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Efficacy and safety of anticoagulation in cardiac arrest: a systematic review and meta-analysis

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Abstract

Background: Evidence on the effectiveness of anticoagulation therapy in patients with cardiac arrest is scarce. We aimed to compare the effectiveness of anticoagulation therapy in patients with cardiac arrest by systematic evaluation and meta-analysis.

Methods: The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines were followed. We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from database inception until December 31, 2022, comparing adjuvant anticoagulation to standard care during cardiac arrest. Odds ratios with 95% confidence intervals were calculated using a random-effects model. The population included adults with cardiac arrest in any setting. Pairs of investigators reviewed studies for relevance, extracted data, and assessed the risk of bias. This study was registered with PROSPERO (International Prospective Register of Systematic Reviews).

Results: Four studies were included in the final meta-analysis (1 randomized controlled trial, 1 nonrandomized controlled trial, and 2 observational studies). A total of 1374 patients (412 in the intervention group and 962 in the control group) were included. The results show that anticoagulant interventions increased return of spontaneous circulation compliance compared with control, improved neurological prognosis, and are potentially associated with in-hospital survival. The risk of bleeding in the intervention and control groups and 24-hour survival between these groups were not significantly different.

Conclusion: Anticoagulation during cardiac arrest was associated with achieving return of spontaneous circulation, improving survival to hospitalization, and potentially ameliorating neurologic prognosis in patients. Moreover, anticoagulation did not increase the incidence of bleeding events.

Keywords: Anticoagulants, Cardiac arrest, Heparin, Meta-analysis

Introduction

The prognosis of out-of-hospital cardiac arrest (OHCA) remains uncertain. Despite effective cardiopulmonary resuscitation (CPR), many complex pathophysiological mechanisms unfold during cardiac arrest, leading to ischemia-reperfusion injury and post–cardiac arrest syndrome (PCAS).[1] Platelet activation and coagulation pathway activation are instigated by hypoxia, ischemia, and systemic inflammatory reactions, resulting in the formation of extensive fibrin within the microcirculation. Microcirculatory thrombosis contributed to the "no-reflow" phenomenon in organs, subsequently causing organ dysfunction.[2–4] One potential theoretical approach to mitigating ischemia-reperfusion injury is the prophylactic administration of thrombolytics and/or anticoagulants during CPR. In addition, cardiac arrests resulting from etiologies such as primary thrombosis of the coronary or pulmonary arteries may be a potential target for such treatment. Although numerous clinical studies and systematic reviews have explored systemic thrombolysis during OHCA, only a few published clinical trials have evaluated the role of heparin or other anticoagulants during CPR.[3,5] Considering the uncertainty surrounding the efficacy of anticoagulation in this population, we conducted a systematic review.

Methods

Protocol and registration

This study strictly followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) checklist. We registered the protocol for this systematic review on PROSPERO (International Prospective Register of Systematic Reviews, CRD42023397361). Due to the use of publicly available data, the approval of the ethics committee was not sought.

Retrieval strategy

For systematic review and meta-analysis, we searched the EMBASE, MEDLINE (via PubMed), Scopus, the Cochrane Central Register of Controlled Trials, and the databases for studies published from inception to December 31, 2023, and included forward and backward

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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citations of published studies. We utilized the keywords "cardiac arrest," "cardiopulmonary arrest," or "circulatory arrest" and various anticoagulant and antiplatelet drugs, including but not limited to "heparin," "low-molecular-weight heparin," "aspirin," and "acetylsalicylic acid." The detailed search strategies are shown in Supplemental Table 1, http://links.lww.com/ECCM/A78. All clinical studies of anticoagulation in patients with cardiac arrest were included without language or date restrictions. Pediatric and animal literature, conference abstracts, editorials, and review articles were excluded.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) population: adults (≥18 years) in any setting (in-hospital or out-of-hospital) with cardiac arrest; (2) intervention: anticoagulants provided during cardiac arrest; (3) comparison: no anticoagulants provided during cardiac arrest; and (4) outcomes: any clinical outcome, including but not limited to return of spontaneous circulation (ROSC), survival (maximum follow-up), 24-hour survival, good neurological prognosis (defined as cerebral performance category 1 or 2), bleeding (defined as hemodynamically compromised, fatal, retroperitoneal hemorrhage, intracranial hemorrhage, and need for blood transfusion). The exclusion criteria were as follows: (1) insufficient patient baseline data, including sex, age, intervention, or survival information and (2) ongoing clinical trials.

