VT. The flow chart for both groups is given in Fig. 1. The first step of the protocol is the reception of a call from a patient with suspected cardiac arrest at the emergency medical service (EMS) dispatching centre. The second step is dispatching of a mobile intensive care unit (MICU) to the scene. The team of this MICU, which includes a physician in many European countries, is in charge of ALS on scene and the study protocol.

As soon as the MICU team arrives on scene, several steps are to be followed:

- the MICU team checks performance of BLS algorithm by bystander or EMT (emergency medical technicians) who arrived previously on scene and/or performs BLS (Fig. 1; 1) as indicated [25];
- the MICU team begins ALS-CPR as indicated in the universal algorithm (see Fig. 1) by attaching a monitor to the patient (Fig. 1; 2), checking the pulse and assessing the cardiac rhythm. The patient treatment differs according to the rhythm;
- ventricular fibrillation/pulseless ventricular tachycardia (VF/VT) (Fig. 1; 3):
  - three shocks are delivered immediately;
  - CPR is performed during 1 min, during which;
  - an endotracheal intubation attempt is performed and if possible mechanical ventilation is initiated (Fig. 1; 5);
  - as soon as an IV line is inserted the patient is randomized (if he/she is eligible), by opening the study drug kit stored in the MICU;
  - the first injection of vasopressor is performed (adrenaline or vasopressin) and the study drug is prepared;
  - the IV line is flushed;
  - the study drug is injected as a single bolus over 5–10 s (Fig. 1; 6). The time of injection is precisely recorded;
  - further resuscitation does not differ with standard ALS as described in international recommendations [25]:
    - sequences of three shocks are delivered every loop;
    - vasopressor boluses are injected every 3 min;
    - an amiodarone injection is given if defibrillation is unsuccessful; and
    - sodium bicarbonate or buffers may be considered after 10 min of unsuccessful resuscitation.
- non-ventricular fibrillation/non-ventricular tachycardia (non-VF/VT) (Fig. 1; 4):
  - a 3-min CPR sequence is performed, during which;
  - endotracheal intubation is performed and if possible mechanical ventilation is initiated (Fig. 1; 5);
  - as soon as an IV line is inserted the patient is randomized by opening the study drug kit stored in the MICU;
  - the first injection of vasopressor is performed (adrenaline or vasopressin) and the study drug is prepared;
  - the IV line is flushed;
  - the study drug is injected as a single bolus over 5–10 s (Fig. 1; 6). The time of injection is precisely recorded.
- further resuscitation does not differ with standard ALS as described in international recommendations [25]:
  - vasopressor boluses are injected every 3 min;
  - sodium bicarbonate or buffers may be considered after 10 min of unsuccessful resuscitation; and
- A reversible cause (Fig. 1; 7) will be considered and treated if appropriate. However, most of these patients will have been excluded by the selection criteria of the study.

The patient is transported to the hospital only when resuscitation is considered to be successful and durable ROSC is obtained on scene. With appropriate continuous monitoring and treatment, the MICU team transports the patient to a participating hospital. On arrival at the emergency room or the ICU (intensive care unit) a prehospital care report, according to the local procedure, and specific
information on the ongoing protocol is given to the hospital team.

**In-hospital period (post-CPR)**

This period starts when a patient is admitted to the hospital and medical responsibility is taken over by the hospital medical team (irrespective of whether it occurs in the emergency room, the ICU or another ward/unit). It ends at hospital discharge. All patients who suffered from out-of-hospital cardiac arrest leading to ALS-CPR should be treated according to standard treatment or normal hospital procedures. Successfully resuscitated patients can be treated by lowering the body temperature (hypothermia) according to local conditions [26]. During the in-hospital phase, patients will be monitored for serious adverse events, intracranial haemorrhage (ICH) and nonserious bleeds. Subjects with clinically suspected stroke at any time after randomization should be taken for immediate (within 24 h) computed tomographic scanning (CT) or magnetic resonance imaging (MRI) to determine whether an ICH has occurred. In addition, all such patients should also be seen by a neurologist who could assist with the completion of the necessary documentation. In case of fatal stroke, if no imaging was performed, an autopsy should be performed whenever possible. Neurological and overall outcome will be evaluated on the day of discharge. Assessment of neurological and overall outcome will be performed according to OPC and CPC by Glasgow-Pittsburgh Outcome Categories.
Follow-up period

