Anti-Xa versus time-guided anticoagulation strategies in extracorporeal membrane oxygenation: a systematic review and meta-analysis

Ariane Willems,[1] [iD] Peter P Roeleveld,[1] Sonia Labarinas,[2]
John W Cyrus,[3] Jennifer A Muszynski,[4] Marianne E Nellis[5]
and Oliver Karam[6]

Abstract

The purpose was to compare time-based vs anti-Xa-based anticoagulation strategies in patients on ECMO. We conducted a systematic review and meta-analysis using multiple electronic databases and included studies from inception to July 19, 2019. The proportion of bleeding, thrombosis, and mortality were evaluated.

Twenty-six studies (2,086 patients) were included. Bleeding occurred in 34.2% (95%CI 25.1;43.9) of the patients with anti-Xa-based versus 41.6% (95%CI 24.9;59.4) of the patients with time-based anticoagulation strategies. Thrombosis occurred in 32.6% (95%CI 19.1;47.7) of the patients with anti-Xa-based versus 38.4% (95%CI 22.2;56.1) of the patients with time-based anticoagulation strategies. And mortality rate was 35.4% (95%CI 28.9;42.1) of the patients with anti-Xa-based versus 42.9% (95%CI 36.9;48.9) of the patients with time-based anticoagulation strategies. Among the seven studies providing results from both anticoagulation strategies, significantly fewer bleeding events occurred in the anti-Xa-based anticoagulation strategy (adjusted OR 0.49 (95%CI 0.32;0.74), $p < 0.001$) and a significantly lower mortality rate (adjusted OR 0.61 (95%CI 0.40;0.95), $p = 0.03$). There was no significant difference in thrombotic events (adjusted OR 0.91 (95%CI 0.56;1.49), $p = 0.71$). In these seven observational studies, only a small fraction of the patients were adults, and data were insufficient to analyze the effect of the type of ECMO.

In this meta-analysis of observational studies of patients on ECMO, an anti-Xa-based anticoagulation strategy, when compared to a time-based strategy, was associated with fewer bleeding events and mortality rate, without an increase in thrombotic events.

Keywords

Extracorporeal membrane oxygenation; anticoagulation; bleeding; thrombosis; mortality; anti-Xa; ACT; aPTT; thromboelastometry

Introduction

Extracorporeal membrane oxygenation (ECMO) is a continuously evolving and invaluable life-support technique for patients with life-threatening cardiac and/or respiratory failure.[1,2] The interaction between blood and an artificial circuit and the presence of shear stress on blood components induces hemostatic disturbances during ECMO making anticoagulation mandatory to maintain circuit patency and to prevent thrombotic complications.[3,4] However, the use of anticoagulation in this critically ill population significantly increases the risk of bleeding. Although greater experience, refined treatment strategies (sedation, ventilation, etc.), and technological advances have contributed to improved survival on ECMO, significant morbidity and mortality

[1]Pediatric Critical Care Medicine, Department of Intensive Care, Leiden University Medical Center, Leiden, The Netherlands
[2]Department of Pediatrics, Section of Critical Care Medicine, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA
[3]Tompkins-McCaw Library for the Health Sciences, VCU Libraries, Virginia Commonwealth University, Richmond, VA, USA
[4]Division of Critical Care Medicine, Nationwide Children's Hospital, Columbus, OH, USA
[5]Pediatric Critical Care Medicine, Department of Pediatrics, NY Presbyterian Hospital – Weill Cornell Medicine, New York, NY, USA
[6]Division of Pediatric Critical Care Medicine, Children's Hospital of Richmond at VCU, Richmond, VA, USA

Corresponding author:
Ariane Willems, Pediatric Critical Care Medicine, Department of Intensive Care, Leiden University Medical Center, Albinusdreef 2, Leiden, 2333 ZA, The Netherlands.
Email: a.m.a.willems@lumc.nl

remain from hemorrhagic and thrombotic complications.[5,6] Maintaining the delicate balance between hemostasis and anticoagulation is challenging but essential for favorable outcome. In most institutions, unfractionated heparin remains the anticoagulation of choice due to its fast onset, short half-life, easy reversal with protamine, and experience of use.[3,7-9] Different tests are used to monitor heparin anticoagulation and the optimal approach is still debated.[10,11] Global assays are based on the time required to generate a clot. Those include activated clotting time (ACT), activated partial thromboplastin time (aPTT), and clotting times generated from viscoelastic testing. Anti-factor Xa (anti-Xa) is a specific test that directly measures heparin inhibition of factor Xa.[7,11] All of the assays present specific advantages and limitations.[12] Furthermore, there are disparities among the different tests in measuring the anticoagulation effect; different studies have shown poor correlations or concordance among them, as they measure different aspects of very complex hemostatic systems.[13-16] Traditionally, ACT and aPTT have been the most widely utilized monitoring assays.[17] However, both may be influenced by different factors independent of heparin activity, such as hemodilution, anticoagulation factor deficiency, platelet function, medication, and many others.[11,18] For this reason, there has been increasing interest in using anti-Xa to monitor and titrate heparin. Multiple studies have demonstrated its reliability as well as a clear heparin dose–response association.[3,7,12] However, few studies have done a direct comparison of the two monitoring strategies and their effect on clinical outcomes.[11,14,15] The goal of this systematic review was to compare the rates of bleeding, thrombosis and mortality in patients on ECMO monitored by clotting time-based anticoagulation strategies versus anti-Xa-based strategies.

Materials and methods

Design

This is a systematic review of observational studies or randomized trials to determine the prevalence of bleeding, thrombosis, and mortality, according to the anticoagulation strategy. The review followed recommendations contained within the PRISMA statement.[19]

Types of studies

We included case series, retrospective or prospective observational studies, and randomized controlled trials, which enrolled critically ill patients on ECMO and reported both the anticoagulation strategy as well as at least one outcome of interest. As the field of

ECMO management is rapidly evolving, we included "grey literature," that is, abstracts of unpublished studies and studies published in non-peer reviewed journals, to insure we assess the most recent data. We excluded case reports, case series of 20 patients or less, reviews not providing original results, studies not in English, studies whose anticoagulation strategy was changed to a drug other than heparin during the course of ECMO support, studies evaluating anticoagulation on other circuits (CRRT) or during bypass, and animal studies.