Data extraction

Study inclusion was determined through independent and duplicate screening of titles and abstracts by 2 reviewers (Zong M and Tian R). Any citations deemed potentially relevant were subjected to full-text review, with reviewers independently extracting data using a standardized form from all eligible studies. The following characteristics were recorded: first author, year of publication, and type of study, total number of patients, intervention, and primary outcome. Any disagreement was resolved through a discussion or a third-person ruling (Zhang J).

Quality assessment

The methodological quality of the included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale[6] for observational studies, Cochrane risk of risk bias[7] for randomized controlled trial (RCT), and nonrandomized controlled trials using MINORS (Methodological Index for Non-Randomized Studies).[8] The quality assessment was conducted independently and repetitively by 2 reviewers (Zong M and Tian R). Any disagreement was resolved through a discussion or third-person ruling (Zhang J).

Statistical analyses

Based on the methodological heterogeneity (ie, study design and risk of bias) between studies, we calculated the odds ratios (ORs) with 95% confidence intervals (CIs) using the random-effects model.[9,10] The I^2 statistic was calculated to evaluate the heterogeneity across outcomes. Significant heterogeneity was identified if the I^2 value exceeded 50%, and the sources of heterogeneity were further discussed. In addition, the sensitivity analyses were performed, sequentially excluding 1 study and merging the remaining studies (n-1) in the meta-analysis. This allowed for an assessment of whether the results of the original meta-analysis were significantly altered by the influence of certain studies, observed through changes in the merged results. Funnel plots were used to qualitatively assess publication bias and quantitatively analyzed with the Egger's test. $P < 0.05$ was considered statistically significant. We performed all analyses using R (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Study characteristics

We identified 14,033 references in our database search. After removing duplicates, we screened 652 records. Subsequently, we reviewed 31 full-text articles, ultimately including 4 studies for meta-analysis (1 RCT, 1 non-RCT, and 2 observational studies) (Fig. 1). A total of 1374 patients (962 in the control group and 412 in the intervention group) were included. The RCT study compared the use of heparin to standard care during CPR for OHCA.[11] For non-RCT study, heparin and tissue plasminogen activators during CPR were compared with standard care for OHCA.[12] The 2 retrospective studies compared aspirin and heparin with standard of care during cardiac arrest.[13,14] In all 4 studies, the mean age of the anticoagulation group was 65.0 ± 12.2 years, and 72.8% of patients were male. The mean age of the control group was 66.4 ± 13.7 years, and 75.2% of patients were male. The initial rhythm was ventricular fibrillation/ventricular tachycardia in 59.9% of the anticoagulated group and 54.4% of the control group. Cardiac causes accounted for 76.5% of and 58.0% of arrest in the anticoagulated and control groups, respectively. The study characteristics are shown in Table 1.

Outcomes

Compared with control, anticoagulant interventions increased ROSC compliance (OR: 2.17; 95% CI: 1.52 to 3.09; I^2 = 0%; 3 studies) and favorable neurological outcome (OR: 2.08; 95% CI: 1.25 to 3.45; I^2 = 0%; 2 studies) and were associated with in-hospital survival (OR: 1.99; 95% CI: 1.27 to 3.11; I^2 = 35.8%; 4 studies). The risk of bleeding (OR: 1.36; 95% CI: 0.23 to 7.88; I^2 = 40.5%; 3 studies) and 24-hour survival (OR: 1.43; 95% CI: 0.91 to 2.25; I^2 = 0%; 2 studies) between the intervention and control groups were not significantly different (Fig. 2).

Sensitivity analysis

Sensitivity analyses were conducted across all results. For hospitalization survival, the combined results were not statistically significant after excluding 1 study,[14] indicating potential heterogeneity. Thus, the random-effects model was used to combine the effect sizes. Notably, the outcomes from the analysis were consistent with the results of the sensitivity analysis (Supplemental Fig. 1, http://links.lww.com/ECCM/A79).

Quality evaluation and publication bias

Regarding the quality of the included studies, 1 RCT demonstrated a moderate risk of bias in missing outcome data and a low risk of bias in the overall. One non-RCT was evaluated using MINORS; the prospective collection of data and baseline equivalence were insufficiently informative, and the sample size calculations were not reported, with moderate overall quality. Two retrospective observational studies were evaluated using Newcastle-Ottawa Quality Assessment Scale, and both scored 8, indicating high quality. Risk-of-bias assessment is provided in the supplementary material (Supplemental Tables 2 [http://links.lww.com/ECCM/A81], 3 [http://links.lww.com/ECCM/A82], 4 [http://links.lww.com/ECCM/A83]). For all outcomes, no evidence of publication bias was observed using either the funnel plot (Supplemental Fig. 2, http://links.lww.com/ECCM/A80) or Egger's test ($P > 0.05$).

