Trials

STUDY PROTOCOL

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Reduced anticoagulation targets in extracorporeal life support (RATE): protocol for a pre-planned secondary Bayesian analysis of the rate trial

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Abstract

Background The RATE trial is a three-arm non-inferiority randomized controlled trial in adult patients treated with extracorporeal membrane oxygenation (ECMO) on the effect of anticoagulation levels on mortality, hemorrhagic, and thrombotic complications. The current protocol presents the rationale and analysis plan for evaluating the primary and secondary outcomes under the Bayesian framework.

Methods This protocol was drafted and submitted before study completion and, thus, the primary analysis. The primary outcome of the Bayesian analysis is mortality at 6 months. The secondary outcomes are severe hemorrhagic and thrombotic complications. We will use an uninformative prior for the primary analysis. Sensitivity analyses will be performed using a skeptical prior and an evidence-based informative prior.

Conclusion The proposed secondary, pre-planned Bayesian analysis of the RATE trial will provide additional information on the effect of different anticoagulation strategies during ECMO on complication rates. This additional Bayesian analysis will likely increase the validity of our results and complement the interpretation of the primary and several secondary outcomes.

Trial registration This trial is registered at https://clinicaltrials.gov/ (NCT04536272), registration date September 2, 2020. This trial is also registered at the Dutch trial register (NL7976).

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Introduction

Based on indication, mortality rates in extracorporeal membrane oxygenation (ECMO) support patients vary between 30 and 60%. For a large part, mortality is treatment-related due to complications. The most worrying complication is ischemic stroke, for which heparin is administered with an activated partial thromboplastin time (aPTT) target 2.0–2.5 times baseline (approximately 60–75 s.). However, there is no proven statistically significant 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 [1]. Both are strongly related to outcome in terms of mortality.

Objectives RATE trial

Our objective is to study if reduced anticoagulation targets during treatment with heparin, or, as a second intervention, treatment with low molecular weight heparin (LMWH), diminish bleeding complications without an increase in thromboembolic complications or a negative impact on outcome in terms of mortality.

Study design

The RATE trial is a three-arm non-inferiority prospective randomized controlled multicenter trial.

All patients who receive ECMO support during the study period in one of the participating centers are considered for enrolment in the study. Randomization will be performed if the patient meets all inclusion criteria and fails to meet all exclusion criteria as previously described in the study protocol [2]. Randomization will be in a 1:1:1 ratio to the three arms, using variable block sizes and stratification by ECMO mode veno-arterial or veno-venous (VA or VV) and study site. Randomization will be processed centrally using a web-based system that will output the randomly selected treatment arm for a given patient (control: a target of 2–2.5 × baseline aPTT, intervention I: a target of 1.5–2.0 × baseline aPTT, intervention II: therapeutic LMWH).

Outcomes

The primary outcome parameter of the RATE trial is a composite endpoint consisting of (1) severe hemorrhagic complications according to the ELSO definitions: clinically overt bleeding with a transfusion requirement of more than 20 ml/kg red blood cell (RBC) transfusions or > 3U RBC in one calendar day; bleeding that is retroperitoneal or pulmonary or involves the central nervous system or bleeding that requires surgical intervention will also be considered major bleeding; (2) severe thromboembolic complication defined as ischemic stroke, limb ischemia, or acute pump failure; and (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.

Sample size

The RATE trial is powered for the primary composite endpoint: (1) severe hemorrhagic complications according to the ELSO definitions; (2) severe thromboembolic complication defined as ischemic stroke, limb ischemia, or acute pump failure; and (3) mortality at 6 months. We estimate that cases reaching the composite endpoint decrease from 70% in the control arm to 60% in each intervention arm. This sample size calculation is made 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 arm. To compensate for a lower effect and potential drop-outs, 330 patients will be enrolled.

Trial status

The inclusion of the RATE trial is completed. The first patient was included on October 22, 2020, and the last on September 12, 2024. The follow-up will be completed on March 11, 6 months after the final inclusion. At this point, the database will be locked.

Framework

A non-inferiority hypothesis testing framework will be used for the primary and secondary endpoints.

The final analysis for the primary and most secondary endpoints is planned when the 6-month follow-up is completed for the last surviving included patient. Longer-term secondary endpoints will be analyzed as soon as data collection is complete.

