Anticoagulation Practices and Mortality in Extracorporeal Cardiopulmonary Resuscitation: A Systematic Review and Meta-Analysis

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Abstract

Objective: This study sought to evaluate the effect of different anticoagulant methods on in-hospital mortality, bleeding, and thromboembolic complications of patients receiving extracorporeal cardiopulmonary resuscitation (ECPR).

Data Sources: We searched the relevant literature concerning ECPR and anticoagulation indexed in PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from 1995 until May 2020.

Study Selection: The anticoagulation information and outcomes data (i.e., anticoagulation targets and strategy, major bleeding and thromboembolic events, and in-hospital mortality rate) were extracted. A random-effects meta-analysis was performed to analyze these data.

Data Extraction: Twenty-seven studies (N = 1,302 patients) were included; of these, 16 studies (n = 672 patients) included data regarding bleeding and thromboembolic complications.

Data Synthesis: The summary prevalence for in-hospital mortality was 70% [95% confidence interval (CI): 65%–74%, I^2 = 68.3%], the summary prevalence for major bleeding was 27% (95% CI: 19%–35%, I^2 = 84.1%), and the summary prevalence for thromboembolic events was 8.7% (95% CI: 5.2%–13.4%, I^2 = 71.4%).

Conclusions: Controversy persists regarding whether to administer loading heparin and in making the choice of target anticoagulant dose. Currently, limited evidence suggests that low target anticoagulant doses may benefit patients. There is a need for further investigation of optimal anticoagulation strategies in patients receiving ECPR, preferably in randomized trials or well-designed observational studies and with clearly defined outcomes.

Introduction

Extracorporeal cardiopulmonary resuscitation (ECPR) refers to the initiation of cardiopulmonary bypass during the resuscitation of a patient in cardiac arrest. The 2019 American Heart Association guidelines recommended that ECPR may be considered in selected patients as rescue therapy when conventional cardiopulmonary resuscitation efforts are failing in settings in which it can be expeditiously implemented and supported by skilled providers [1]. Anticoagulation is inevitable during ECPR and is also crucial for favorable outcomes [2]. Unfractionated heparin is the most commonly used anticoagulant during ECPR. The Extracorporeal Life Support Organization recommends continuous infusion of unfractionated heparin (usually receiving an initial bolus of 50–100 units/kg body weight) targeting an activated clotting time (ACT) of 180 to 220 seconds during venoarterial extracorporeal membrane oxygenation (ECMO) [3]. However, no clear recommendation pertaining to ECPR exists, although some centers choose to increase the initial bolus of unfractionated heparin or lower the target ACT for fear of bleeding complications. We therefore performed the present systematic review and meta-analysis to evaluate the use of

anticoagulation targets and strategies in adult patients on ECPR and the prevalence of bleeding, thrombosis, and in-hospital mortality.

Methods

We searched multiple literature databases to find studies reporting the effects of different anticoagulant targets on in-hospital mortality, bleeding, and thromboembolic complications among ECPR patients. This study is based on the Cochrane Review Methods [4].

2.1 Design

We searched for English-language articles in PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) published from 1995 until May 2020 without restrictions on the year of publication or type of publication. The following keywords and MeSH terms were applied in Medline: “extracorporeal cardiopulmonary resuscitation,” “anticoagulation,” and “resuscitation” (See Appendix 1 for a more comprehensive list). Search strategies were adapted for other databases based on the MEDLINE strategy. After the initial electronic search, we hand-searched for further relevant articles and reviewed the bibliographies of selected studies. Articles identified as possibly relevant were assessed individually for study inclusion. Studies were finally included if they had a clear description of the anticoagulation strategy, anticoagulation target, mortality rate prior to hospital discharge, and complications (both hemorrhagic and thromboembolic).

2.2 Study selection

Studies were assessed for inclusion independently by two reviewers (SJK and SWL) based on pre-defined selection criteria. These two reviewers independently assessed the titles and abstracts of identified studies and then assessed the reports to ensure that they met our inclusion criteria. Any disagreement was discussed by the two reviewers. We excluded reports that did not completely fulfill our inclusion criteria. Studies were included in our meta-analysis if they contained (1) adult (age ≥ 18 years) patients with (2) either in-hospital or out-of-hospital cardiac arrest, (3) data about the anticoagulant method and target, and (4) reported outcomes (i.e., in-hospital mortality, bleeding, and thromboembolic complications). We excluded any studies that (1) included pediatric patients (age < 18 years), (2) had no clear data about the anticoagulant target and method, or (3) were case reports. Studies that included duplicated patient cohorts were also not included.