Types of participants

We included studies that enrolled subjects on ECMO. Patients were further categorized as neonates (less than 28 days), children (28 days to 18 years), and/or adults.

Types of interventions

Based on the primary test used to adapt anticoagulation on ECMO, anticoagulation strategies were categorized as either time-based [ACT, aPTT, rotational thromboelastometry (ROTEM) or thromboelastography (TEG)] or anti-Xa-based, when the anticoagulation strategy was adapted according to the anti-Xa levels.

Types of outcome measures

Our primary outcome was bleeding events on ECMO, as defined by the authors of each study. Our secondary objectives were thrombotic events on ECMO, also as defined by the authors of each study, as well as mortality rate (either mortality on ECMO or mortality at hospital discharge, as defined by the authors).

Search methods for identification of studies

For this systematic review, we performed a search in Ovid MEDLINE, Ovid Embase, and Cochrane from the inception of the database to July 19, 2019. The search included keywords and controlled vocabulary for ECMO and anticoagulation (supplemental Table A). We imported the results to Covidence (version v1238, Melbourne, Australia), which automatically detected duplicates.

Selection of studies

Six reviewers (AW, PR, MN, LS, JM, and OK) independently examined all potential studies and decided on their inclusion in the review (Figure 1). We independently evaluated each study based on its methods and outcomes. We performed this process without blinding
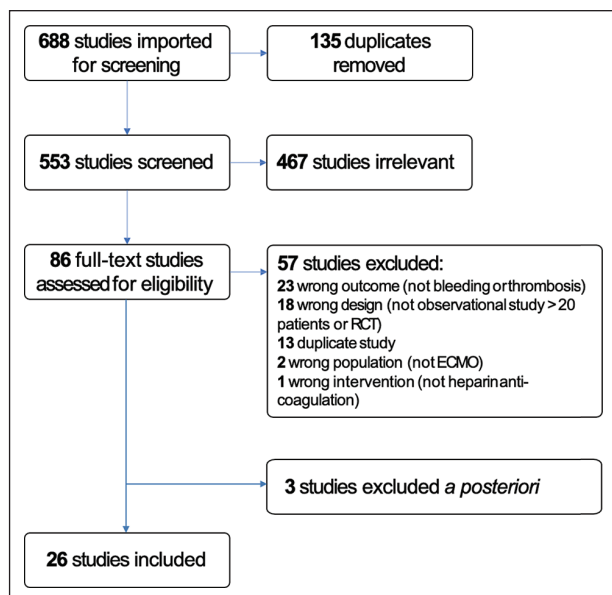
Figure 1. PRIMSA diagram detailing the search and selection process applied during the systematic analysis.

of study authors, institutions, journals of publication, or results. We resolved disagreements by additional evaluation by another author.

Data extraction and management

For each study included in the systematic review, two authors independently extracted data. We resolved disagreements by discussion. If required, we contacted study authors to ask for relevant data (e.g. specifying the primary test used to adapt anticoagulation, definition of clinical outcomes). The corresponding authors were emailed twice, within a 2-week period. If they did not respond, we then tried a final time to contact them via LinkedIn or Doximity.

Assessment of risk of bias in included studies

We evaluated the validity and design characteristics of each study looking for aspects of major potential biases (study participation, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis).[20] Two authors reviewed and ranked each study's quality factor separately and defined studies as having low risk of bias only if they adequately fulfilled all of the criteria.

Assessment of proportions

We reported the proportions and their 95% Confidence Interval (95%CI) as the number of patients with the

outcomes of interest (bleeding, thrombosis, or death) over the total number of patients enrolled in the study. To account for small proportions and interval confidences close to 0, we pooled the individual proportions using arcsin transformation.[21]

Assuming each study estimated a study-specific true effect, we used random-effect models to pool odds ratios. Such models assume no a priori knowledge about the association between the real, or apparent, intervention effects; the differences between the studies are considered to be random. These models account for heterogeneity, with the center of this distribution describing the average of the effects, and its width describing the degree of heterogeneity. We used the DerSimonian-Laird random-effect method in the presence of significant heterogeneity.[22]

Assessment of heterogeneity

We explored heterogeneity using the I^2 statistic. An I^2 statistic higher than 50% represents substantial heterogeneity.[23]

Funnel plot

We planned to explore funnel plot asymmetry, as a surrogate for potential publication biases, solely in randomized controlled trial, as the performance of funnel plots is observational studies has not been thoroughly validated.[24] As our systematic review did not include randomized controlled trials, we were not able to compute funnel plots.

Subgroup analysis

To further explore heterogeneity, we planned to conduct two subgroup analyses, comparing studies according to the age category (neonates vs children vs adults) and according to the type of ECMO support (veno-venous (V-V) versus veno-arterial (V-A)). A posteriori, we also conducted a subgroup analysis of abstracts-only versus peer-reviewed full manuscripts.

Sensitivity analysis

To further explore the effect of risk of bias, we conducted a sensitivity analysis, removing studies with a high risk of bias.

Statistical analyses

Pooled proportion with 95% CI and random-effects model were undertaken using OpenMeta(Analyst) (http://www.cebm.brown.edu/openmeta/).

Results

Description of studies

We identified a total of 688 references, of which 135 were duplicates and therefore removed from review, leaving a total of 553 studies that were screened. 467 studies were irrelevant leaving 86 full text articles. We reached out to the corresponding authors of eleven studies, nine of which provided the requested data,[25–32] two of which did not respond within the predefined time,[33,34] and one of which responded to our first email, but not to follow-up questions.[35] The latter three were excluded. There were also five abstracts [28,36–39] that were duplicates of other abstracts[40] or full texts.[41–43]

Therefore, 26 studies met eligibility criteria (Figure 1). Of these, 11 were only available as abstracts.[26,29–32,40,44–48]

Overall, the 26 studies enrolled 2,086 patients, of which 127 (6%) were specifically in neonates, 605 (29%) in neonates and children, 1,055 (51%) in children, and 299 (14%) in adults.