The primary analysis of the RATE trial will be conducted according to the frequentist statistical principles. This statistical analysis plan is reported and published in Trials [10]. The results of these analyses are often interpreted in a dichotomous matter, based on the *p*-value chosen as the threshold for "statistical significance" and "no evidence of effect" is confounded with "evidence of no effect." Bayesian analysis may provide information on the probability of benefits and harms, which may be more easily interpretable and less susceptible to the long-standing tradition of misinterpreting results achieved

using frequentist statistics. Therefore, we will also perform an analysis using the Bayesian approach described below.

Rationale for Bayesian inference

There has been an uptick in the use of Bayesian inference in clinical trials [1–3]. Often-cited advantages are a gain in statistical power due to the ability to test sequentially and incorporate prior knowledge [4]. This means that Bayesian inference may be profitably used when, due to time or resource constraints, the sample size would be underpowered in the context of more traditional analysis strategies. Furthermore, Bayesian parameter estimation does not yield dichotomous results and therefore facilitates clinical interpretation of results of secondary outcomes or subgroup analysis that would yield type II errors under a frequentist testing framework.

Generally, Bayesian inference features three elements: the prior, the likelihood, and the posterior. The prior is typically specified as a probability distribution over plausible parameter values. It does not incorporate any information provided by the data, nor should it be influenced by it (but see, e.g., [5]). Instead, the prior reflects a priori knowledge about plausible parameter values (e.g., in situations where one-sided testing makes sense, the prior would assign zero probability to the area of the parameter space that is not included in the one-sided alternative). The likelihood contains the information provided by the data. It reflects what the data tells us we should believe about possible parameter values. The posterior reflects what we should believe about possible parameter values, incorporating both our a priori belief (i.e., the prior) and the data (i.e., the likelihood).

Thus, the specification of the prior is one of the strengths of the Bayesian approach, but it comes with a cost: careful specification of the prior is essential to ensure the results of statistical inference are not driven by a poorly chosen prior. The typical solution to this is to perform a kind of sensitivity analysis, where the same analysis is conducted through the lens of a skeptic (i.e., a conservative prior), through the lens of a believer (i.e., a liberal prior), and through the lens of someone agnostic (i.e., an uninformative prior) [6, 7]. Ideally, the resulting posteriors converge qualitatively for the different types of prior distributions. More detailed expositions on Bayesian inference are available elsewhere (e.g., [8]). In the next section, we describe the Bayesian approach in the context of the current trial data. None of the authors are aware of the trial results except for the occurrence of complication and mortality rates in the control group based on the interim analysis of the RATE trial.

Outcomes of the current analysis

The primary outcome of this analysis will be mortality at six months. In addition, we use thrombotic and hemorrhagic complications as secondary outcomes, using the same definitions as in the published protocol and mentioned in the "Outcomes" section. For each outcome, we will compute posteriors, which reflect the absolute risk difference (ARD) and the natural logarithm (log) of the risk ratio (RR) between the two arms. Having a total of three arms—(1) UFH with a target of 2–2.5×baseline aPTT (usual care, about 60–75 s), (2) UFH with a target of 1.5–2.0×baseline (45–60 s), and (3) therapeutic dosage LMWH (guided by weight and renal function)—arms 2 and 3 will be compared to arm 1. We define the minimally clinically important difference (MCID) in terms of ARD to be −5% for mortality and −10% for both thrombotic complications and hemorrhagic complications, based on standards of the Knowledge Institute of the Federation of Medical Specialists ("Kennisinstituut MSF") [9, 10].

Prior specification

Prior distributions were derived from reported event rates in low-dose and full-dose heparin conditions. Specifically, we used normal priors with a mean equal to the log RR and a standard deviation (SD) equal to the standard error of the log RR. We will use an uninformative prior for the primary analysis. As such, the posterior probability distribution derived from this prior will be primarily informed by the results from the RATE trial. Sensitivity analyses will be performed using a skeptical prior and an evidence-based informative prior (see Table 1).

Skeptical priors were constructed based on expected rates of mortality, thrombotic complications, and hemorrhagic complications in the control group in the RATE trial. In each case, we assumed a 90% skeptic rate, meaning that there was a 90% prior probability that assumed that there was no clinically meaningful difference between groups (see [6] for a similar approach).