2.3 Data extraction and quality assessment

We extracted information concerning the number of patients, anticoagulation targets and strategies, major bleeding and thromboembolic events, and in-hospital mortality. We grouped the literature according to the anticoagulation target. We defined a low ACT as an ACT of less than 180 seconds, a medium ACT as a target ACT of 180 to 220 seconds, and a high ACT as a target ACT of more than 220 seconds (i.e., less than the target recommended by the Extracorporeal Life Support Organization of 180–220 seconds).

Some articles monitored the anticoagulation level using the activated partial thromboplastin time (usually 50–60 seconds or 2–2.5 times the normal value) and these articles were analyzed separately. We attempted to contact study authors to acquire missing data when possible. All included studies were assessed for bias using the Newcastle–Ottawa Scale [5].

2.4 Data synthesis and analysis

The prevalence estimates for mortality, major bleeding, and major thromboembolic events were calculated by pooling study-specific data. We conducted a random-effects meta-analysis incorporating the DerSimonian and Laird method [6]. The Freeman–Tukey double arcsine transformation was used to stabilize variances for study-specific data with no events [7]. Estimates were presented as proportions with 95% confidence intervals (CIs) and represented in forest plots. Heterogeneity was reported using I^2, with I^2 values greater than 50% considered to represent a significant amount of heterogeneity. We performed subgroup analyses, evaluating each anticoagulation target individually. Publication bias was assessed by funnel plotting and Egger's test. The effect of individual studies was examined by excluding each study serially in a sensitivity analysis. All analyses were performed using Stata version 11 (StataCorp LLC, College Station, TX, USA). A p-value of less than 0.05 was considered to be statistically significant.

Results

We retrieved a total of 1,739 studies from the three databases and five additional papers via hand-searching. After preliminary screening, we conducted full-text evaluations of 173 of the studies. Among them, 27 (n = 1,302 patients) contained information on anticoagulation and mortality rate (23 determined mortality at discharge time, while 4 papers adopted 30 days as the time point)Table 1 and Fig.4. All articles were observational studies, including four case series, four case–control studies, and 19 cohort studies, while the countries of publication included France (n = 5 articles), South Korea (n = 8 articles), the United States (n = 3 articles), Germany (n = 3 articles), Japan (n = 2 articles), Australia (n = 1 article) Italy (n = 2 articles), Singapore (n = 1 article), China (n = 1 article), and Poland (n = 1 article). All selected articles were scored on the Newcastle–Ottawa Scale, with two articles receiving nine stars, eight articles receiving eight stars, eight articles receiving seven stars, four articles receiving six stars, and five articles receiving five stars. All included articles were published after 2009.

3.1 In-hospital mortality rate

The combined in-hospital mortality rate was 70% (95% CI: 65%–74%, I^2 = 68.3%), while the in-hospital mortality rate of the low-anticoagulation-target group was 61% (95% CI: 49%–74%, I^2 = 76.5%), the in-hospital mortality rate of the moderate-anticoagulation-target group was 67% (95% CI: 59%–75%, I^2 = 71.3%), the in-hospital mortality rate of the high-anticoagulation-target group was 78% (95% CI: 72%–83%, I^2 = 47%), and the in-hospital mortality rate in the APTT-target group was 68% (95% CI: 61%–75%, I^2 = 0)Fig. 1.

3.2 Bleeding

A total of 16 articles contained information on bleeding and thromboembolic events. The overall incidence of bleeding complications in patients was 27% (95% CI: 19%–35%, I^2 = 84.1%), while the incidence of bleeding complications in the low-anticoagulation-target group was 26% (95% CI: 18%–35%, I^2 = 0), the incidence of bleeding complications in the moderate-anticoagulation-target group was 24% (95% CI: 6%–43%, I^2 = 93.7%), the incidence of bleeding complications in the high-anticoagulation-target group was 28% (95% CI: 21%–35%, I^2 = 0), and the incidence of bleeding complications in the APTT-target group was 32% (95% CI: 14%–50%, I^2 = 77.8%)Fig. 2. Separately, the incidence of bleeding complications in the no-loading-dose group was 24% (95% CI: 16%–32%, I^2 = 60.7%) and the incidence of bleeding complications in the loading dose group was 29% (95% CI: 16%–42%, I^2 = 90%)(Supplemental Digital Content – Fig. 1).