All of the studies were observational studies. Seven (27%) provided outcomes for both anticoagulation strategy groups, reporting a comparison of outcome before versus after change in their anticoagulation protocol. Among these, six enrolled only neonates and/or children,[26,29,43,46,47,49] whereas one enrolled both children and adults (although there were only 17/349 (5%) adults).[50] The remaining 19 (73%) studies provided outcomes for only one anticoagulation strategy. One study enrolled V-V patients only,[32] two V-A patients only,[30,51] and 15 a mix of both supports,[7,27,40–43,47,49,50,52–56] whereas eight did not report the type of support.[26,29,31,44–46,48,57] The studies are described in supplemental Table B.

Anticoagulation strategies

Eight of the 26 studies (31%) included in our analysis did not fully describe the goals of their anticoagulation strategies.[26,29,30,32,44–47] Five studies used the ELSO guidelines,[7,27,51,56,57] that is, in non-bleeding patients, anticoagulation with unfractionated heparin to achieve an ACT time between 180 and 220 seconds or an anti-Xa of 0.3–0.7 IU/mL (https://www.elso.org/portals/0/files/elsoanticoagulationguideline8-2014-table-contents. pdf). Two studies used thromboelastogram, in some[31] or all patients.[48] The remaining studies reported either different ACT, aPTT and anti-Xa goals than those specified by ELSO, differentiating between bleeding status and/or type of ECMO support.[25,31,40,41,43,49,50,52–55] Of these, only one study compared two different anticoagulation goals (aPTT <45 vs aPTT 50–70) which was designed to support the feasibility of a larger randomized controlled trial. And although it was not adequately powered, it reported no differences in bleeding or thrombotic events, and mortality.[41]

Assessment of the risk of bias

We assessed that the risk of bias was low in 10 studies,[7,25,41–43,49–51,53,56] moderate in 12 studies,[27,29–32,40,46–48,52,54,57] and high in 4 studies.[26,44,45,55] The full assessment is shown in Table 1.

Proportion of bleeding

Among anti-Xa-based anticoagulation series, bleeding occurred in 34.2% of the patients (95%CI 25.1;43.9, $I^2 = 88.93$, $n = 897$, Figure 2(a)). Among time-based anticoagulation series, bleeding occurred in 41.6% of the patients (95%CI 24.9;59.4, $I^2 = 96.86$, $n = 1,064$, Figure 2(b)). Using a random-effect on the seven studies providing results from both strategies,[26,29,43,46,47,49,50] there were significantly fewer bleeding events in the anti-Xa-based anticoagulation strategy: adjusted OR 0.49 (95%CI 0.32;0.74), $p < 0.001$, $I^2 = 47.14$, $n = 1,082$, Figure 2(c).

Proportion of thrombosis

Among anti-Xa-based anticoagulation series, thrombosis occurred in 32.6% of the patients (95%CI 19.1;47.7, $I^2 = 94.79$, $n = 789$, Figure 3(a)). Among time-based anticoagulation series, thrombosis occurred in 38.4% of the patients (95%CI 22.2;56.1, $I^2 = 96.82$, $n = 1,050$, Figure 3(b)). Using a random-effect on the seven studies providing results from both strategies,[26,29,43,46,47,49,50] there was no significant difference in thrombotic events: adjusted OR 0.91 (95%CI 0.56;1.49), $p = 0.71$, $I^2 = 54.98$, $n = 1,082$, Figure 3(c).

Mortality rate

Among anti-Xa-based anticoagulation series, the mortality rate was 35.4% (95%CI 28.9;42.1, $I^2 = 72.96$, $n = 790$, Figure 4(a)). Among time-based anticoagulation series, the mortality rate was 42.9% (95%CI 36.9;48.9, $I^2 = 70.29$, $n = 1,078$, Figure 4(b)). Using a random-effect on the seven studies providing results from both strategies,[26,29,43,46,47,49,50] there was a significantly lower mortality rate: adjusted OR 0.61 (95%CI 0.40;0.95), $p = 0.03$, $I^2 = 58.70$, $n = 1,082$, Figure 4(c).

Subgroup analysis based on age categories

As shown in supplemental Figure A, there is a wide heterogeneity among the outcomes for each age category

Table 1. Assessment of the risk of bias.