For the endpoints "mortality," "thrombotic complications," and "hemorrhagic complications" relevant to the current Bayesian analysis, informative priors could not be derived from the available literature. The most recent systematic review and meta-analysis, which includes comparative studies of the safety and efficacy addressing the clinical effectiveness of low-dose versus standard-dose heparin in patients supported with ECMO, included six publications with 592 patients and reflects the latest results on hemorrhagic and thrombotic complications and mortality of low-dose versus standard-dose heparin for patients receiving ECMO[11]. Although this

Table 1 Prior distributions of outcome parameters

	Priors	Mean (log RR)	SD (log RR)	Rationale
Mortality	Uninformative	0	3	Let data exert maximum influence
	Skeptical	0	0.11	Assuming 38% mortality in the control group based on interim analysis and a 10% probability of an MCID (> 5% reduction ARD)
	Informative	**NA**	**NA**	**NA**
Thrombotic complications	Uninformative	0	3	Let data exert maximum influence
	Skeptical	0	0.69	Assuming 17% thrombotic complications in the control group based on interim analysis and a 10% probability of an MCID (> 10% reduction ARD)
	Informative	NA	NA	NA
Hemorrhagic complications	Uninformative	0	3	Let data exert maximum influence
	Skeptical	0	0.14	Assuming 60% hemorrhagic complications in the control group based on interim analysis and a 10% probability of an MCID (> 10% reduction ARD)
	Informative	**NA**	**NA**	**NA**

MCID minimally clinically important difference, *ARD* absolute risk difference, *SD* standard deviation, *RR* risk ratio, *Log* logarithm, *NA* not applicable

systematic review is currently the best available evidence, it cannot be used for informative priors as the information is based mainly on observational studies, and the results are overly optimistic (relative risk for low-dose heparin for mortality 0.70; for thrombotic complications 1.36; and hemorrhagic complications 0.72).

Posterior calculation and software

We will present posterior distributions for mortality, thrombotic complications, and hemorrhagic complications under each of the three presented priors in terms of log RRs. We will also present results in terms of multiple ARDs to facilitate interpretation. We will include probabilities for benefits (i.e., negative ARD), harm (i.e., positive ARD), benefits higher than MCID (i.e., ARD < MCID; see the "Outcomes of the current analysis" section), and harms no greater than -MCID (i.e., ARD < -MCID; non-inferiority). It is pathophysiologically unlikely that less anticoagulation will lead to fewer thrombotic complications and vice versa for hemorrhagic complications; therefore, we will only analyze the clinical logical ARDs. See Table 2 for the overview of the ARDs analyzed.

Analyses will be performed using a Bayesian logistic regression model that we implemented in the "rstan" R package [12], incorporating No-U-Turn sampling (4 chains, 2500 burn-ins, thinning of 2, and 25,000 saved iterations per chain), yielding a total of 100,000 samples.

Table 2 MCID and ARD

	MCID	Positive ARD	Negative ARD
Mortality	−5%	0%, 2%, 5%, 10%	−0%, −2%, −5%, −10%
Thrombotic complications	−10%	0%, 2%, 5%, 10%	-
Hemorrhagic complications	−10%	-	−0%, −2%, −5%, −10%

MCID minimally clinically important difference, *ARD* absolute risk difference

Conclusion

This Bayesian statistical analysis plan for the RATE trial includes a detailed predefined description of how data will be analyzed and presented for our secondary analyses. We have included detailed descriptions of the statistical considerations aimed at limiting selective reporting bias. This statistical analysis plan will likely increase the validity of our results.

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None.

Authors' contributions
The Dutch ECLS study group led by WvdB conceived the study and developed the original protocol. DVR, ML, and OvM wrote the first draft of this manuscript, with edits from all authors. All authors reviewed and approved the final manuscript.

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Data availability
The study data is available from the corresponding author upon reasonable request after an embargo of 6 months after publication.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the MREC of the University Medical Center Groningen. Written informed consent to participate and publication of study data will be obtained from all participants or their legal representatives.

Consent for publication
Not applicable—no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of trial results.

Informed consent materials are available upon request from the corresponding author.

Competing interests
The authors declare that they have no competing interests.

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