Reduced Anticoagulation Targets in Extracorporeal life support (RATE)

TEMPLATE RESEARCH PROTOCOL

(September 2018)

- May 2015: adaptation section 11.5: text in accordance to old and new Measure regarding Compulsory Insurance for Clinical Research in Humans
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PROTOCOL TITLE 'Reduced Anticoagulation Targets in Extracorporeal life support (RATE)'

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: ECMO treatment has a mortality of 38%, for a large part treatment related due to complications. The most feared complication is ischemic stroke for which heparin is administered with an aPTT target 2.0-2.5 times baseline (approximately 60-75 sec). However, there is no relation between aPTT and the occurrence of stroke (1.2%), but there is a relation with the much more frequent occurrence of bleeding complications (55%) and blood transfusion. Both are strongly related to outcome.

Objective: Our objective is to study if reduced anticoagulation targets diminish bleeding complications without an increase in thromboembolic complications or a negative impact on outcome.

Study design: Three-arm non-inferiority RCT.

Study population: All adult Dutch patients treated with ECMO during the 30 months of the study.

Intervention: Randomization between heparin administration with a target of 2-2.5 times baseline aPTT (usual care, about 60-75 sec.), 1.5-2.0 times baseline aPTT (45-60 sec.) or low molecular weight heparin (LMWH) guided by weight and renal function.

Main study parameters/endpoints: The primary outcome parameter is a combined endpoint consisting of: 1) major bleeding including hemorrhagic stroke according to the ELSO definitions; 2) severe thromboembolic complication defined as ischemic stroke, limb ischemia (not related with distal perfusion catheter), or acute pump failure with emergency exchange; 3) mortality at 6 months.
Secondary outcome parameters are: 1) blood transfusions; 2) health related quality of life (HR-QoL) at 6 months; 3) exchange of the membrane oxygenator; 4) vessel thrombosis after ECMO removal detected by echography; 5) pulmonary embolism; 6) costs; 7) the individual components of the composite outcome; and 8) all thromboembolic complications combined.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: We estimate that with an aPTT target of 45-60 sec. or with use of LMWH the primary endpoint will be met in 60% of patients compared to 70% with usual care. Apart from anticoagulation targets, treatment will be as usual so study participation will not lead to a burden for the patient, e.g. no extra blood sampling, tests or visits. After 6 months

the patients will be contacted for a short questionnaire to measure health-related quality of life. A risk may be that reduced anticoagulation target or anticoagulation with LMWH is inferior to standard practice. A benefit may be that reduced anticoagulation target or anticoagulation with LMWH is superior to standard practice.

1. INTRODUCTION AND RATIONALE

Extracorporeal life support (ECLS) by means of extracorporeal membrane oxygenation (ECMO) utilization can support the heart and lung for an extended period of time, up to months, and is deployed in the Intensive Care Unit (ICU).[1] ECMO seems an efficient therapy in terms of survival benefit, but mortality is still high (38%).[2] In part this is due to irreversible disease, but there is also significant treatment related mortality. Exposure of blood to the nonbiologic surfaces of an extracorporeal circuit initiates a complex inflammatory response involving both the coagulation and the inflammatory response pathway. The most feared complication is a thromboembolic stroke due to clotting related to the ECMO system. To prevent this, patients are treated with systemic anticoagulation using heparin with an aPTT target of 2.0-2.5 times baseline (approximately 60-75 sec.). This target is adapted from other diseases or indications for therapeutic anticoagulation and not validated. In recent years materials have been improved, e.g. heparin coated cannulas, but anticoagulation targets remained unchanged.

More important, there seems to be no relation between the level of anticoagulation and the occurrence of a thromboembolic stroke (1.2%). In contrast there is however a strong relation between level of anticoagulation and the occurrence of bleeding complications (55%) as well as the need for blood transfusion which is directly related with poor outcome.[1, 2] Moreover, fatal hemorrhagic stroke is far more frequent than fatal thromboembolic stroke (www.elso.org).

A small recent French study randomized 32 patients to therapeutic anticoagulation with heparin (target aPTT between 50 and 70 s) or lower dose heparin aiming for activated partial thromboplastin time < 45 s.[3] A total of 43 bleeding events occurred in 14 patients (43.8%). The most common source of bleeding was ECMO cannula sites. Intracranial hemorrhage occurred in one patient who was in the therapeutic anticoagulation group. There was no difference in number of patients with bleeding (seven patients [43.8%] in each group; $p = 1.0$) or in number of bleeding events between groups. When considering transfusion requirements, 94% of patients received at least one RBC unit in the therapeutic anticoagulation group versus 63% in the low-dose anticoagulation ($p = 0.03$). Seven patients had clinical thrombosis, 3 in the low dose and 4 in the therapeutic dose group. Although this study does not provide evidence on the optimal anticoagulation protocol for patients undergoing ECMO, it shows the feasibility of a larger study to evaluate the safety and efficacy of low-dose anticoagulation compared with therapeutic anticoagulation in patients receiving ECMO.

Safety and potential superiority of subcutaneously administered LMWH compared to intravenous UFH have been described for therapeutic anticoagulation in critically ill patients.[4, 5] LMWH is therefore the method of choice for anticoagulation in the ICU. Additionally, safety and efficacy of LMWH have been demonstrated in the setting of anticoagulation for extracorporeal circuits, namely renal replacement therapy.[6] Furthermore LMWH is the preferred substance for anticoagulation of LVAD patients at the ICU. Doses used are the equivalent of the doses used for anticoagulation with heparin, but LMWH leads to a more balanced anticoagulation.

One monocenter study retrospectively compared the risk of hemorrhagic and thromboembolic events in lung transplant patients undergoing perioperative ECMO anticoagulated with LMWH versus those anticoagulated by means of unfractioned heparin (UFH).[7] LMWH was given in a fixed half therapeutic dose regimen of 2 × 0.5 mg enoxaparin/kg bodyweight/day without guidance by antiXa values. Dosing of UFH was guided by at least twice daily measurements of activated partial thromboplastin time (aPTT) aiming for goal values of 1.5 times the baseline value. They observed no differences in regard to risk of bleeding or transfusion requirements. However, patients who received LMWH subcutaneously had a lower risk of thromboembolic events compared to those anticoagulated by means of intravenous UFH.

Another single-center, observational study showed feasibility of prophylactic anticoagulation with enoxaparin during the course of veno-venous ECMO in nonsurgical patients.[8] However, they experienced more acute pump failure so prophylactic use of LMWH seems a bridge too far for testing in a RCT.

Taken together, one might postulate that intensive heparin treatment in this case might lead to more problems than benefit. However, there is a paucity of studies evaluating different anticoagulation strategies in patients supported with ECMO and there are no randomized trials comparing one strategy to another. A comprehensive guideline for the use and monitoring of anticoagulation during ECMO therapy may be found on the ELSO website (http://www.elsonet.org). This guideline stops short of any one mandate, given the lack of evidence in favor of most of the practices reviewed. Rigorous evaluations of anticoagulation use in ECMO patients are therefore urgently needed.[9] Our primary research question is if anticoagulation with heparin with reduced anticoagulation targets or anticoagulation with LMWH leads to a reduction in the occurrence of major bleeding without an increase in thromboembolic complications or a negative effect on outcome compared to the standard practice of high anticoagulation targets with heparin. We expect fewer complications with subsequent medical costs savings and improvement of survival and quality of life 6 months after initiation of ECMO therapy, resulting in less costs per quality-adjusted life year (QALY) for both interventions.

2. OBJECTIVES

Our objective is to study if reduced anticoagulation targets diminish bleeding complications without an increase in thromboembolic complications or a negative impact on outcome.

We consider the intervention, low dose heparin or LMWH, to be successful if there are fewer patients with serious bleeding complications without compromising more thromboembolic complications or higher mortality, with the possible increase in the number of ischemic strokes being offset by a possible decrease in hemorrhagic stroke.

3. STUDY DESIGN

DESIGN

Phase 3, three-armed, randomized, non-inferiority open-label study.

STUDY POPULATION/DATA SOURCES

All patients who receive ECMO treatment during the study period in one the participating centers from which (deferred) informed consent is obtained. Patients in whom the ECMO is only used to bridge a procedure like a high risk percutaneous coronary intervention or during surgery are excluded.