3.3 Thromboembolic events

The incidence of complications in all patients with embolism was 8.7% (95% CI: 5.2%–13.4%, I^2 = 71.4%), while the incidence of thromboembolic events in the low-anticoagulation-target group was 5.4% (95% CI: 0.6%–22.1%, I^2 = 83.2%), the incidence of thromboembolic events in the moderate-anticoagulation-target group was 6.9% (95% CI: 1.9%–14.1%, I^2 = 74.6%), the incidence of thromboembolic events in the high-anticoagulation-target group was 11.8% (95% CI: 4.3%–22.1%, I^2 = 67.1%), and the incidence of thromboembolic events in the APTT-target group was 12.4% (95% CI: 3.7%–25.1%, I^2 = 71.1)(Fig. 3). Also, the incidence of thromboembolic events in the no-loading-dose group was 8.2% (95% CI: 3.4%–14.8%, I^2 = 67.1%), while that of thromboembolic events in the loading dose group was 9.3% (95% CI: 3.9%–16.3%, I^2 = 77.1%)(Supplemental Digital Content – Fig. 2).

Discussion

In this investigation of published literature, a total of 1,302 patients were included from 27 studies. Through meta-analysis, the incidence rates of ECPR in-hospital mortality and bleeding and embolism complications were described. This study found that the combined mortality rate of patients was 70%, while subgroup analysis showed that the anticoagulation target group experienced the lowest rate of in-hospital deaths (61%) and the high-anticoagulation-target group experienced the highest rate of in-hospital deaths (78%). Moreover, 27% of patients had bleeding complications, with the highest rate of such found in the APTT-target group (32%). The incidence of combined thromboembolic events was 8.7% and thromboembolic events were least frequent in the low anticoagulation group and most frequent in the APTT-target group. During subgroup analysis of whether to use loading-dose anticoagulation, we determined that the incidence of bleeding complications in the group with no loading dose was lower than that in the loading-dose group (24% vs. 29%) and there was no significant difference apparent in the incidence of thromboembolic events between these two groups (8.2% vs. 9.3%).

Bleeding and thromboembolic events are some of the main complications of ECPR. As such, the question remains whether loading-dose heparin should be used for anticoagulation and the choice of anticoagulant intensity during ECMO operation remains a focus of current debate. At present, ACT and APTT are the main methods for monitoring the coagulation function of patients. In 2017, a meta-analysis article published by Sy [35] reported the combined hospital death of patients receiving venoarterial ECMO support, where the rate of bleeding complications was 59%, the incidence of bleeding complications was 27%, and the incidence of thromboembolic events was 8%. However, this report included only a small number of ECPR patients and did not conduct relevant analysis in the ECPR population. In contrast, the present study reported an in-hospital mortality rate of 70%, which is significantly higher than that of ECMO-assisted patients under noncardiopulmonary resuscitation, while the incidence of bleeding and thromboembolic events is basically the same.

Meanwhile, subgroup analysis showed that the application of loading-dose heparin may increase the incidence of bleeding complications and did not significantly reduce the incidence of embolic complications. Although the high-anticoagulation-target-dose group has a greater incidence of bleeding complications, its incidence of embolic complications was also the most. This may be because a majority of studies include avascular necrosis of the lower limbs under the umbrella of embolic complications, but the main reason for lower-limb ischemia may be that the diameter of the arterial cannula is too large and lower-extremity arterial obstruction caused by bleeding of the puncture site is instead the cause of true thrombosis. The establishment of superficial femoral vein collateral circulation could effectively reduce the occurrence of lower-extremity ischemic complications.

This study has some limitations that should be noted: for example, the first 27 articles included were not studies on ECPR anticoagulation and embolism complications but were instead all observational studies with low scores and high heterogeneity in each article. Among them, only 16 articles had bleeding and embolism records with mention of thromboembolic events. Second, in the past 10 years, ECPR equipment has been continuously improved. The extensive use of heparin coatings in tubing and membrane lung materials has made it possible to reduce the anticoagulant strength, which may also have caused possible research bias. Again, differences in the definitions of bleeding and embolism complications will also lead to bias. Most studies limit bleeding to the puncture site, cerebral hemorrhage, and gastrointestinal hemorrhage and bleeding related to cardiopulmonary resuscitation injuries such as intrathoracic hemorrhage and alveolar hemorrhage may not be included in the statistics of bleeding complications.