Studies	Study participation	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and presentation	Overall quality
Anton-Martin[53]	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊕⊖	⊕⊕⊕	⊕⊕⊕
Arnouk[56]	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊕⊖	⊕⊕⊕	⊕⊕⊕
Aubron[41]	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕
Bembea[7]	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊖⊖	⊕⊕⊕	⊕⊕⊕
Bingham[25]	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊖⊖	⊕⊕⊕	⊕⊕⊕
Buttram[26]	⊕⊖⊖	⊕⊕⊕	⊕⊖⊖	⊕⊖⊖	⊕⊖⊖	⊕⊖⊖
Byrnes[51]	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊖⊖	⊕⊕⊕	⊕⊕⊕
Diaz[44]	⊕⊕⊖	⊕⊕⊖	⊕⊖⊖	⊕⊖⊖	⊕⊖⊖	⊕⊖⊖
Henderson[55]	⊕⊕⊖	⊕⊕⊕	⊕⊕⊕	⊕⊖⊖	⊕⊖⊖	⊕⊖⊖
Heyrend[45]	⊕⊖⊖	⊕⊕⊖	⊕⊖⊖	⊕⊖⊖	⊕⊖⊖	⊕⊖⊖
Hobson[46]	⊕⊕⊖	⊕⊕⊖	⊕⊕⊕	⊕⊖⊖	⊕⊕⊖	⊕⊕⊖
Hundalani[27]	⊕⊕⊖	⊕⊕⊖	⊕⊕⊕	⊕⊖⊖	⊕⊕⊖	⊕⊕⊖
Irby[57]	⊕⊕⊖	⊕⊕⊖	⊕⊕⊕	⊕⊖⊖	⊕⊕⊖	⊕⊕⊖
Kamdar[29]	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊖⊖	⊕⊕⊖	⊕⊕⊖
Kilgallon[47]	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊖⊖	⊕⊕⊕	⊕⊕⊖
McMichael[42]	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊕⊖	⊕⊕⊕	⊕⊕⊕
Moynihan[54]	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊖⊖	⊕⊕⊕	⊕⊕⊖
Niebler[43]	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊖⊖	⊕⊕⊕	⊕⊕⊕
Northrop[50]	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊖⊖	⊕⊕⊕	⊕⊕⊕
O'Meara[52]	⊕⊕⊖	⊕⊕⊖	⊕⊕⊕	⊕⊖⊖	⊕⊕⊕	⊕⊕⊖
Sleeper[30]	⊕⊕⊖	⊕⊕⊕	⊕⊕⊕	⊕⊖⊖	⊕⊕⊕	⊕⊕⊖
Vandenbriele[40]	⊕⊕⊖	⊕⊕⊖	⊕⊖⊖	⊕⊖⊖	⊕⊕⊕	⊕⊕⊖
Venado[31]	⊕⊕⊖	⊕⊕⊕	⊕⊖⊖	⊕⊖⊖	⊕⊕⊖	⊕⊕⊖
Wallskog[48]	⊕⊕⊖	⊕⊖⊖	⊕⊖⊖	⊕⊕⊖	⊕⊕⊕	⊕⊕⊖
Yu[49]	⊕⊕⊕	⊕⊕⊕	⊕⊕⊕	⊕⊖⊖	⊕⊕⊕	⊕⊕⊕
Zogheib[32]	⊕⊕⊖	⊕⊕⊕	⊕⊕⊕	⊕⊖⊖	⊕⊕⊕	⊕⊕⊖

⊕⊕⊕: Low risk of bias; ⊕⊕⊖: Moderate risk of bias; ⊕⊖⊖: High risk of bias.

(adults, children, neonates, and both neonates and children). Among the seven studies providing results from both strategies, there was one study enrolling only neonates (127 subjects),[29] two enrolling only children (325 subjects)[43,47] and one enrolling 332 children and 17 adults (349 subjects),[50] and three enrolling both neonates and children (264 subjects).[26,46,47] None were enrolling only adults.
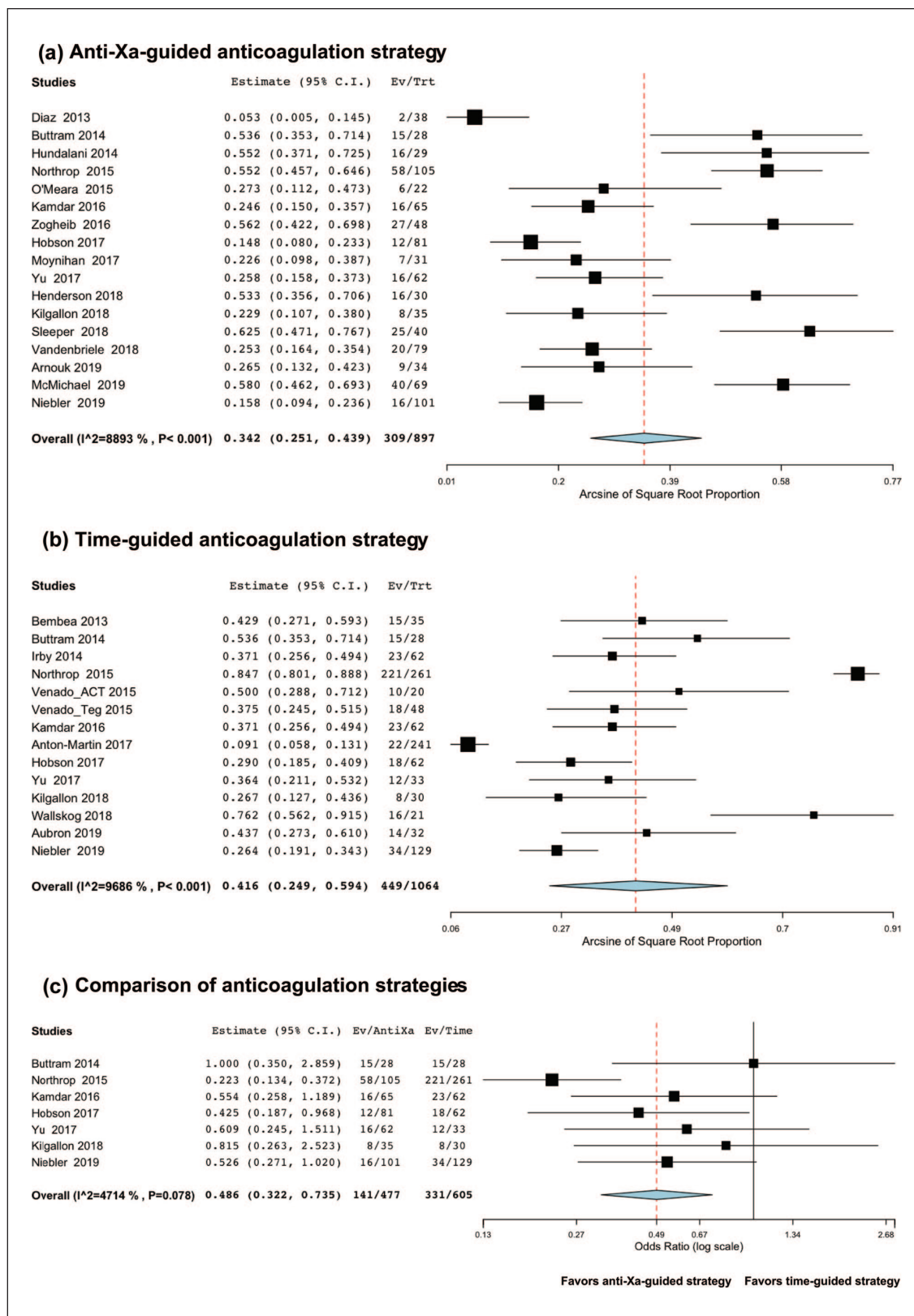
Among those seven studies, there were significantly fewer bleeding events associated with the anti-Xa based strategy in the subgroup of studies enrolling only children (adjusted OR 0.39 (95%CI 0.20;0.76); supplemental Figure B1)). There were significantly fewer thrombotic events in the subgroup of studies enrolling both neonates and children (adjusted OR 0.45 (95%CI 0.25;0.82)) but significantly more thrombotic events in the subgroup of studies enrolling only children (adjusted OR 1.50 (95%CI 1.01;2.23); supplemental Figure B2)). There was a significantly decreased mortality rate for the subgroup of studies enrolling both neonates and children (adjusted OR 0.44 (95%CI 0.24;0.80)) and in the subgroup of neonates only (adjusted OR 0.41 (95%CI 0.18–0.93); supplemental Figure B3)).