INTERVENTION

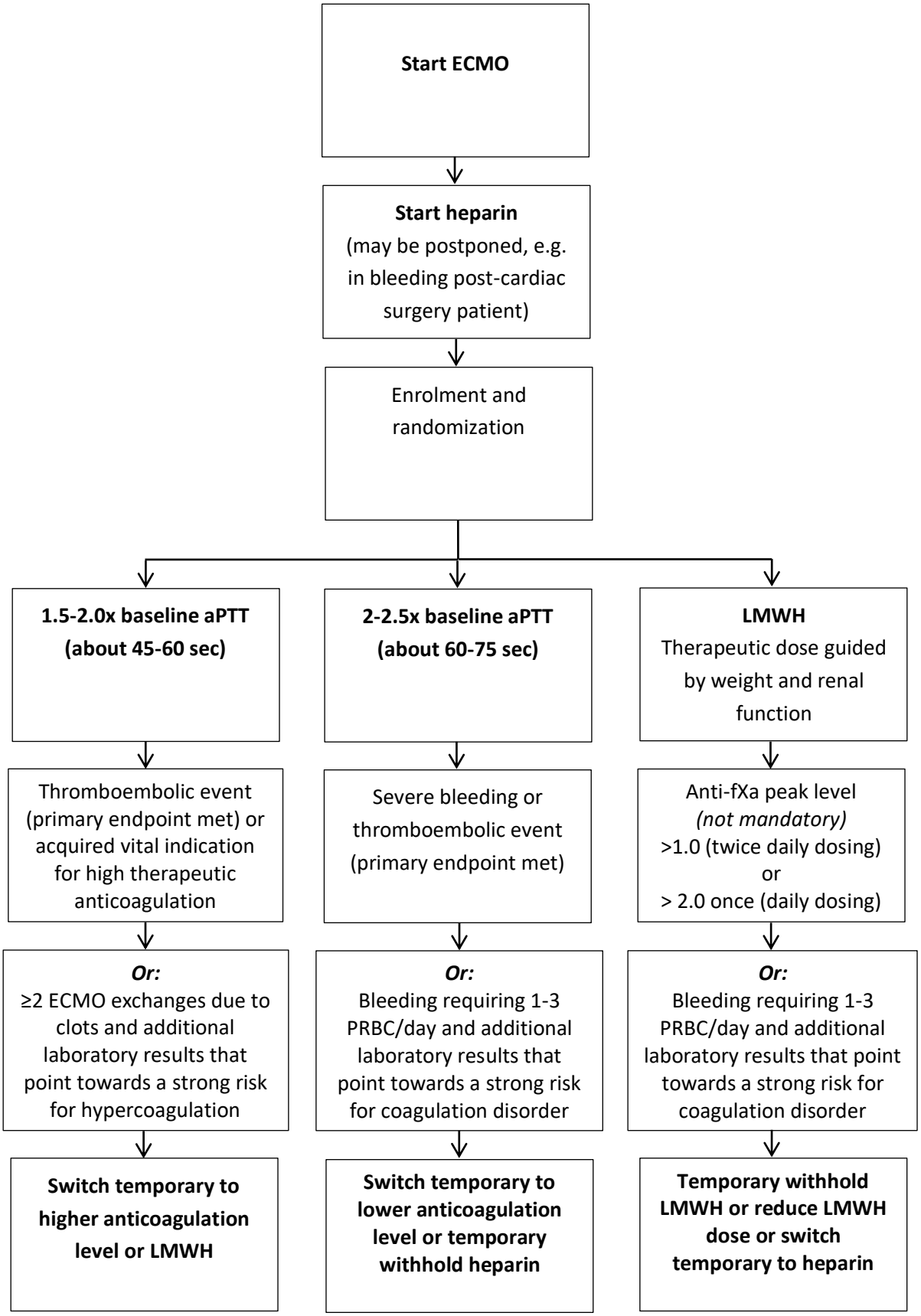
Randomization between a target of 2-2.5x baseline aPTT (usual care, about 60-75 sec.), 1.5-2.0x (45-60 sec.) and therapeutic LMWH guided by weight and renal function (see Table LMWH).

Table LMWH. Suggestions for therapeutic dose LMWH based on weight and renal function

LMWH	**<50 kg**	**50-70 kg**	**70-90 kg**	**>90 kg**
Nadroparine • Fraxiparine® • Fraxodi®	2dd3800 IE 1dd7600 IE	2dd5700 IE 1dd11400 IE	2dd7600 IE 1dd15200 IE	2dd9500 IE 1dd 19000 IE
	<60 kg	**60-80 kg**	**80-100 kg**	
Enoxaparine • Clexane®	2dd60 mg	2dd80 mg	2dd200 mg	
Tinzaparine • Innohep®				
Dalteparine • Fragmin®				
creatinine clearance 30-50 ml/min:	25% dose reduction			
creatinine clearance < 30 ml/min:	50% dose reduction and consider monitoring anti-Xa activity			

Crossover is allowed based on the instructions in the flowchart shown below and described in detail in paragraph 8.2.

Flowchart. Decision tree randomization and crossover.



DATA-ANALYSIS/SAMPLE SIZE CALCULATION

An intention-to-treat analysis will be performed for the primary endpoint based on treatment allocation. Achieved aPTT levels will be compared between the two treatment arms that uses heparin.

If non-inferiority is proved in this study, the primary end point will then be analyzed for superiority with the use of a z test of proportions, performed according to the normal approximation of the binomial distribution.

COST EFFECTIVENESS ANALYSES

The difference in costs for use of heparin and aPTT measurements will be neglectable. Cost-effectiveness will be based on reduced costs of blood transfusions and interventions for bleeding (e.g. surgery, interventional radiology) as well as improved outcome. All medical cost items expected to be affected by the ECMO therapy will be measured and valued according to the Dutch standard guidelines for economic evaluations, e.g. blood transfusion, number of ECMO replacements, surgery, and hospital length of stay.
Health gains will be measured in terms of QALYs based on EQ-5D-5L defined utilities. The BIA will be performed from a healthcare perspective to inform decision makers about the financial consequences of reduced anticoagulant targets in ECMO treatment in Dutch healthcare. The model will take changes in the availability and adoption of the reduced anticoagulant targets into account by calculating the financial consequences of five scenarios with a time horizon of 5-10 years.

4. STUDY POPULATION

4.1 Population (base)

The study population will consist of adult patients with severe heart or lung failure, admitted to the intensive care unit. Eligible patients are all patients who receive ECMO treatment during the study period in one the participating centers from which (deferred) informed consent is obtained. In general, according to the ELSO guidelines, ECMO can be considered in acute severe heart or lung failure with high mortality risk despite optimal conventional therapy.
This study will be performed by the Dutch ECLS Study Group, which consist of almost all current ECMO centers in the Netherlands and together treat more than 300 ECMO patients each year. Our ongoing registry has included 431 patients from January 2018 until July 2019 [see http://dutcheclsstudygroup.nl/]. We are aware that enrolment in a randomized controlled trial is more difficult than a registry, but the number of eligible patients during the study period of 30 months is at least 750. It is thus more than feasible to recruit 330 patients within the proposed 2.5 years of the study.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- ECMO treatment during the study period in one the participating centers
- (deferred) informed consent
- Age above 18

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patients in whom the ECMO is only used to bridge a procedure like a high risk percutaneous coronary intervention or during surgery
- No (deferred) informed consent
- Vital indication for robust anticoagulation (e.g. mechanic mitral valve, pulmonary embolism, clot in cardiac ventricle)
- History of heparin induced thrombocytopenia (HIT)

4.4 Sample size calculation

We expect that with a target of 1.5-2.0x baseline aPTT or with LMWH the primary composite endpoint will be reached in 60% of patients compared to 70% in usual care. To show non-inferiority with a significance level (alpha) of 5%, power of 80% and a non-inferiority limit (delta) of 7.5% the corresponding sample size is 91 patients per group. In other words, if there is a true difference in favor of the experimental treatment of 10%, then 91 patients per group are required to be 80% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favor of the standard group of more than 7.5%, thus 75,25% in the intervention group(s) compared to 70% in usual care. To compensate for a lower effect and drop-outs 330 patients will be enrolled. Drop-outs are defined as withdrawal of informed consent or lost to follow-up.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Patients will be randomized between heparin administration with a target of 2-2.5x baseline aPTT (usual care, about 60-75 sec.), a target of 1.5-2.0x baseline aPTT (45-60 sec.) or therapeutic LMWH guided by weight and renal function.