Conclusions

At present, there is still controversy regarding whether to administer loading heparin and in making the choice of target anticoagulant dose. Currently, limited evidence suggests that a low target anticoagulant dose may benefit patients. However, there is a need for further investigation of the best anticoagulation strategy in ECPR, preferably via randomized trials or well-designed observational studies with clearly defined outcomes.

Declarations

Ethical Approval and Consent to participate

Not applicable

Consent for publication

All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript in accordance with ICMJE criteria This article is original, has not already been published in a journal, and is not currently under consideration by another journal.We agree to the terms of the BioMed Central Copyright and License Agreement.

Availability of supporting data.

Not applicable

Competing interests

There is no competing interests about this article.

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Authors' contributions

LZ and XW contributed to the study concept and design.

LZ and MW contributed to the acquisition of the data.

LZ, ML and LL contributed to the analysis and interpretation of the data.

LZ, ML and CL contributed to drafting of the manuscript.

XW,ML and CL contributed to critical revision of the manuscript for important intellectual content.

LZ and ML contributed to the statistical expertise.

All authors read and approved the final manuscript.

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Table

Table 1. Summary of studies reporting on ECPR anticoagulation strategy and associated outcomes

Study	Population	Anticoagulation strategy	Mortality, n (%)	Bleeding events, n (%)	Thromboembolic events, n (%)
Low ACT					
Sang Jin Han (2015) [8]	37	Loading dose Target ACT 140–180 s	30 (81.1%)	8 (21.6%)	0
Tomasz Darocha (2016) [9]	10	No loading dose Target ACT 140–160 s	3 (30%)	2 (20%)	0
Blumenstein, J (2016) [10]	52	No loading dose Target ACT 160–180 s	38 (73.1%)	17 (32.7%)	9 (17.3%)
Francesca Cesana (2017) [11]	63	No loading dose Target ACT 160–180 s	50 (87.7%)	Unavailable	Unavailable
Le Pennec-Prigent, S. (2017) [12]	26	Loading dose Target ACT 150–180 s	13 (50%)	Unavailable	Unavailable
Kim, Y. O. (2020) [13]	69	Loading dose Target ACT 150–180 s	37 (53.6%)	Unavailable	Unavailable
Medium ACT					
Cédric Daubin (2009) [14]	17	Loading dose Target ACT 150–200 s	4 (23.5%)	2 (11.8%)	8 (47.1%)
Kagawa, E. (2010) [15]	77	Loading dose Target ACT 150–200 s	47 (61%)	49 (63.3%)	15 (19.5)
Sawamoto, K. (2014) [16]	26	No loading dose Target ACT 150–200 s	16 (61.5%)	Unavailable	Unavailable
Jennifer Brunet (2015) [17]	29	No loading dose Target ACT 150–200 s	23 (79.3%)	Unavailable	Unavailable

Yoshiaki Iwashita (2015) [18]	32	Loading dose Target ACT 180–200 s	23 (71.9%)	3 (9.4%)	0
Dong Hee Kim (2016) [19]	85	No loading dose Target ACT 180–200 s	68 (80%)	10 (11.8%)	7 (8.2%)
Michael A (2016) [20]	23	No loading dose Target ACT 180–200 s	15 (65.2%)	3 (13%)	0
Jung, C. (2016) [21]	117	Loading dose Target ACT 160–200 s	84 (71.8%)	Unavailable	Unavailable
Tae Sun Ha (2017) [22]	35	Loading dose Target ACT 150–200 s	25 (71.4%)	13 (37.1%)	1 (2.9%)
J. J. Min (2018) [23]	23	Loading dose Target ACT 150–200 s	17 (73.9%)	Unavailable	Unavailable
High ACT					
Tae Gun Shin (2011) [24]	85	Loading dose Target ACT 180–220 s	56 (65.9%)	Unavailable	Unavailable
Su Jin Kim (2014) [25]	55	No loading dose Target ACT 200–220 s	47 (85.5%)	13 (23.6%)	3 (5.5%)
Johnson, N. J. (2014) [26]	26	No loading dose Target ACT 180–220 s	22 (84.6%)	6 (23.1%)	8 (30.8%)
Yanyan Zhao (2015) [27]	24	No loading dose Target ACT 180–220 s	16 (66.7%)	8 (33.3%)	1 (4.2%)
Kilsoo Yie (2015) [28]	60	Loading dose Target ACT 170–210 s	48 (80%)	20 (33.3%)	6 (10%)
Sung Woo Lee (2017) [29]	111	No loading dose	90 (81.1%)	Unavailable	Unavailable