Subgroup analysis based on type of ECMO

Among the seven studies providing results from both strategies, three did not specify the type of ECMO,[26,29,46] and four enrolled both patients supported by V-V and V-A ECMO.[43,47,49,50] Therefore, we were unable to analyze the potential interaction of the type of ECMO on the association between anticoagulation strategies and clinical outcomes.

Subgroup analysis of abstract-only versus peer-reviewed full manuscripts

Among the seven studies providing results from both strategies, four were abstracts-only[26,29,46,47] and three were full texts.[43,49,50] There were significantly fewer bleeding events associated with the anti-Xa based strategy in both subgroups (adjusted OR 0.61 (95%CI 0.37;0.95, $I^2 = 0$, $p = 0.03$) for abstracts-only versus adjusted OR 0.39 (95%CI 0.20;0.76, $I^2 = 65.71$, $p = 0.006$) for full manuscripts; supplemental Figure C1)). There were significantly more thrombotic events in the subgroup of full manuscript studies (adjusted OR 1.50

(a) Anti-Xa-guided anticoagulation strategy

Studies	Estimate (95% C.I.)	Ev/Trt
Diaz 2013	0.053 (0.005, 0.145)	2/38
Buttram 2014	0.536 (0.353, 0.714)	15/28
Hundalani 2014	0.552 (0.371, 0.725)	16/29
Northrop 2015	0.552 (0.457, 0.646)	58/105
O'Meara 2015	0.273 (0.112, 0.473)	6/22
Kamdar 2016	0.246 (0.150, 0.357)	16/65
Zogheib 2016	0.562 (0.422, 0.698)	27/48
Hobson 2017	0.148 (0.080, 0.233)	12/81
Moynihan 2017	0.226 (0.098, 0.387)	7/31
Yu 2017	0.258 (0.158, 0.373)	16/62
Henderson 2018	0.533 (0.356, 0.706)	16/30
Kilgallon 2018	0.229 (0.107, 0.380)	8/35
Sleeper 2018	0.625 (0.471, 0.767)	25/40
Vandenbriele 2018	0.253 (0.164, 0.354)	20/79
Arnouk 2019	0.265 (0.132, 0.423)	9/34
McMichael 2019	0.580 (0.462, 0.693)	40/69
Niebler 2019	0.158 (0.094, 0.236)	16/101
Overall (I^2=8893 % , P< 0.001)	**0.342 (0.251, 0.439)**	**309/897**

Arcsine of Square Root Proportion
0.01 0.2 0.39 0.58 0.77

(b) Time-guided anticoagulation strategy

Studies	Estimate (95% C.I.)	Ev/Trt
Bembea 2013	0.429 (0.271, 0.593)	15/35
Buttram 2014	0.536 (0.353, 0.714)	15/28
Irby 2014	0.371 (0.256, 0.494)	23/62
Northrop 2015	0.847 (0.801, 0.888)	221/261
Venado_ACT 2015	0.500 (0.288, 0.712)	10/20
Venado_Teg 2015	0.375 (0.245, 0.515)	18/48
Kamdar 2016	0.371 (0.256, 0.494)	23/62
Anton-Martin 2017	0.091 (0.058, 0.131)	22/241
Hobson 2017	0.290 (0.185, 0.409)	18/62
Yu 2017	0.364 (0.211, 0.532)	12/33
Kilgallon 2018	0.267 (0.127, 0.436)	8/30
Wallskog 2018	0.762 (0.562, 0.915)	16/21
Aubron 2019	0.437 (0.273, 0.610)	14/32
Niebler 2019	0.264 (0.191, 0.343)	34/129
Overall (I^2=9686 % , P< 0.001)	**0.416 (0.249, 0.594)**	**449/1064**

Arcsine of Square Root Proportion
0.06 0.27 0.49 0.7 0.91

(c) Comparison of anticoagulation strategies

Studies	Estimate (95% C.I.)	Ev/AntiXa	Ev/Time
Buttram 2014	1.000 (0.350, 2.859)	15/28	15/28
Northrop 2015	0.223 (0.134, 0.372)	58/105	221/261
Kamdar 2016	0.554 (0.258, 1.189)	16/65	23/62
Hobson 2017	0.425 (0.187, 0.968)	12/81	18/62
Yu 2017	0.609 (0.245, 1.511)	16/62	12/33
Kilgallon 2018	0.815 (0.263, 2.523)	8/35	8/30
Niebler 2019	0.526 (0.271, 1.020)	16/101	34/129
Overall (I^2=4714 % , P=0.078)	**0.486 (0.322, 0.735)**	**141/477**	**331/605**