5.2 Use of co-intervention (if applicable)

Non applicable

5.3 Escape medication (if applicable)

Non applicable

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Both heparin and LMWH belongs to the Heparin group. The Anatomical Therapeutic Chemical (ATC) Classification System uses the ATC code B01AB for the Heparin group

This group comprises heparin preparations, including products for non-therapeutic use, e.g. for rinsing of indwelling vein cannulas. Heparin sodium and heparin calcium are classified at the same 5th level, i.e. B01AB01. The low molecular weight heparins are classified at separate 5th levels. The individual heparin and LMWH's commonly used in The Netherlands are:

- ATC code B01AB01 heparin
- ATC code B01AB05 enoxaparin
- ATC code B01AB06 nadroparin
- ATC code B01AB09 danaparoid
- ATC code B01AB10 tinzaparin

6.2 Summary of findings from non-clinical studies

This product has been available for many years and its side effects and clinical profile are well-understood, therefore no further data from non-clinical studies is provided.
Heparin already has a marketing authorization and is not used different from the authorized form nor used for an unauthorized indication. The heparin already in stock at the participating hospitals is used. No heparin is assembled (formulated or packaged) especially for this study. All participated hospitals use heparin assembled by their central pharmacy or external pharmacies; heparin is never prepared locally at the ICU by nurses.

6.3 Summary of findings from clinical studies

INTRODUCTION

Objectives

The objective of this review of the literature is to give insight in: 1) the current practice of anticoagulation during ECMO support; 2) past or ongoing research on this topic, and 3) the added value of the proposed research. For this purpose, a broad exploration of several medical databases has been performed including the National library of medicine,

Cochrane library, International Standard Randomized Controlled Trial Number, ClinicalTrials.gov, Nederlands Trial Register, and the ZonMw website.

Coagulation in patients with ECMO support

Extracorporeal life support (ECLS) for patients with acute cardiac or respiratory failure, has improved survival for subsets of critically ill children and adults. The devices are intricate and complex, allowing blood to bypass the heart or lungs (or both). As blood flows through these artificial devices, normal hemostasis is disrupted, coagulation is promoted, and in the absence of anticoagulation, a thrombus may form in the device, resulting in device failure or embolic stroke. Therefore, anticoagulation is necessary to prevent thrombus formation and maintain device function. However, patients on ECMO support also have very high bleeding rates. Titrating anticoagulation to prevent hemorrhagic complications and thrombotic events can be a challenge. Substantial variability remains in the approach to anticoagulant and antiplatelet therapy for patients on ECMO, largely because of the lack of high-quality data. Improvements in the individualized titration of antithrombotic intensity are expected to enhance outcomes. Several factors pertaining to both the device and the patient should be considered when attempting to optimize this delicate balance.[1]

ECLS includes oxygenation of the blood provided through an artificial lung (extracorporeal membrane oxygenator; ECMO) with return to the circulation via the vein (veno-venous; VV) or artery (veno-arterial; VA). In VV mode, the artificial lung is in series with the native lungs and replaces lung function. In VA mode, the artificial lung is in parallel with the native lungs and replaces both heart and lung functions.

Exposure of blood to the large surface of the ECMO circuit initiates the contact factor pathway, activates platelets, and induces an inflammatory response. To prevent the circuit from clotting, anticoagulation is necessary. Generally, this is achieved using unfractionated heparin (UFH). However, titrating the intensity of anticoagulation to prevent the ECMO circuit from clotting and prevent bleeding in the patient remains a major challenge. Hemorrhagic and thrombotic complications, including intracranial hemorrhage, embolic stroke, surgical bleeding, and circuit thrombosis, are common and occur in up to 50% of patients [Table 1]. These complications have a significant impact on morbidity and mortality.

Approach to anticoagulation in ECMO

UFH remains the primary anticoagulant used in ECMO. Benefits of UFH include clinician familiarity, short half-life, and reversibility, although it is a challenging drug to titrate, particularly in critically ill patients. There is considerable interpatient variation, in part

related to the nonspecific binding of heparin to various plasma proteins. This nonspecific protein binding can cause heparin resistance, which refers to lack of an anticoagulant effect despite high doses of heparin. Low levels of AT also contribute to heparin resistance.

Most patients receive a bolus of UFH (2500 U) at the time of ECMO cannulation, although this may be withheld or reduced in patients with recent surgery or bleeding. This is instantly followed by a continuous infusion of UFH for the duration of ECMO therapy. The use of antiplatelet therapy is uncommon, but may be continued in patients who have additional indications for antiplatelet therapy as it does not seem to increased bleeding risk.[2]

Monitoring heparin

Several coagulation assays can be used to monitor and titrate UFH. In an attempt to reduce high complication rates, many centers have incorporated additional coagulation assays, including aPTT, heparin anti-Xa level, AT activity, and TEG, in their routing monitoring. In most international centers including all Dutch centers patients are preferably treated with systemic anticoagulation using heparin with an aPTT target of 2.0-2.5 times baseline (approximately 60-75 sec.). Of note, this target is adapted from other diseases or indications for therapeutic anticoagulation and not validated. In recent years materials have been improved, e.g. heparin coated cannulas, but anticoagulation targets remained unchanged.

More important, there seems to be no relation between the level of anticoagulation and the occurrence of a thromboembolic stroke (1.2%). In contrast there is however a strong relation between level of anticoagulation and the occurrence of bleeding complications (55%) as well as the need for blood transfusion which is directly related with poor outcome.[3-5] Moreover, fatal hemorrhagic stroke is far more frequent than fatal thromboembolic stroke.[6] Taken together, one might postulate that intensive heparin treatment in this case might lead to more problems than benefit. However, there is a paucity of studies evaluating different anticoagulation strategies in patients supported with ECMO and there are no randomized trials comparing one strategy to another. A comprehensive guideline for the use and monitoring of anticoagulation during ECMO therapy may be found on the ELSO website (http://www.elsonet.org & https://www.elso.org/portals/0/files/elsoanticoagulationguideline8-2014-table-contents.pdf). This guideline stops short of any one mandate, given the lack of evidence in favor of most of the practices reviewed. Rigorous evaluations of anticoagulation use in ECMO patients are therefore urgently needed.[7]

LITERATURE SEARCH

The search terms ECMO ‘or’ ECLS ‘and’ coagulation ’or’ anticoagulation was used in the National library of medicine and Cochrane Library which retrieved 429 articles. After exclusion of non-adult studies, case reports, and studies on HIT or acquired von Willebrand syndrome and impaired platelet function (although relevant within the context of occurrence of bleeding complications), 24 studies remained. Ten studies compare ways of heparin monitoring, e.g. aPTT, TEG, anti-fXa or ACT.[8-17]
One study showed the results of a survey on anticoagulation and transfusion practice during adult ECMO support. A multiple-choice question survey was sent to 166 international institutions of which 54 responded. They found that there appears to be a significant practice variation among institutions regarding anticoagulation and transfusion during adult ECMO support and conclude that the lack of standard practices among institutions may reflect a paucity of data regarding optimal anticoagulation and transfusion for patients requiring ECMO.[18]
Several excellent expert opinions are available which contents are used throughout the application and the introduction of this attachment.[19-23]

Completed or ongoing trials on anticoagulation during ECMO support
The search terms ECMO or ECLS were used in the International Standard Randomized Controlled Trial Number (ISRCTN), ClinicalTrials.gov, Nederlands Trial Register, and ZonMw. No completed or ongoing trials on anticoagulation practices are registered in any of the medical trials databases.
However, we are aware of a small cohort study published as an abstract during the 46th Critical Care Congress in Honolulu.[24] In this single center study 123 patients undergoing VV- ECMO were retrospectively reviewed and three sequential eras of anticoagulation strategy were compared: activated clotting time (ACT: 160-180 sec), high aPTT (60-80 sec), and low aPTT (45-55 sec). Both major bleeding and thromboembolic events were statistically significantly lower with a low aPTT target compared to the two other strategies. This study is the closest resemble to an RCT, but to our knowledge this study is not yet published as a full paper. Furthermore, this was no prospective randomized trial.

Cohort studies on anticoagulation during ECMO support
Two other cohort studies require attention. A cohort study in 61 patients from Germany in which VV-ECMO patients were treated with prophylactic dosage of LMWH found fewer

bleeding complications, but in 5 patients the pump unexpectedly stopped due to thrombotic occlusion.[25] Although none of the patients had an ischemic stroke, in four patients severe thrombotic and thromboembolic events occurred. So, in conclusion, the effect of heparin on prevention of ischemic stroke is unclear, but is probably limited. However, additional reasons for administration of anticoagulation is prevention of thromboembolic events other than stroke and preventing the ECMO circuit from clotting which is potentially fatal.

In a South-Korean study heparin was stopped for three or more days because of thrombocytopenia ACT > 230 sec, bleeding complications, or the need for other surgical procedures in 29 patients (group A) and compared with 24 patients in which heparin was continuously infused during the entire ECMO process (group B).[26] There were no intracardiac, intravascular, or intracircuit thrombotic complications in group A. There was no difference in outcome between the two groups and the authors conclude that heparin discontinuation can be considered in a select group of patients with coagulation abnormalities or bleeding.