This is the time period starting from discharge from the hospital and lasts up to day 30 from randomization. The following will be reported:

- death of any cause;
- primary cause of death;
- neurological and overall outcome (OPC/CPC);
- total strokes and disabling stroke;
- modified Rankin scale for patients who had a nonfatal stroke; and
- re-admission to hospital and the primary reason given.

One-year follow up

The patient’s vital status will be established 1 year after randomization. This may be carried out by a clinic appointment or by contact (phone or mail) with the patient, a family member or the family physician. This 1-year follow up will not delay database lock and reporting, which will be carried out based on the in-hospital and 30-day follow-up data.

Statistical methods

The primary aim of the trial is to demonstrate superiority in the intent-to-treat analysis of tenecteplase over placebo with regard to the primary endpoint as the incidence of 30-day survival (30 daysurv). The null and alternative hypotheses are as follows:

\[ H_0 : 30 \text{ daysurv}_{\text{tenecteplase}} / 30 \text{ daysurv}_{\text{placebo}} \]
\[ H_1 : 30 \text{ daysurv}_{\text{tenecteplase}} / 30 \text{ daysurv}_{\text{placebo}} \]

Planned analyses

An intent-to-treat analysis (ITT) of all patients randomized (irrespective of which study treatment was given or if any study treatment was received) will be carried out. In addition, an exploratory analysis (PP) of all patients randomized and treated without major protocol violations will be carried out. Pre-defined major protocol violations/deviations are:

- missing data for the primary/coprimary efficacy endpoints; and
- no study drug received.

Baseline characteristics will be tabulated and comparability/differences between the treatment groups will be examined by means of descriptive statistics.

The primary ITT analysis on the primary endpoint (incidence of 30-day survival) will be carried out by the chi-squared test on proportions (alpha level 5%, two-sided). In addition, the 95% confidence interval on the relative risk will be presented. The secondary ITT analysis on the coprimary endpoint (incidence of hospital admission) will be carried out by the chi-squared test on proportions. For reasons of multiple testing (in case of a negative primary ITT analysis), the two-sided alpha level is fixed to 3.6%, assuming a correlation of approximately 90% with the primary endpoint. Furthermore the corresponding confidence interval on the relative risk will be presented. In addition, the survival status will be analyzed by presenting Kaplan-Meier-curves, and the treatment differences will be compared by means of a log-rank test.

No alpha adjustment for multiple testing on further ITT efficacy/safety endpoints and/or any exploratory analysis is foreseen. All (dichotomized) endpoints will be analyzed by a chi-squared test on proportions, and the 95% confidence intervals on the relative risk will be presented. In general, relative risks will be correlated to the risk differences for an overall assessment of the effect size. Potentially important prognostic factors for the efficacy/safety endpoint will be explored and utilized as covariates in the relative risk analyses by means of logistical regression or the Cox model. (Serious) adverse events will be tabulated per treatment group.

All stroke events will be blindly reviewed by independent neurologists and neuro-radiologists of the Stroke Evaluation Panel (SEP). On the basis of the stroke event documentation the SEP will assess and classify each stroke event as:

- primary haemorrhagic;
- ischaemic;
- ischaemic with haemorrhagic conversion;
- not consistent with stroke;
- confirmed not haemorrhagic; or
- nonclassifiable.

In addition, subgroup analyses are planned to focus on different issues, for example:

- age;
- confirmed primary cause for cardiac arrest: cardiac vs. noncardiac origin;
- initial electrocardiogram (ECG) rhythm: VT/VF vs. non-VT/non-VF;
- percutaneous coronary intervention (yes/no);
- therapeutic hypothermia (yes/no);
- bystander CPR (yes/no);
- blood glucose level at hospital admission;
- temperature at hospital admission; and
- blood pressure at hospital admission.