		Target ACT 200–220 s			
Ellouze, O. (2018) [30]	65	Loading dose Target ACT >200 s	49 (75.4%)	Unavailable	Unavailable
APTT					
Mégarbane, B. (2007) [31]	17	No loading dose Target 2–2.5 times APTT	13 (76.5%)	8 (47.1%)	0
Haneya, A. (2012) [32]	85	Loading dose Target APTT 50–60 s	56 (65.9)	15 (17.6%)	14 (16.5%)
Lazzeri, C. (2013) [33]	16	No loading dose Target APTT > 2 times the normal value	12 (75%)	Unavailable	Unavailable
Mark Dennis (2016) [34]	37	Loading dose Target APTT 50–70 s	24 (64.9%)	14 (37.8%)	7 (18.9%)

Figures

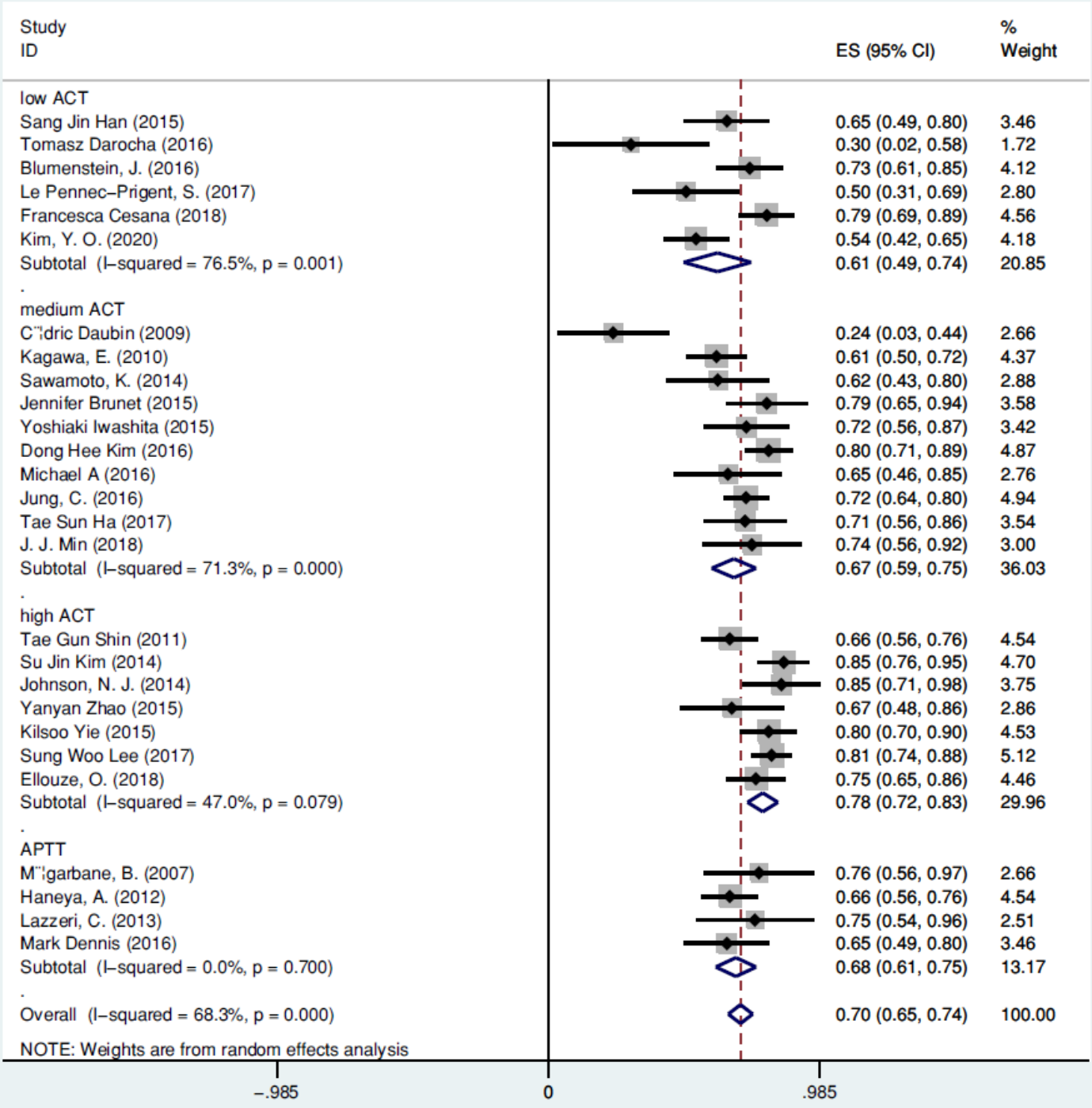

Figure 1

Meta-analysis of in-hospital mortality rate among ECPR patients stratified by anticoagulation strategy.

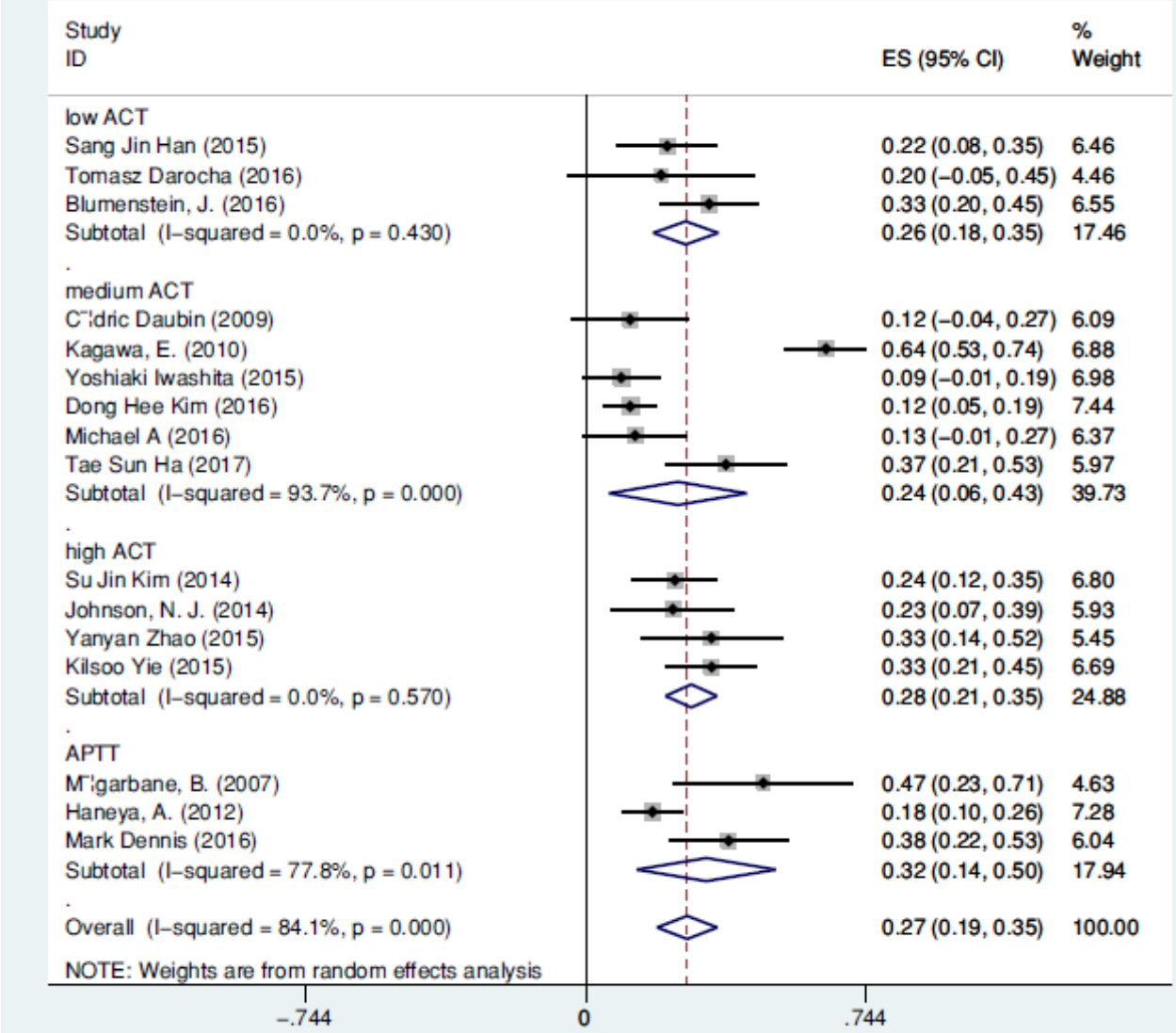

Figure 2

Meta-analysis of the prevalence of major bleeding events among ECPR patients stratified by anticoagulation strategy.