Prediction studies

Several studies assessed predictive factors of bleeding events in adults undergoing ECMO. A single center retrospective study in 147 patients found that higher aPTT (defined as highest aPTT on the day prior to the bleeding event) [adjusted OR 3.00, 95 % CI 1.64–5.47], APACHE III score [OR 1.01, 95 % CI 1.01–1.02] and ECMO following surgery [OR 3.04, 95 % CI 1.62–5.69] were independently associated with greater risk of bleeding occurrence.[27] A similar association between bleeding and higher aPTT was found when non-post-surgical VA ECMO was considered separately. The authors suggest that better control of the aPTT may improve patients' outcome.

On the other hand, a study totaling 102 patients found that percentage of aPTT > 50 sec. predicts of venous thrombosis and thromboembolism: OR 0.974 (95% CI 0.952-0.997).[28]

In our single center retrospective study in 164 patients we found that only aPTT was independently associated with occurrence of bleeding complications; adjusted hazard ratio per second increase of aPTT for the development of bleeding was 1.015 (95% CI 1.002-1.028) for the mean aPTT in the previous 24 hours prior to the event.[3]

Systematic reviews

Two recent systematic reviews, largely by the same authors, were published on anticoagulation practices during VV- ECMO [4] and VA- ECMO.[29]

VV- ECMO

A total of 18 studies (n=646) were included; 17 studies enrolled patients with acute respiratory distress syndrome. Across all studies, the duration of VV-ECMO support ranged from 4 to 20 days. Patients received an average of 2.3 (63.9) units of transfused red blood cells per day. The bleeding rate across all studies was 16%, and the rate of thrombosis was 53%. Among seven studies (199 patients) targeting a specified activated partial thromboplastin time (aPTT), there were 37 (19%) major bleeding episodes and 53 (27%) major thromboses. Among five studies (43 patients) with aPTT targets of 60 seconds or greater, there were 24 (56%) bleeding episodes and 3 (7%) clotting events. Three studies (156 patients) with an aPTT target under 60 seconds reported 13 (8%) and 50 (32%) significant bleeding and thrombotic events, respectively. The most commonly reported thrombotic events were circuit-related clotting and deep-vein thrombosis. Although this is not mentioned in this systematic review, when major bleeding and thrombosis events are combined and compared between aPTT targets, an aPTT target under 60 seconds had a RR of 0.64 95% CI 0.48-0.87) for major events compared to an aPTT target of 60 seconds or greater.

The authors conclude that an aPTT strategy of less than 60 seconds may be associated with fewer life-threatening bleeds, but this conclusion is based on a limited number of uncontrolled observational studies that included no comparison groups. A strategy aimed at minimizing anticoagulation and life-threatening hemorrhagic complications may be appropriate in that the majority of thrombotic complications reported in the studies we reviewed were related to device circuits, and may have been relatively insignificant clinically, but this is still unproven. The lack of high-quality evidence justifies and highlights the need for randomized, controlled trials of anticoagulation strategies for patients on VV-ECMO.

VA- ECMO

Twenty-six studies (1496 patients) were included. Ten studies only had patients with post-cardiotomy shock, 4 studies only included extracorporeal cardiopulmonary resuscitation patients, and 10 studies had a mixture of patients. Most studies (n=17) were low quality with a Newcastle-Ottawa Scale score ≤5. The summary prevalence of major bleeding was 27% (95% CI 18%-35%), with considerable between-study heterogeneity (I^2=91%). Major bleeding requiring reoperation was the most common bleeding event. The summary

prevalence of thromboembolic events was 8% (95% CI, 4%-13%; I^2 = 83%). Limb ischemia, circuit-related clotting, and stroke were the most commonly reported events. No comparisons could be made between studies with a high or low aPTT target.
The authors conclude that optimal targets and strategies for anticoagulation in VA-ECMO are unclear. Evaluation of major bleeding and thromboembolic events is limited by study quality and between-study heterogeneity. Clinical trials are needed to investigate the optimal anticoagulation strategy.

The intensive care medicine research agenda on ECMO

A clinical review from an international group of experts already concluded in 2016 that rigorous evaluations of anticoagulation use in ECMO patients are needed, since practice vary widely.[30] In 2017 the intensive care medicine research agenda on ECMO was published in Intensive Care Medicine, the journal of the European Society of Intensive Care Medicine (ESICM) that included what the international group of experts recommend as the top 10 studies/trials to be carried out in the next 10 years, and what are expected outcomes/results of these trials.[7] It may come as no surprise that one if the recommended studies to be performed is a RCT of reduced anticoagulation or alternative anticoagulant drugs in ECMO patients. Reducing anticoagulation might result in fewer bleeding complications and ultimately better short- and long-term outcomes, especially in patients on VV-ECMO. Alternative anticoagulant drugs together with better monitoring of the balance between coagulation and anticoagulation might also improve patient outcomes.

TABLE 1: Common adverse events by age and indication encountered during the course of ECMO [Adapted from: Thiagarajan RR, et al. Extracorporeal Life Support Organization Registry International Report 2016. *ASAIO J* 2017 January;63(1):60-67][6]

	Neonate (%)	Pediatric (%)	Adult (%)
Respiratory			
Mechanical: pump malfunction	1.6	2.2	1.5
Mechanical: oxygenator failure	5.7	10.6	9.1
Cannula hemorrhage	7.9	18.3	13.2
Surgical hemorrhage	6.3	12.6	10.5
Pulmonary hemorrhage	4.5	8.1	6.1
CNS hemorrhage	7.6	6.4	3.9
CNS infarction	6.8	4.2	2.0
Renal failure	7.8*	12.9*	9.3†
Hyperbilirubinemia	7.3	5.2	8.7
Infection	5.8	16.8	17.5
Cardiac			
Mechanical: pump malfunction	1.5	1.8	0.8
Mechanical: oxygenator failure	6.1	7.2	6.6
Cannula site hemorrhage	10.7	15.6	18.5
Surgical site hemorrhage	29.3	28.9	20.2
Pulmonary hemorrhage	5.2	5.3	3.1
CNS hemorrhage	11.3	5.3	2.2
CNS infarction	3.4	5.0	3.8
Renal failure	12.3*	7.2*	12.3†
Hyperbilirubinemia	4.9	7.2	12.2
Infection	7.1	11.0	13.0

Renal failure: serum creatinine *>1.5; †>3.0 mg/dl; hyperbilirubinemia: total bilirubin > 2 mg/dl or indirect bilirubin > 15 mg/dl.
CNS, central nervous system; ECLS, extracorporeal life support.

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6.4 Summary of known and potential risks and benefits

A risk may be that reduced anticoagulation target or anticoagulation with LMWH may lead to more thromboembolic event without a reduction in hemorrhagic complications. A benefit may be that reduced anticoagulation target or anticoagulation with LMWH will lead to a reduction in hemorrhagic complications and subsequent blood transfusion without an increase in thromboembolic events or mortality.

6.5 Description and justification of route of administration and dosage

Heparin is administrated intravenously using an aPTT guided dosage. LMWH is given subcutaneously based on weight and renal function and may be guided by activated fX

6.6 Dosages, dosage modifications and method of administration

Dose may be modified based on aPTT (heparin) or change in weight, renal function or anti-fXa (LMWH) or clinical complications mentioned in primary and secondary outcomes or HIT.

6.7 Preparation and labelling of Investigational Medicinal Product

Heparin already has a marketing authorization and is not used different from the authorized form nor used for an unauthorized indication. The heparin already in stock at the participating hospitals is used. No heparin is assembled (formulated or packaged) especially for this study. All participated hospitals use heparin assembled by their central pharmacy or external pharmacies; heparin is never prepared locally at the ICU by nurses.

6.8 Drug accountability

The heparin or LMWH products that are already in stock in the participating hospitals are used. No medication is assembled (formulated or packaged) especially for this study. No shipment, receipt, disposition, return and destruction of the investigational medicinal products are needed.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary outcome parameter is a composite endpoint consisting of: 1) severe hemorrhagic complications according to the ELSO definitions (see below); 2) severe thromboembolic complication defined as ischemic stroke, limb ischemia, or acute pump failure; 3) mortality at 6 months.

This composite outcome was designed to capture the net clinical effect of reduced anticoagulation targets, e.g. a reduction of major bleeding not counteracted by an increase in thromboembolic complications. Mortality is part of the composite outcome to capture unknown or unmeasured effects of reduced anticoagulation.