Odds Ratio (log scale)
0.13 0.27 0.49 0.67 1.34 2.68

Favors anti-Xa-guided strategy   Favors time-guided strategy

Figure 2. Meta-analysis of the proportion of bleeding according to the anticoagulation strategy (anti-Xa-guided vs time-guided). Overall, there were fewer bleeding events among anti-Xa-based anticoagulation series, bleeding occurring in 34.2% of the patients (Figure 2(a)) versus 41.6% of the patients in the time-guided studies (Figure 2(b)). Using a random-effect on the seven studies providing results from both strategies, there was significantly fewer bleeding events in the anti-Xa-based anticoagulation strategy (adjusted OR 0.49, $p < 0.001$), Figure 2(c).
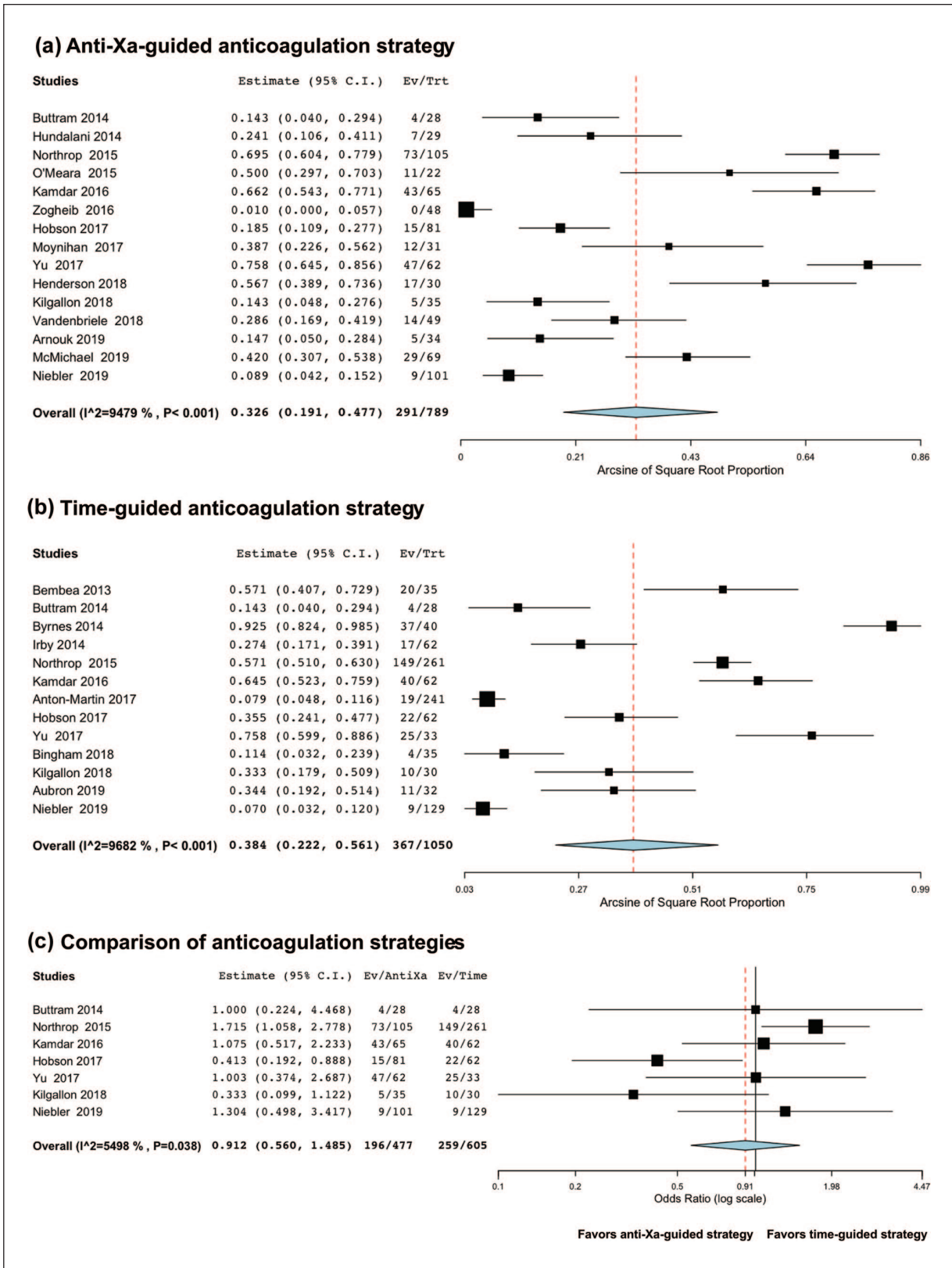
Figure 3. Meta-analysis of the proportion of thrombosis according to the anticoagulation strategy (anti-Xa-guided vs time-guided). Overall, there were fewer thrombotic events among anti-Xa-based anticoagulation series, thrombosis occurring in 32.6% of the patients (Figure 3(a)) versus 38.4% of the patients in the time-guided studies (Figure 3(b)). Using a random-effect on the seven studies providing results from both strategies, there was no significant difference in thrombotic events (adjusted OR 0.91, *p* = 0.71, Figure 3(c)).
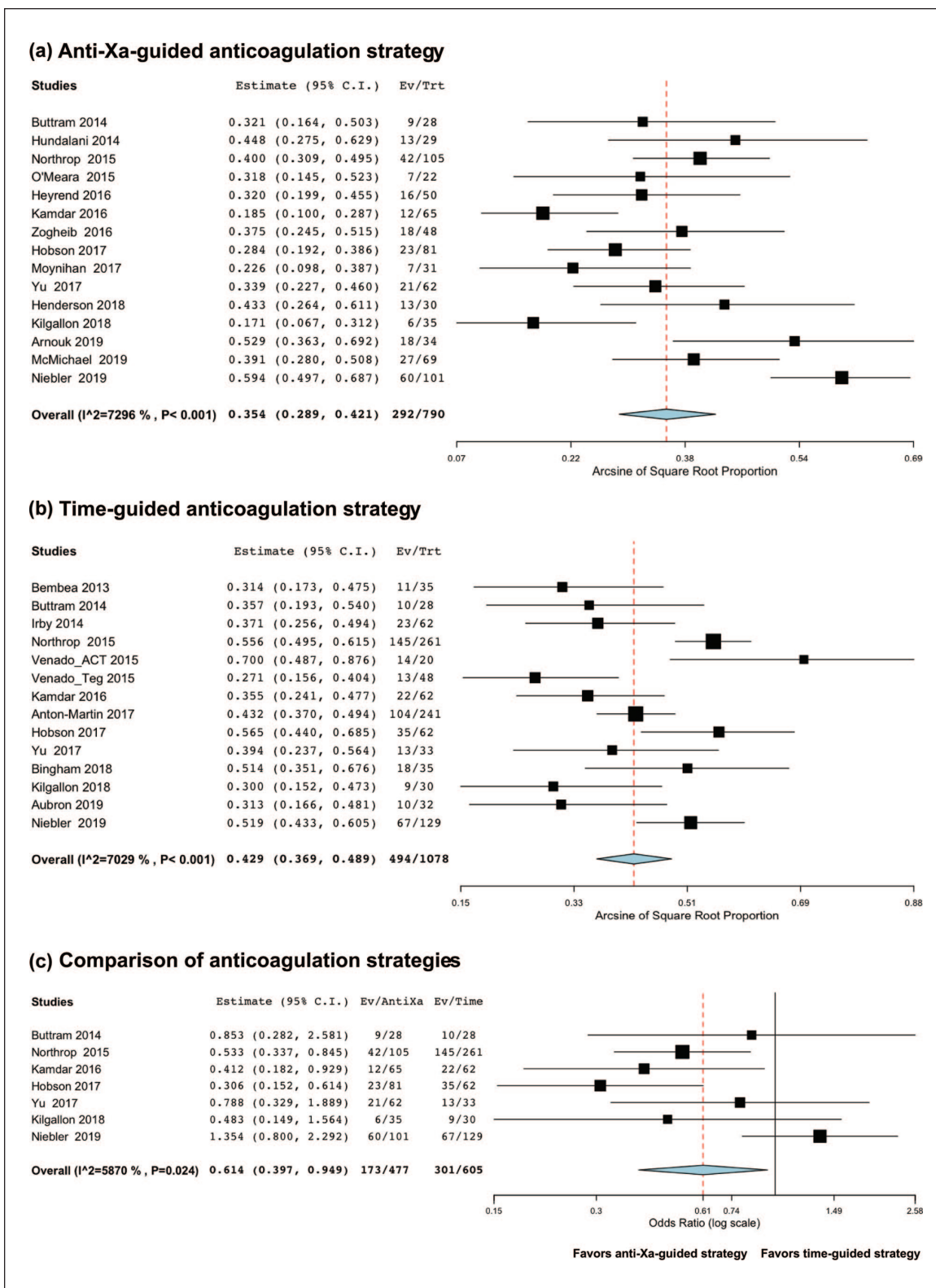
Figure 4. Meta-analysis of the mortality rate according to the anticoagulation strategy (anti-Xa-guided vs time-guided). Overall, there was a lower mortality rate among anti-Xa-based anticoagulation series, bleeding occurring in 35.4% of the patients (Figure 4(a)) versus 42.9% of the patients in the time-guided studies (Figure 4(b)). Using a random-effect on the seven studies providing results from both strategies, there was significantly lower mortality rate in the anti-Xa-based anticoagulation strategy (adjusted OR 0.61, $p < 0.03$, Figure 4(c)).