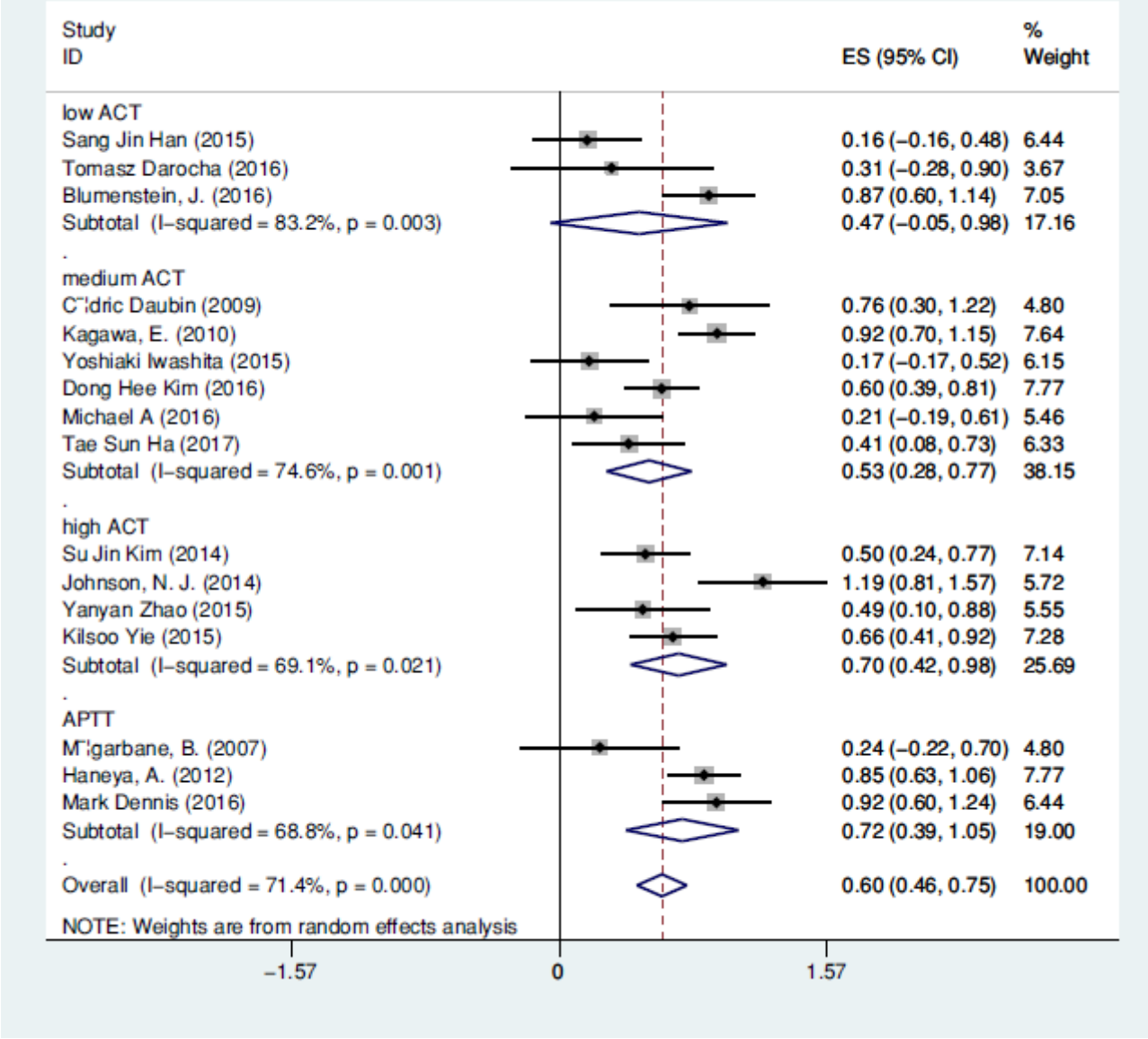

Figure 3

Meta-analysis of the prevalence of thromboembolic events among ECPR patients stratified by anticoagulation strategy.