Severe hemorrhagic complications will be registered according to the ELSO Registry Data Definitions (version Feb 26th 2019) and is defined as any bleeding requiring >3U packed red blood cell (PRBC) or whole blood transfusion per calendar day or other intervention such as surgical or endoscopic intervention. Bleeding that involves the central nervous system is also considered major bleeding.[6] A calendar day is chosen over a 24 hour period because 24 hours could start or stop at any time and increases the likelihood of an error in data entry.

8.1.2 Secondary study parameters/endpoints

Secondary endpoints are all other variables that may be affected by anticoagulation regime. Secondary outcome parameters are: 1) blood transfusions; 2) quality of life (HR-QoL) at 6 months; 3) exchange of the membrane oxygenator (ECMO); 4) vessel thrombosis after ECMO removal detected by echography (see below); 5) pulmonary embolism; 6) costs; 7) the individual components of the composite outcome; 8) all thromboembolic complications combined; and 9) all hemorrhagic complications combined.

Within 72 hours after ECMO removal a standardized echography of the large veins are performed by a radiologist or skilled intensivist. If a venous thrombus is detected it

is left to the judgement of the treating physician or hospital guideline if and how long this is treated with anticoagulants.

8.1.3 Other study parameters

Baseline characteristics, disease characteristics, aPTT and anti-fX levels

8.2 Randomization, blinding and treatment allocation

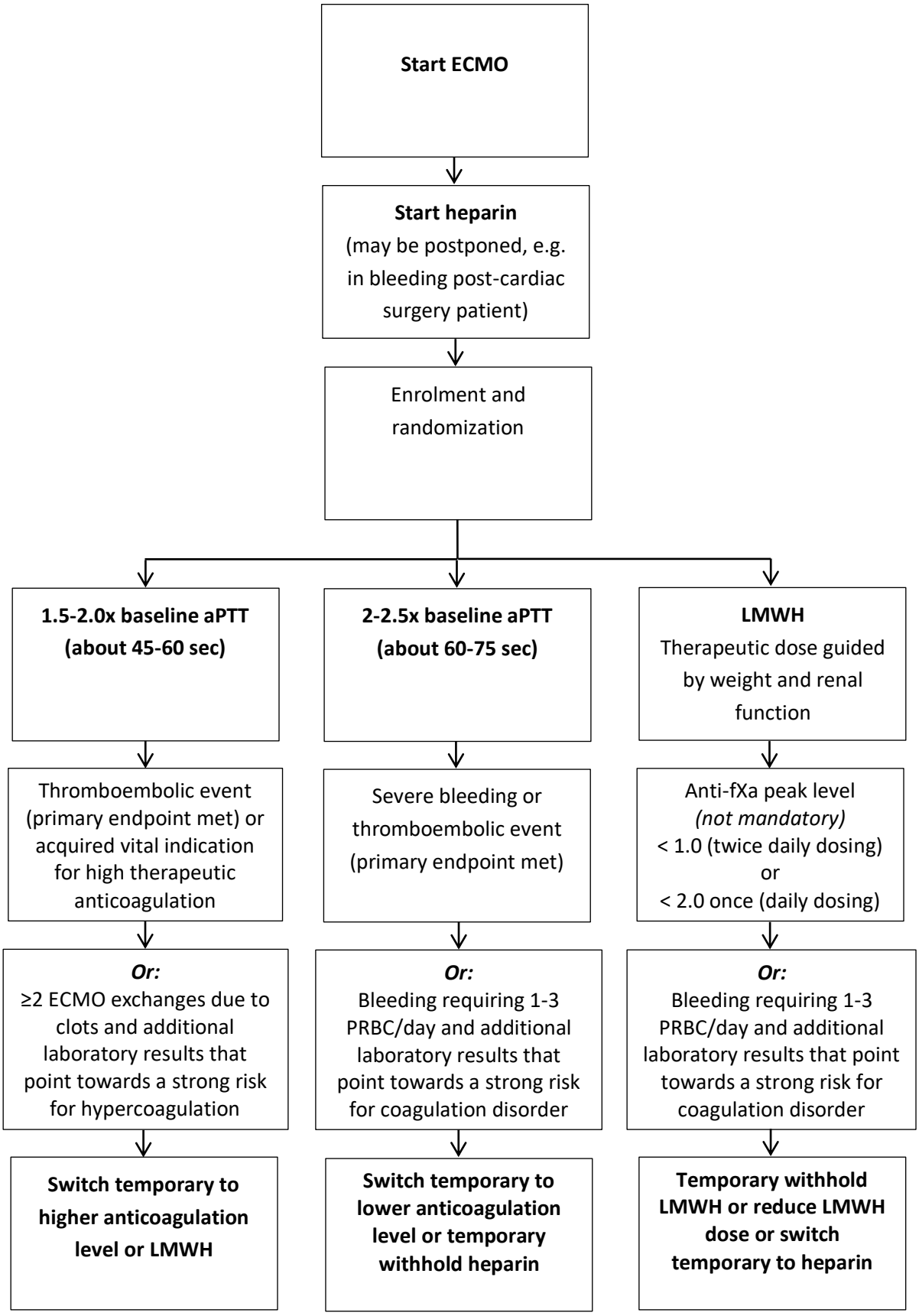
Phase 3, three-armed, randomized, non-inferiority open-label study. All patients who receive ECMO treatment during the study period in one the participating centers can be considered for enrolment in the study. Randomization will be 1:1:1, using variable block sizeand stratified by ECMO mode (VA or VV) and study site. Randomization will be performed if the subject meets all inclusion/exclusion criteria and will be processed centrally by means of a web-based system that will provide the randomization treatment arm (a target of 2-2.5x baseline aPTT, 1.5-2.0x or therapeutic LMWH). The online system (ALEA Research®) is constructed and validated for randomization and data management and has an audit trail. Contact persons of all participating centers can sign in and randomize their patients.
As the design is open label, that is single-blind (the patient),no indications for breaking the randomization code is provided in the protocol. Randomization is communicated with the local principal investigator of each participating hospital who further carries out the necessary arrangements. Based on the aPTT levels achieved concealed allocation can be controlled.

Crossover
We have a strong belief that less intensive anticoagulation reduce the chance of meeting the primary outcome, but to randomize between usual care and a lower anticoagulation target is a simplification of the problem. How much anticoagulation is needed to maintain circuit patency will vary according to an individual patient's coagulation status.
Occasionally physicians decide to change the level of anticoagulation based on complications or risk profile. To cover this in the current study design we chose to perform a three-armed RCT in which crossover to another arm than allocated is allowed based on any of the following:
1) meeting one of the components of the primary outcome; 2) an acquired vital indication for high therapeutic anticoagulation, e.g. mechanical heart valve or pulmonary embolism;

3) additional laboratory results, e.g. Hb, platelets, PT, anti-fXa, fV, fibrinogen, D-dimer, ATIII, and ROTEM/TEG that points towards a strong risk for coagulation disorder or hypercoagulation. These additional laboratory measurements are not required according to the study protocol, but are part of standard care in most centers, although type, availability (ROTEM/TEG), and frequency of measurements may differ. We deliberately chose not to requisite anti-Xa activity to monitor LMWH (if allocated) as there is a low correlation with heparin activity and target ranges are not validated for this indication. Furthermore, in our experience anti-Xa guided LMWH/heparin therapy leads to an increase in heparin administration, which is what we like to avoid.

Crossover to another treatment than allocated is in principle temporary. It is the intention to return to the treatment allocation as soon as possible. The timing of the reversion is left to the consideration of the treating physician. Crossover will be mentioned in the CRF and the primary and secondary outcome parameters will be measured and mentioned in the CRF after crossover as well. The primary analysis will be intention-to-treat based on treatment allocation. See also Flowchart below.

Flowchart. Decision tree randomization and crossover.



8.3 Study procedures

Eligible patients will be randomization between a target of 2-2.5x baseline aPTT (usual care, about 60-75 sec.), 1.5-2.0x (45-60 sec.) and therapeutic LMWH guided by weight and renal function (see Table LMWH below). No additional invasive procedures are performed in the course of the research. Only laboratory or radiological tests that are part of routine medical treatment are used for the CRF if relevant. Quality of life assessment (EQ-5D-5L) after 6 months will be recorded by means of a structured telephone interview for all patients.