(95%CI 1.01;2.23, $I^2 = 0$, $p = 0.04$); supplemental Figure C2)). There was a significantly lower mortality rate in the subgroup of abstract-only studies (adjusted OR 0.42 (95%CI 0.27;0.65, $I^2 = 0$, $p < 0.001$); supplemental Figure C3)).

Sensitivity analysis based on quality of evidence

Among the seven studies providing results from both strategies, three had a low risk of bias,[43,49,50] three had a moderate risk of bias,[29,46,47] and one had a high risk of bias.[26] For this sensitivity analysis, we removed the latter. Using a random-effect on the remaining studies, there were significantly fewer bleeding events in the anti-Xa-based anticoagulation strategy: adjusted odds ratio 0.44 (95%CI 0.29;0.67), $p < 0.001$, $I^2 = 44.52$, $n = 1,026$, supplemental Figure C1. There was no significant difference in thrombotic events: adjusted odds ratio 0.89 (95%CI 0.52;1.54), $p = 0.69$, $I^2 = 62.47$, $n = 1,026$, supplemental Figure C2. There was a significant lower mortality rate: adjusted odds ratio 0.56 (95%CI 0.36;0.96), $p = 0.03$, $I^2 = 64.92$, $n = 1,026$, supplemental Figure C3.

Discussion

In this systematic review and meta-analysis, we compared time-guided versus anti-Xa-guided anticoagulation strategies for heparin titration in patients on ECMO. We found that there were significantly fewer bleeding events and a lower mortality rate in the anti-Xa-based anticoagulation strategy. In these observational studies, only a small fraction of the subjects were adults, and data were insufficient to analyze separately V-V and V-A ECMOs. Furthermore, the overall quality of evidence was moderate.