No formal interim analysis is foreseen. The safety of the trial is monitored continuously by an independent Data and Safety Monitoring Board (DSMB) which is empowered to make recommendations to the study chairman. Any such recommendations from the DSMB and any consequences following from them will be described fully when the results are published.
Sample-size calculation

Based on previous studies in cardiac arrest and registry data, it is estimated that the primary endpoint (incidence of 30-day survival) in the placebo group will be approximately 10%. Assuming an incidence for the 30-day survival of 10% in the placebo group, a sample size of approximately $2 \times 500$ patients is necessary to demonstrate, by means of a chi-squared test on proportions (two-sided, alpha = 5%, power > 85%), an improvement (superiority) of at least 7% absolute with tenecteplase.

Ethics, informed consent and subject information

Appropriate ethical and legal approvals were obtained from the local authorities and Ethics Committees before study initiation. As only patients who are not able to give their written informed consent (patients with cardiac arrest) will be included in this study, special attention will be paid to the ethical considerations and relevant local legal requirements. For patients unable to give their informed consent (owing to unconsciousness), their participation may be acceptable if the Independent Ethics Committee (IEC) or the Institutional Review Board (IRB) approves the protocol and the investigator who intends to enroll the subject in this study thinks that the participation may be of potential benefit to and in the interest of the individual subject.

If applicable and according to local law, the subject’s legal representative will be informed on behalf of the subject.

Three different ‘information and consent procedures’ are foreseen in this trial:

1 Retrospective information and consent for continuing participation, collection, and use of collected data for subjects who survived cardiac arrest.
2 Retrospective information and consent for continuing participation, collection, and use of collected data for legal representatives of subjects who survived cardiac arrest but with inadequate consciousness.
3 Retrospective information and consent for continuing collection, and use of collected data for legal representatives of the subject who died owing to cardiac arrest.

Discussion

The current study protocol is the first international randomized, controlled trial on thrombolytic treatment during CPR in out-of-hospital patients with cardiac arrest of presumed cardiac origin. Recent clinical case reports, small case series and clinical studies [18,21,27,28] have suggested that fibrinolysis during CPR can contribute to haemodynamic stabilization and long-term survival in patients suffering cardiac arrest following acute myocardial infarction and massive pulmonary embolism. These studies, however, were not randomized and were underpowered to show a long-term benefit of thrombolytic therapy. Although several studies evaluating CPR interventions were able to show a benefit of a given intervention in regards of hospital admission or even short-term survival, there is usually a sharp decrease in survival rate once patients are admitted to the hospital after ROSC. Fibrinolysis may ameliorate post-resuscitation reperfusion injury, as this drug improves microcirculation rapidly [15,29]. Thus, it may be possible that a patient who is initially stabilized on the scene is less likely to suffer significant organ pathology after admission to the intensive care unit. This hypothesis is supported by data from patients who were treated with fibrinolysis during CPR, underwent prolonged resuscitation efforts which took in some cases up to 90 min, and then had a full neurological recovery upon hospital discharge [28,30,31].

The primary endpoint of the study is survival after 30 days. This is an important difference from all of the studies on fibrinolysis during CPR performed already, which were not randomized or powered to show a benefit in outcome after 30 days [18–20,27]. However, as outcome after 30 days is likely to be also influenced by various interventions performed during the hospital stay of the patient that may mask a beneficial effect of fibrinolysis during CPR, in the recent trial hospital admission was chosen as a co-primary endpoint.