Table LMWH. Suggestions for therapeutic dose LMWH based on weight and renal function

LMWH	<50 kg	50-70 kg	70-90 kg	>90 kg
Nadroparine				
• Fraxiparine®	2dd3800 IE	2dd5700 IE	2dd7600 IE	2dd9500 IE
• Fraxodi®	1dd7600 IE	1dd11400 IE	1dd15200 IE	1dd 19000 IE
	<60 kg	**60-80 kg**	**80-100 kg**	
Enoxaparine				
• Clexane®	2dd60 mg	2dd80 mg	2dd200 mg	
Tinzaparine				
• Innohep®				
Dalteparine				
• Fragmin®				

creatinine clearance 30-50 ml/min: 25% dose reduction
creatinine clearance < 30 ml/min: 50% dose reduction and consider monitoring anti-Xa activity

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

The study will continue until 330 patients are enrolled. If a subject is withdrawn for medical reasons the primary endpoint will still be reached and the subject is included in the primary outcome analysis (intention-to-treat). If informed consent is withdrawn the primary endpoint will not be reached and the subject will be replaced to retain statistical power.

8.6 Follow-up of subjects withdrawn from treatment

See paragraph 8.5

8.7 Premature termination of the study

The coordinating investigators have the right to discontinue the clinical study at any time for medical or procedural reasons.
The following criteria are defined on which basis the Safety Committee may decide to terminate the trial prematurely:

- Any serious adverse event
- A proven superiority (p<0.0151*, two-sided)* of reduced anticoagulation target or LMWH over standard treatment or a proven superiority (p<0.0151*, two-sided)* of standard treatment over reduced anticoagulation target or LMWH determined during the interim analyses after 150 patients (see chapter 10.4).

The Safety Committee reports its recommendations in verbal and in writing to the Principal Investigator. The Principal Investigator is responsible for further dissemination. The coordinating investigator will ensure appropriate archiving of Safety Committee recommendations (in addition to the Safety Committee own archiving). For further detail regarding Safety Committee and interim analyses see the relevant chapters in this protocol.

In case the study will be terminated prematurely the Principal Investigator will inform the METC, the sponsor and the local principal investigators of the study as soon as possible.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event. In the current study severe hemorrhagic complications (severe bleeding, hemorrhagic stroke), severe thromboembolic complication (ischemic stroke) and mortality are considered serious adverse events.

Of note, clinical research involving critically ill patients illustrates several concerns with the existing system for monitoring adverse events. Morbidity and mortality rates are high among patients in the intensive care unit (ICU). In this particular study population mortality rates exceed 50%. Critical illness itself often reflects a series of established or acquired complications that evolve, resolve or persist. Therefore,

whether enrolled in a trial or not, ICU patients are particularly likely to experience clinical events that fall within the definition of a serious adverse event. These events include death, nosocomial infection and laboratory test results indicating potentially dangerous physiologic abnormalities. Thus, if the foregoing definition is strictly applied, a high proportion of ICU patients may experience a serious adverse event.

We propose the following solutions for more rational reporting of SAEs in this study:

- We clearly describe the SAEs we plan to identify and report in this protocol and CRF for review by the METc and safety committee.
- We have labelled these adverse events as primary or secondary outcomes.
- Adverse events already defined and reported as study outcomes are not also labelled and reported as SAEs.
- SAEs are limited to serious events that are known to result from the study drug or that might reasonably occur as a consequence of the study drug.
- SAEs and deaths are reported in the 3 arms of the trial, examined at an interim analysis and after completion.
- Periodic reports (every 3 months) of SAEs will be reported through the web portal ToetsingOnline to the accredited METC that approved the protocol and the safety committee. However, caution should be exercised to avoid definitively attributing AEs or death to the study drug as the trial is unfolding.
- Since case fatality in the patient population under study is known to be around 50%, line listing of deaths will be performed, with reporting once per three months. This reporting will be the responsibility of the study coordinator and the primary investigator.
- As SAEs in the patient population under study is known to be around 60-70% line listing of SAE and case fatality per treatment allocation will be reported in the annual safety report and in the scheduled interim analysis including predefined stopping rules. The primary endpoint will also be part of the scheduled interim analysis including predefined stopping rules.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);

2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorized medicinal product;
   - Investigator's Brochure for an unauthorized medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every 3 months to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

The local principal investigator will immediately report all SUSARs to the project leader or his representative who will subsequently report to the sponsor.
As allocation is known in this open label study an abnormal distribution of SUSARs between the two study groups will be immediately recognized and reported.

Of note: the authorized medicinal products used in this study are used for decades in the population under study so no SUSARs are expected to occur in this study.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

We have appointed a Safety Committee to perform interim analyses for safety, futility or positive efficacy so that the Steering Committee can remain blinded for the outcome of the study. Chair of the Safety Committee will be Prof. dr. Dylan W. de Lange from the UMC Utrecht. The other members will be Dr. David J. van Westerloo, intensivist at the Leiden UMC and Prof. dr. Nicole P. Juffermans, intensivist at Amsterdam UMC, location AMC. All members have no conflict of interest with the sponsor of this study.

The Safety Committee will:

- monitor recruitment figures and losses to follow-up
- monitor evidence for treatment harm (AEs, SAEs, deaths)
- monitor overall conduct, data quality, including completeness, encouraging collection of high quality data.

- make recommendations that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups
- perform the pre-planned interim analysis and recommend on continuation of the study accordingly
- suggest additional data analyses
- give uncalled-for recommendations based for example on data from recently presented studies
- give uncalled-for recommendations if the assumptions made for the sample size calculation of the study prove to be incorrect. The assumptions may pertain to patient accrual and the incidence of the primary outcome event.

Because of the expected high proportion of patients with a poor outcome in the patient group under study, and the consequent overlap between safety endpoints and the primary endpoint, the evaluation of safety by the Safety Committee will be quantitative and qualitative.

Formal statistical methods

One formal interim analysis on efficacy is planned after 150 (45%) patients are included. Stopping criteria follow the O'Brien-Fleming based α-spending function will be applied, hence interim analysis boundaries are as follows:

Interim	Nominal two-sided α	Lower Z-value for difference	Upper Z-value for difference
150 patients	0.01	- 2.576	2.576
Final analysis	0.05	-1.96	1.96

In case additional interim analyses are considered necessary or the timing changes, criteria will be adapted according the O'Brien-Fleming based α-spending function.
These criteria will be used as guidance in an overall assessment, as the Steering Committee supports the view voiced by Canner, on behalf of the Coronary Drug Project (1981), that in clinical trial decision making "No single statistical decision rule or procedure can take the place of the well-reasoned consideration of all aspects of the data by a group of concerned, competent and experienced persons with a wide range of scientific backgrounds and points of view."

The Safety Committee will monitor differences in rates of occurrence of case-fatalities between treatment groups as well as other safety aspects. Summaries will be provided such that events can be categorized and compared between treatment groups in a clinically meaningful way. Substantial differences guided by statistical criteria (two-sided p-value < 0.01) and/or clinical judgment may lead to a recommendation to discontinue the trial for safety reasons, when weighed against potential intervention benefits.

It is the sponsor's obligation to inform the Safety Committee of concerns regarding the safety of the subjects. Such concerns could refer to (new) side effects, data from other studies etc.

The advice(s) of the Safety Committee will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the Safety Committee, the sponsor will send the advice to the reviewing METC; including a note to substantiate why (part of) the advice of the Safety Committee will not be followed.

10. STATISTICAL ANALYSIS

Baseline characteristics, raw distributions on the CPC, and scores of secondary outcome measures will be presented in a descriptive way. Missing data will be clearly mentioned in the results and tables. Subjects lost to follow-up will be mentioned in the flowchart of the study.

10.1 Primary study parameter(s)

The primary analysis will be a single comparison between the treatment groups of the primary outcome measure after six months. This analysis will be performed according to the intention-to-treat principle. To assess the effect of treatment with lower anticoagulation targets or LMWH with standard care, an absolute risk reduction of poor outcome and its corresponding 95% confidence interval will be calculated. The confidence interval of the risk reduction will be compared with the non-inferiority marge of 7.5% of both intervention arms adjusted for center and ECMO mode.

10.2 Secondary study parameter(s)

For secondary outcome measures, between-group differences will be analyzed by means of independent samples t-tests, chi-square test, or Mann-Whitney tests, where appropriate and adjusted for center an ECMO mode. If necessary, multivariable regression analysis will be used to adjust for imbalances in main prognostic variables between intervention and control group.

10.3 Other study parameters

Cost effectiveness analyses

The difference in costs for use of heparin and aPTT measurements will be neglectable. Cost-effectiveness will be based on reduced costs of blood transfusions and interventions for bleeding (e.g. surgery, interventional radiology) as well as improved outcome. All medical cost items expected to be affected by the ECMO therapy will be measured and valued according to the Dutch standard guidelines for economic evaluations, e.g. blood transfusion, number of ECMO replacements, surgery, and hospital length of stay.
Health gains will be measured in terms of QALYs based on EQ-5D-5L defined utilities.
The BIA will be performed from a healthcare perspective to inform decision makers about the financial consequences of reduced anticoagulant targets in ECMO treatment in Dutch healthcare. The model will take changes in the availability and adoption of the reduced

anticoagulant targets into account by calculating the financial consequences of five scenarios with a time horizon of 5-10 years.