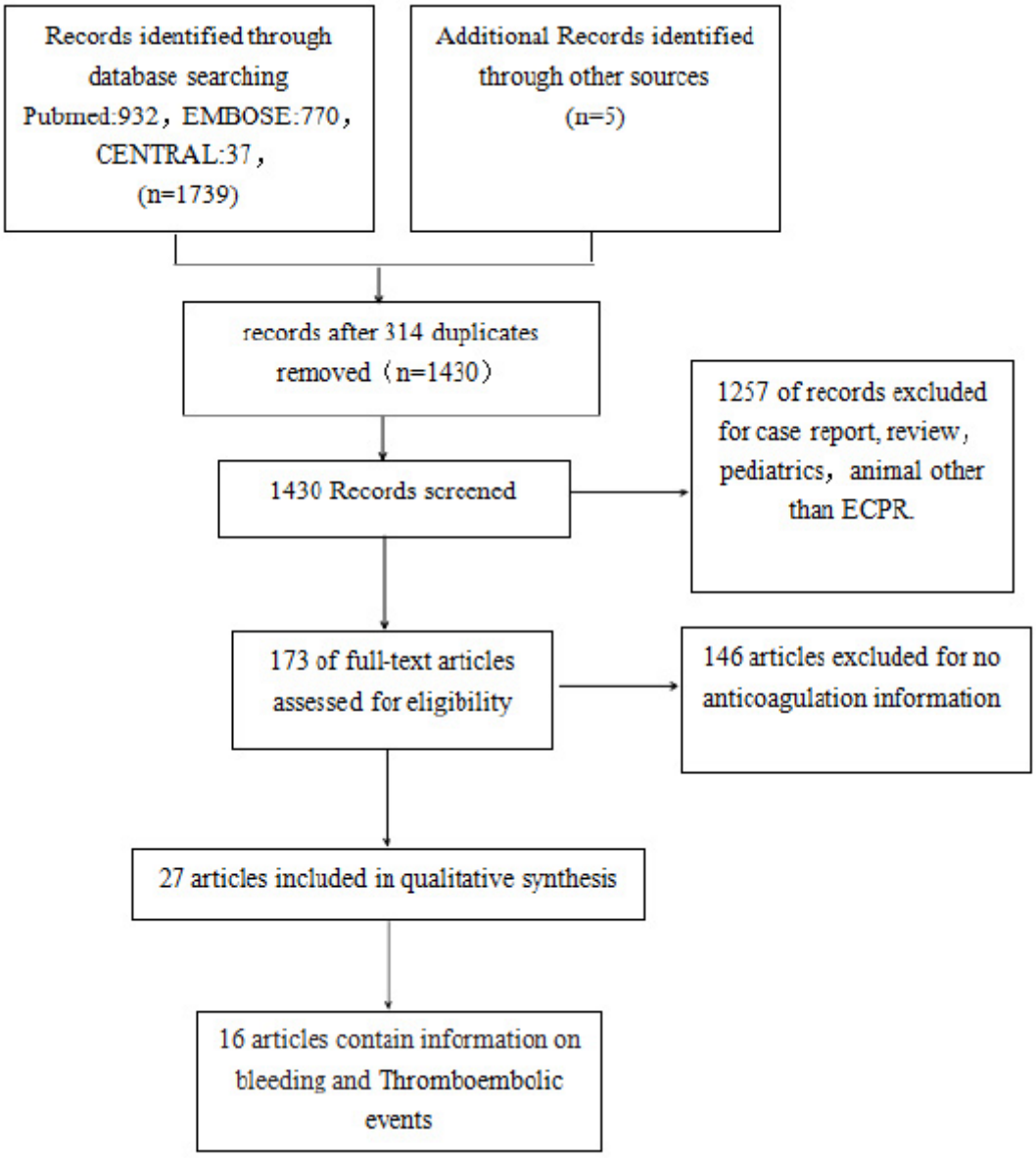

Figure 4

Flowchart of study selection for meta-analysis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1.doc
- FigS1.eps
- FigS2.eps
- FigS3.eps