To assess the effects of fibrinolysis on surviving cardiac arrest for 30 days, it is necessary to exclude patients who may not have any chance of survival beyond the first 24 or 48 h. In the multicentre vasopressin study, both witnessed and unwitnessed cardiac arrest patients were included [32]. From the results of that study, it was suggested that the chance of hospital discharge was low after any cardiac arrest interval that was longer than 10 min. For this reason, it was decided that the maximum ischaemia or cardiac arrest time in the prehospital phase was allowed to be 10 min until CPR was initiated. In contrast to other studies on cardiac arrest that included only cardiac arrest patients presenting with a specific initial ECG rhythm, such as ventricular fibrillation/pulseless ventricular tachycardia [5] or pulseless electrical activity [21], the TROICA study allows patients with any initial ECG rhythm to be included. While it may be beneficial to include ventricular fibrillation patients only, such as in the European hypothermia after cardiac arrest trial [5], even a patient with a very short ischaemia time, and thus with a potentially good cerebral prognosis, may have pulseless electrical activity or asystole. Therefore, we decided not to exclude patients with cardiac arrest owing to their initial ECG rhythm. In addition, the TROICA study does not have an upper age limit. In the multicentre vasopressin study, several patients > 65 years with excellent neurological recovery were identified, therefore indicating that age is no disease in cardiac arrest management. Also, it is an ethical dilemma if a given age such as 75 years would be an upper limit for fibrinolysis treatment, as the age itself usually does not describe adequately the physiologic status of the patient. Thus, we felt that by allowing any cardiac rhythm and no upper age limit into the trial but limiting the time duration of ischaemia, patients are selected best on the basis of having a chance to survive; while excluding patients who most likely do not have a chance to survive cardiac arrest because of
circumstances that cannot be influenced by resuscitation strategies, such as prolonged ischaemia.

The exclusion criteria of the TROICA study are designed to leave patients out of the study with an underlying pathophysiology that is either adversely affected by fibrinolysis, or where the underlying reason for cardiac arrest cannot be reversed with fibrinolysis. For example, fibrinolysis is obviously of no benefit if patients suffer cardiac arrest owing to haemorrhagic shock such as after rupture of an aortic aneurysm, gastrointestinal bleeding or trauma. Also, respiratory pathology-mediated cardiac arrest is quite common, such as in drug overdose/heroin addicts, carbon monoxide poisoning, drowning, and other asphyxia events such as hanging suicide. These exclusion criteria were also used by several other large studies focusing on specific interventions in patients with cardiac arrest [5,21,33].

Combining fibrinolytic treatment with standardized CPR represents a potential increase in bleeding risk. Therefore, in the past thrombolytic therapy during and in the early phase after CPR has been commonly contraindicated. However, this contraindication, which has repeatedly been underlined by various authors and medical societies [34–36], appears to be questionable based on the available studies on fibrinolysis during or after CPR [23]. Early clinical experience with fibrinolysis after CPR in nearly 200 patients suffering from acute myocardial infarction revealed no markedly increased risk of severe bleeding complications [37–39]. In addition, currently available data on bleeding complications owing to fibrinolysis during CPR either in hospital [19,20] or out-of-hospital [18,27] do not suggest a clinically relevant increase in severe bleeding complications. However, because no large-scale controlled clinical trials have been conducted, data from randomized multi-centre studies are needed to answer definitively the open questions of the relationship between safety and efficacy of this treatment option during and after CPR [22].

In the international ILCOR guidelines for ALS-CPR [25], heparin is not part of the recommended treatment of cardiac arrest. In myocardial infarction heparin is given mainly to prevent reocclusion, and as this is not the primary aim in cardiac arrest heparin might only increase the potential bleeding risk. Therefore, heparin will not be coadministered with tenecteplase, and be given only in the hospital as needed as part of standard treatment in patients where myocardial infarction and pulmonary embolism is confirmed.

One important limitation of the TROICA trial should be noted. Ventricular fibrillation patients undergoing successful initial countershocks with immediate return of spontaneous circulation will not be randomized; thus, it is possible that fibrinolysis may miss an important cohort of patients, some of whom may survive with a risk of lasting complications from in situ thrombus or fibrin deposition that might have been avoided by treatment. However, patients requiring defibrillation are generally not treated with early thrombolytic therapy as a matter of routine.

In conclusion, the TROICA study is designed to evaluate the efficacy and safety of thrombolytic treatment as a new and promising therapeutic option for patients suffering prehospital cardiac arrest owing to presumed cardiac origin.

References

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