10.4 Interim analysis (if applicable)

A pre-specified, unblinded interim analysis will be performed when the first 150 patients have been enrolled in the study. An independent statistician will perform this analysis and the results will be presented to the Safety Committee. In addition to the usual tasks of the Safety Committee (safety based on SAE and predefined stopping rules based on the primary endpoint), the commission is to calculate the power for non-inferiority, conditioned on the difference between treatments with respect to outcome rates and on the non-inferiority margin of 7.5%. If the conditional power is 50-79%, the sample size will be re-estimated to maintain a conditional power of 80%.

If the difference between the treatments groups will be significant at alfa level of 1% the trial will be stopped because of “proof beyond reasonable doubt” that intervention treatment is non-inferior to standard treatment.

If the periodic list of primary and secondary endpoints in this open label study suggest a unexpected large trend towards inferiority or superiority of one of the allocated groups an advanced interim analysis may be suggested by the Safety Committee or METC.

Interim analyses will be performed by the Safety Committee. See chapter 9.5 for details of statistical methods and stopping rules.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

11.2 Recruitment and consent

Eligible patients are recruited as soon as possible following initiation of ECMO treatment. In view of the prevention of thromboembolic complications it is important to start the intervention as soon as possible. Regardless of treatment allocation a bolus of 2500U of heparin is given during cannulation and continuous heparin administration is started immediately thereafter with a dosage guided by aPTT levels (or weight and renal function in case of LMWH), hence anticoagulation will be given according to the allocation of the randomization to all eligible patients.

The patients eligible for this study are critically ill and usually sedated and not able to provide informed consent. The study intervention regards an emergency intervention that has to be applied without delay and fulfills the ethical requirement of clinical equipoise. The study participant can benefit from the intervention, but up to now there is a state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment (lower anticoagulation targets or not). Some centers in the Netherlands apply heparin with target levels similar aimed for in this study and others do not. Furthermore, the eligible patients have an extremely high risk of dying (the indication for ECMO is a mortality probability of more than 80% with conservative therapy) and the legal representatives will therefore be in a disturbed mental state complicating an immediate informed decision. For the present study, the local investigator or research nurse will inform the patient about the study intervention if and when his consciousness recovers (deferred consent). As the patient usually remains unable to communicate for several weeks the legal representative is contacted as soon as possible and ask deferred proxy consent for use of the study data.The rationale for the deferred consent procedure is the clinical equipoise of the interventions, the emergency of the intervention and the possible benefit for the patient with a positive benefit risk ratio. If the patient has died at that time, the study data will be used. The rationale for the latter is that the legal representatives have no independent right on inspection or say on of therapeutic or study data (CCMO: “De nabestaanden hebben geen zelfstandig recht op inzage van de tijdens

de behandeling en het onderzoek verkregen gegevens en hebben daar ook geen zeggenschap over. Van toestemming voor het gebruik van de data door de nabestaanden kan daarom ook geen sprake zijn). Furthermore, possible refusal may cause selection bias and this is ethically unwanted (CCMO: het introduceren van selectiebias door het moeten vragen van toestemming aan de nabestaanden, mocht daar een grond voor zijn, ethisch niet wenselijk is)."

11.3 Objection by minors or incapacitated subjects (if applicable)

Due to the nature of the study population all subjects are incapacitated adults at the time of informed consent for which reason the method of deferred consent is used in all cases. Minors are not recruited.

11.4 Benefits and risks assessment, group relatedness

We estimate that with an aPTT target of 45-60 sec. or with use of LMWH the primary endpoint will be met in 60% of patients compared to 70% with usual care.
Apart from anticoagulation targets, treatment will be as usual so study participation will not lead to a burden for the patient, e.g. no extra blood sampling, tests or visits. After 6 months the patients will be contacted for a questionnaire to measure health-related quality of life. A risk may be that reduced anticoagulation target or anticoagulation with LMWH is inferior to standard practice. A benefit may be that reduced anticoagulation target or anticoagulation with LMWH is superior to standard practice.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The investigator will set up a Trial Master File at the beginning of the study. The list of essential documents will be in accordance with the GCP-guidelines. The essential documents that make up the file will be stored in a secure but accessible manner. All essential documents will be legible and accurate. The participating centers will keep copies of relevant documents, including essential center-specific documents.

For each randomized patient a digital Case Record Form (CRF) will be completed. The CRF consists of a sequential set of instructions with provision for data recording. All randomized patients are identified by a Patient Identification Number (PIN) in combination with a center number. Trial personnel will not pass names outside the local hospital. The investigator will insure that patients' anonymity is maintained. On screening forms, digital or paper CRFs or other documents submitted to the coordinating center, patients will not be identified by their names but by a PIN in combination with a center number. The subject identification code list will be safeguarded by the investigator.

Central data management will be performed in REDCap (Research Electronic Data Capture) by technicians and data managers of the Trial Coordination Center (Department of Epidemiology, University Medical Center Groningen). Internet-based remote data capture will be used for entering, managing and validating data from the investigative sites.
REDCap is a secure web application for building and managing online surveys and databases powered by Vanderbilt University Medical Center (1211 Medical Center Drive, Nashville, TN 37232, USA). REDCap is designed to meet industry regulations, including:

- FDA 21CFR Part 11 Rule (March 20, 1997),
- ICH; Good Clinical Practice: Consolidated Guideline (May 9, 1997)
- FDA Guidance for Industry “Computerized Systems Used In Clinical Trials” (May 10, 1999)

The data will be kept for at least 25 years.

12.2 Monitoring and Quality Assurance

Monitoring will be executed in compliance with the NFU (The Netherlands Federation of University Medical Centers)-guideline “Quality Assurance of research involving human subjects 2.0”. Monitoring will be performed by an independent and qualified monitor.
To ensure patient’s rights, wellbeing and safety, compliance as well as quality of data, the monitor will visit the sites on a regular basis. For this study the risk classification is considered low (based on the NFU guideline), which implies monitoring of at least 1 visit per site per year. Frequency of the visits depends on the actual patient inclusion rate and the observed events and deviations on a site.
The monitor will verify the following items: patient flow (inclusion and dropout rate); Informed Consent Forms (presence, dates, signatures); Trial Master File and Investigator Site File (presence of all essential documents); in- and exclusion criteria; primary endpoint; SAEs / SUSARs (missed events, reporting procedures); study treatment (patient instructions, administration, accountability). Source data verification will be performed for a selection of patients on a pre-selected set of data (focused on endpoints and safety). Source documents are defined as the patient’s hospital medical records, clinician notes, laboratory print outs, digital and hard copies of imaging, memos, electronic data etc.
The monitor will verify the compliance to study procedures, Standard Operating Procedures and other instructions. The presence of certificates, Standard Operating Procedures and instructions related to devices, facilities, laboratories, pharmacy and other departments involved will be checked.

Findings from the monitoring visits will be reported by the monitor to the sponsor-investigator through a monitoring visit report. It is the responsibility of the sponsor-investigator to follow up on findings, deviations, queries or other issues where required.

12.3 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

The study will be registered in a public trial registry (clinicaltrials.gov) before the first patient is recruited. The results of this study will be disclosed unreservedly.

STRUCTURED RISK ANALYSIS

12.7 Potential issues of concern

Heparin and LMWH are registered products and already frequently used in critically ill patients among which, but not restricted to, patients treated with ECMO. More anticoagulation is associated with less thromboembolic complications and more hemorrhagic complications. Formally, we have the opinion that chapter 13.1 can be skipped, but we decided to maintain this chapter to allows an efficient communication with the METC.

a. Level of knowledge about mechanism of action

See: https://www.uptodate.com/contents/heparin-and-lmw-heparin-dosing-and-adverse-effects

Heparins, including unfractionated heparin and a variety of low molecular weight (LMW) heparin products, are used extensively as anticoagulants. Heparin is an endogenously produced, linear polysaccharide that consists of repeating units of pyranosyluronic acid and glucosamine residues. Endogenous heparin and heparin-binding proteins have a variety of anticoagulant, anti-inflammatory, and possibly anti-angiogenic effects, which are incompletely understood.