To our knowledge, this is the first meta-analysis comparing time-based guided anticoagulation with anti-Xa-guided heparin anticoagulation on ECMO in neonates, children and adults for both V-A- and V-V-ECMO. A recent systematic review evaluated different laboratory measures of heparin anticoagulation in children on ECMO.[58] The authors showed that anti-Xa was the only test to strongly correlate with heparin dose. These results are not surprising if we consider the physiologic background of these different tests. The anti-Xa concentration directly measures heparin inhibition of factor Xa and indirectly "estimates" the plasmatic unfractionated heparin concentration contrary to the ACT and the aPTT. Anti-Xa is a pharmacokinetic test. ACT is a whole-blood test that measures the time for initial fibrin formation. Similar to the ACT, aPTT evaluates contact-activation in the intrinsic pathway, in plasma. These are both pharmacodynamic tests, which are prolonged in the presence of heparin, but also influenced by various other factors, such as the level of coagulation factors and platelet count in the case of the ACT.[11] In this recent study, none of the coagulation tests were significantly associated with hemorrhagic and thrombotic complications; this might be due to scarce clinical data in the studies that were included in this systematic review.[58] Two other systematic reviews evaluating anticoagulation on ECMO looked at the relationship between different tests and goals in specific ECMO populations.[17,59] Unfortunately, none evaluated anti-Xa anticoagulation strategies. The first was undertaken in adults on V-A-ECMO and found fewer major bleeding events in the lower ACT goal (ACT<180 seconds) with similar thrombotic events and in-hospital mortality compared with the higher goal (ACT>180 seconds).[17] In this analysis, most included studies were assessed as being at high risk of bias and did not assess the association between anticoagulation strategies and complications. The second, undertaken in adults on V-V-ECMO for respiratory failure, compared ACT versus aPTT anticoagulation strategies and showed a significantly lower bleeding and thrombotic rate in the aPTT approach group.[59] Here too, the results must be interpreted with caution as there were only few studies, the overall quality of evidence was low, and major thrombosis usually consisted of circuit clotting, with little information on the clinical consequences of these events. In addition, mortality could not be evaluated as most of the aPTT studies did not report this outcome. However, the authors reported that within aPTT-targeted protocols, patients for which the aPTT goal was <60 seconds, experienced fewer bleeding episodes but more clotting events than in patients where the aPTT goal was >60 seconds. In our review, we did not compare different anticoagulation goals as this was beyond our scope. Although this study suggests that anti-Xa-guided heparin titration in ECMO is associated with decreased bleeding and mortality rates, the current evidence does not investigate the outcomes associated with anticoagulation protocols coupling anti-Xa with traditional coagulation tests and/or point-of-care coagulation tests (TEG or ROTEM) or even thrombin generation tests. Some experts believe the latter test evaluates other aspects of anticoagulation, that are not assessed with the anti-Xa test, which could lead to excessive anticoagulation in specific subgroups of patients.[11] Management of anticoagulation on ECMO using point-of-care coagulation tests (TEG or ROTEM) have been studied. The current evidence suggests these tests have a poor to moderate correlation with traditional coagulation tests. Furthermore, the concordance between TEG and ROTEM is poor, yielding sometimes contradictory results.[60] Studies assessing the benefits of a combined

approach to manage anticoagulation on ECMO are also needed. We strongly recommend additional studies, including randomized controlled trials, to further investigate the optimal anticoagulation strategy.

Limitations

Some limitations have to be recognized. First, the main limitation of this meta-analysis is the huge heterogeneity between studies, including both patient and outcome variability. The definitions of bleeding and thrombotic events were heterogeneous. Furthermore, it was difficult to distinguish between patient and circuit complications, and it was not possible to stratify patients based on surgical versus percutaneous, or central versus peripheral cannulation. Additionally, interventions were heterogeneous between studies, as we grouped time-based anticoagulation strategies (ACT, aPTT, and R on TEG), each having different thresholds for each test. Of note, although TEG provides various measures, the only TEG studies included in the systematic review looked solely at the R time for anticoagulation management. Second, our study included only few high-quality studies (supplemental Table B). Moreover, there were no randomized controlled trials comparing a time-based to an anti-Xa based anticoagulation therapy, only observational studies, most having a retrospective design, for which selection biases could not be excluded. Third, the subgroup analyses were performed in pediatric studies only, with few studies within each age group, and a wide heterogeneity within each category, so these results should be viewed as hypothesis-generating only. Fourth, inclusion of abstracts further worsened the heterogeneity, as the definitions of outcomes and goals of anticoagulation were often not available, due to limitations in the number of words. In addition, inclusion of abstracts, that often lack of peer review and contain less information, might hinder their validity and the results of our meta-analysis. However, as suggested in the literature, we decided to include them to guard against publication bias,[61] although it is possible that only the studies with the most extreme results are published. Because of small numbers of ECMO patients in individual centers resulting in small studies, our topic is particularly vulnerable to publication bias and because of the delay between completing a study and publication, published abstracts may represent more current information certainly in the rapidly evolving field of ECMO management and research. Furthermore, meta-analyses that exclude grey literature likely overrepresent studies with statistically significant findings, inflate effect size estimates, and provide less precise effect size estimates than meta-analyses including grey literature.[62] A subgroup analysis comparing abstract-only versus peer-reviewed full manuscripts confirmed the decreased risk of bleeding in the anti-Xa-based anticoagulation strategy in the peer-reviewed studies. As this result remain consistent with the overall results, it can be considered robust. However, the decreased mortality rate was not observed in the full manuscripts, probably due to a lack of power, whereas the risk for thrombosis was increased in that subgroup. Therefore, these results should be interpreted with caution. Fifth, more than half of the studies included in this systematic review did not specifically compare different anticoagulation strategies. We attempted to address this heterogeneity by performing sub-analyses and sensitivity analyses, which led to similar results. Finally, we included all eligible studies irrespective of the date of publication, although ECMO technology and indications have considerably evolved the last decade. However, all of the included studies were published within the last 8 years.

Conclusion

In a meta-analysis of observational studies of patients on ECMO, an anti-Xa-based anticoagulation strategy, when compared to a time-based strategy, was overall associated with fewer bleeding events and a decreased mortality rate, without an increase in thrombotic events in patients on ECMO. Only large pragmatic trials will result in definitive conclusions on optimal anticoagulation monitoring during ECMO. Further research, including large pragmatic randomized controlled trials, are urgently needed to identify optimal anticoagulation strategies on ECMO. In addition, there is a need for new testing methods as the current knowledge is based tests with significant limitations. A combined approach including point-of-care tests could refine anticoagulation management but needs rigorous assessments.

ORCID iD

Ariane Willems ⓘD https://orcid.org/0000-0003-1303-5942

Supplemental Material

Supplemental material for this article is available online.

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