The form of heparin used clinically as an anticoagulant is isolated from porcine (pig) or bovine (cow) intestines. It has a mixture of different-length polysaccharides, with a mean size of approximately 45 saccharide units, corresponding to a mean molecular weight of approximately 15,000 daltons (range 3000 to 30,000 daltons). Low molecular weight (LMW) heparins are derived via enzymatic or chemical depolymerization of unfractionated heparin, resulting in a product with a mean length of approximately 15 saccharide units and a mean molecular weight of approximately 4000 to 5000 daltons (range 2000 to 9000 daltons). Fondaparinux, which consists of the minimal AT-binding region of heparin, contains five saccharide units (ie, pentasaccharide) and has an approximate molecular weight of 1700 daltons.

Heparins act indirectly by binding to antithrombin (AT, formerly called AT III, also known as heparin cofactor I) rather than by binding directly to coagulation factors (figure 1). Binding of heparin to AT is mediated by a unique pentasaccharide sequence in heparin that is randomly distributed along the heparin chains. The binding site for heparins on AT is located at the AT amino terminus. Binding of heparin to this site on AT induces a conformational change in AT, which converts AT from a slow to a rapid inactivator of coagulation factors (eg, thrombin [factor IIa], factor Xa). The enhancement of AT anticoagulant activity by heparins is on the order of 1000- to 4000-fold.

Both unfractionated and LMW heparins efficiently inactivate factor Xa via AT. However, unfractionated heparin is a much more efficient inactivator of thrombin because thrombin inactivation requires the formation of a ternary complex between heparin, AT, and thrombin, and this ternary complex can form only when heparin chains are at least 18 saccharide units long. These 18-saccharide-long units are present to a much smaller extent in LMW heparins and are absent from fondaparinux. Thus, unfractionated heparin, LMW heparin, and fondaparinux all inactivate factor Xa, but unfractionated heparin also inhibits thrombin. Fondaparinux appears to have nearly pure anti-factor Xa activity.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

Heparin and LMWH are registered products and are used extensively as anticoagulants in critically ill patients among which, but not restricted to, patients treated with ECMO.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

This product has been available for many years and its side effects and clinical profile are well-understood, therefore no further data is provided.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Unfractionated heparin
Heparin is metabolized in the reticuloendothelial system and the liver, and it is excreted in the urine. Renal function does not affect elimination at therapeutic doses, although renal elimination may play a role at very high doses. However, dose adjustment is not used in patients with renal insufficiency or renal failure.

The onset of heparin action when administered intravenously is instantaneous; plasma levels following subcutaneous administration peak at two to four hours, with considerable individual variation. The metabolism of heparin is complex and dose-dependent, with a half-life of approximately 45 minutes to one hour.

Heparin is not intended for intramuscular use and cannot be given orally.

Variable bioavailability of unfractionated heparin is due in part to competitive occupation of binding sites by proteins other than antithrombin (AT) and coagulation factors, including plasma proteins, proteins secreted by platelets (eg, platelet factor 4), and proteins secreted by endothelial cells. Some of these heparin-binding proteins are acute phase reactants that may be increased substantially in acutely ill patients.

Low molecular weight (LMW) heparins
LMW heparins are metabolized in the liver and excreted by the kidney. Renal clearance contributes approximately 10 to 40 percent. Patients with renal impairment may have reduced clearance of LMW heparins, with marginally increased plasma levels in individuals with mild to moderate renal insufficiency. Individuals with creatinine clearance <30 mL/min have a significantly increased plasma level (eg, by approximately 65 percent) and generally require dose adjustment.

Plasma levels peak at approximately three to five hours after subcutaneous administration and at approximately two hours after intravenous administration. When administered subcutaneously (the most common route of administration), the half-life of LMW heparins ranges from three to seven hours if renal function is normal. Steady state levels are reached on approximately day two to three of therapy.

e. Analysis of potential effect
Once an initial dose has been administered, therapeutic (full-dose) heparin administration is monitored using a combination of clinical assessment and laboratory testing. The infusion rate is adjusted based on results of laboratory testing, e.g. aPTT or anti-factor Xa activity. LMW heparins are typically administered subcutaneously in fixed or weight-based dosing without monitoring, and no laboratory assessment of the LMW heparin anticoagulant effect has been correlated with clinical endpoints.

f. Pharmacokinetic considerations

See section d. Selectivity of the mechanism to target tissue in animals and/or human beings

g. Study population

The study population will consist of critically ill adult patients with heart or lung failure, admitted to the intensive care unit. Patients may be in cardiogenic shock. Pregnancy is no contra-indication as magnesium is safe for both mother and the fetus. Some heparin solutions contain the preservative benzyl alcohol, which undergoes oxidation to benzoic acid and then conjugation in the liver before being eliminated. This metabolic pathway is not well developed in infants, and benzyl alcohol has been associated with serious adverse events such as metabolic acidosis and even death in pediatric patients. Thus, preservative-free solutions should be used during pregnancy.
Heparin and LMWH are registered products and are used extensively as anticoagulants in critically ill patients among which, but not restricted to, patients treated with ECMO.

h. Interaction with other products

The anticoagulant effect of heparin can be increased by medications that have an effect on coagulation, e.g. NSAID's, SSRI's, vitamin K, protein C, or antiplatelets.

i. Predictability of effect

See paragraph e. Analysis of potential effect

j. Can effects be managed?

Reversal

The management of bleeding in a patient receiving heparin depends upon the location and severity of bleeding, the underlying thromboembolic risk, and the current aPTT (for heparin) or anti-factor Xa activity (for LMW heparin). As an example, a patient with minor skin bleeding in the setting of a mechanical heart valve (high thromboembolic risk) and a therapeutic aPTT may continue heparin therapy, whereas a patient with major intracerebral bleeding in the setting of a venous thromboembolism several months prior who is receiving heparin bridging perioperatively may require immediate heparin discontinuation and reversal with protamine sulfate. Clinician judgment and early involvement of the appropriate consulting specialists is advised.

Urgent reversal (protamine)

The need for urgent heparin reversal is individualized according to the site and severity of bleeding and the degree of anticoagulation. If urgent reversal is required, heparin is discontinued and protamine sulfate is administered at a dose calculated based on the dose of heparin administered and the elapsed time since the last heparin dose. Importantly, protamine sulfate is administered by slow intravenous infusion; the infusion rate should not exceed 20 mg/minute and the total dose should not exceed 50 mg in any 10-minute period.

Unfractionated heparin

Full neutralization of heparin effect is achieved with a dose of 1 mg protamine sulfate/100 units of heparin. Because of the relatively short half-life of intravenously administered heparin (approximately 30 to 60 minutes), the dose of protamine sulfate is calculated by estimating the amount of heparin remaining in the plasma at the time that reversal is required. If this information is not immediately available, administration of a single dose of 25 to 50 mg can be given and the aPTT or anti-factor Xa activity rechecked.
If heparin had been given by subcutaneous injection, repeated small doses of protamine may be required because of prolonged heparin absorption from the various subcutaneous sites.

LMW heparin

Unlike its efficacy with unfractionated heparin, protamine does not completely abolish the anti-Xa activity of LMW heparins, but it may neutralize the higher molecular weight

fractions of heparin, which are thought to be most responsible for bleeding. For patients who experience bleeding while receiving LMW heparin, protamine sulfate may be used at the following doses:

- Enoxaparin administered in the previous eight hours: 1 mg protamine per 1 mg of enoxaparin.

- Enoxaparin administered more than eight hours ago, or if it has been deemed that a second dose of protamine is warranted: 0.5 mg protamine per 1 mg of enoxaparin.

- Dalteparin, tinzaparin, or nadroparin: 1 mg protamine per 100 anti-factor Xa units of LMW heparin.

Of note, protamine is a protein derived from fish sperm and it carries a small but potential risk of anaphylaxis in individuals who have previously been exposed, including diabetic patients who have received protamine-containing insulin (eg, NPH, PZI), and individuals with fish allergy (protamine is derived from fish). However, unless such an allergy is known, the benefits of protamine administration to manage bleeding are likely to greatly outweigh this potential risk. The product information carries a Boxed Warning regarding the risks of hypotension, cardiovascular collapse, non-cardiogenic pulmonary edema, catastrophic pulmonary vasoconstriction, and pulmonary hypertension for patients who have previously received protamine sulfate or other protamine-containing drugs. Patients at increased risk who are receiving protamine should be monitored closely, and access to therapies for anaphylaxis should be available. Thrombocytopenia following protamine administration has also been reported.

12.8 Synthesis

Heparins, including unfractionated heparin and a variety of low molecular weight (LMW) heparin products, are used extensively as anticoagulants and possess a favorable safety profile and are frequently used in critically ill patients with target serum levels as in the current study. A risk may be that reduced anticoagulation target or anticoagulation with LMWH is inferior to standard practice. A benefit may be that reduced anticoagulation target or anticoagulation with LMWH is superior to standard practice. We consider the study as low risk with no major risks for the subjects participating in the study.

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