Discussion

This meta-analysis suggests that adjuvant anticoagulation in patients with OHCA increases the achievement of ROSC and improves in-

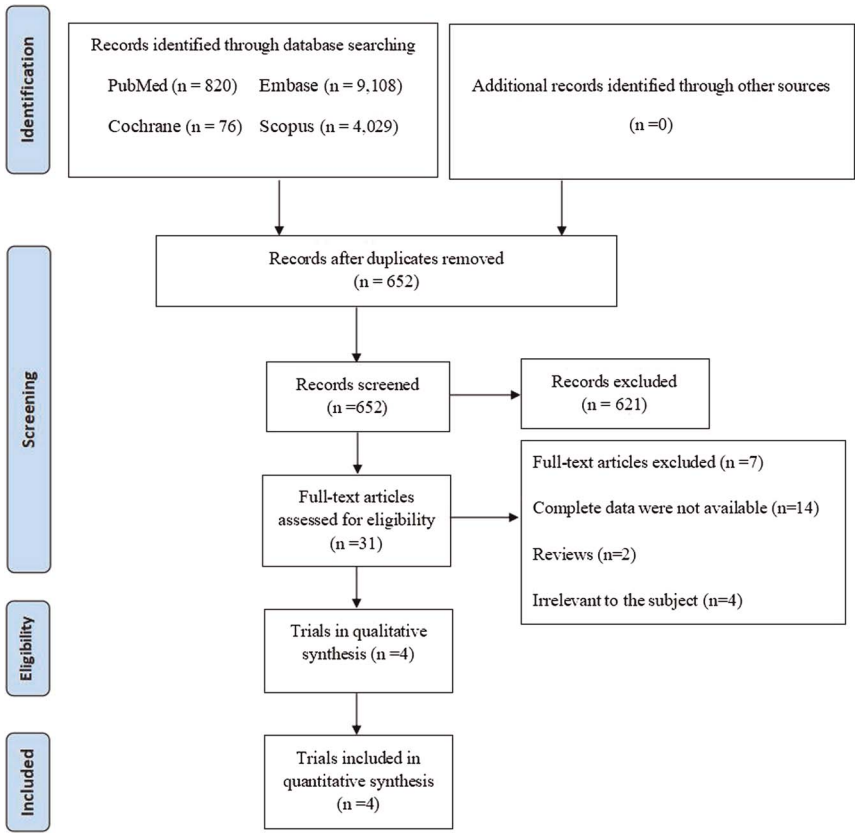

Figure 1. PRISMA diagram for identification of relevant studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1

Baseline Characteristics of Studies Included for Analysis

Author (Year)	Study Type	Country	Patient Characteristics	Intervention	Location of CA	Patients (Total/ Intervention/ Control)	Endpoints
Knor et al.[11] (2011)	Randomized multicenter	Czech Republic	Patient age (mean ± SD), 64.5 ± 11.8 Male patients (%), 76 (86.4%)	10,000 IU heparin	OHCA	88/41/47	Primary: major bleeding <48 hours Secondary: 3-month mortality and neurological outcomes
Böttiger et al.[12] (2001)	Prospective single-center	Germany	Patient age (mean ± SD), 62.3 ± 10.6 Male patients (%), 64 (71.1%)	5000 IU heparin and 50 mg rt-PA	OHCA	90/40/50	Primary: safety (bleeding related complications), ROSC, CICU admission Secondary: 24-hour and in-hospital mortality
Grabmaier et al.[13] (2018)	Retrospective multicenter	Germany	Patient age (mean ± SD), 63.8 ± 13.7 Male patients (%), 304 (79.1%)	500 mg aspirin and 5000 IU heparin	OHCA	384/128/256	Primary: survival to hospital discharge Secondary: safety (bleeding-related complications)
Grabmaier et al.[14] (2020)	Retrospective multicenter	Germany	Patient age (mean ± SD), 68.2 ± 13.3 Male patients (%), 579 (71.3%)	500 mg aspirin and 5000 IU heparin	OHCA	812/203/609	Primary: neurological outcome Secondary: ROSC, ROSC at hospital admission, 24-hour survival and survival to hospital discharge

CA, cardiac arrest; CICU, cardiac intensive care unit; IU, international unit; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; rt-PA, tissue plasminogen activators; SD, standard deviation.

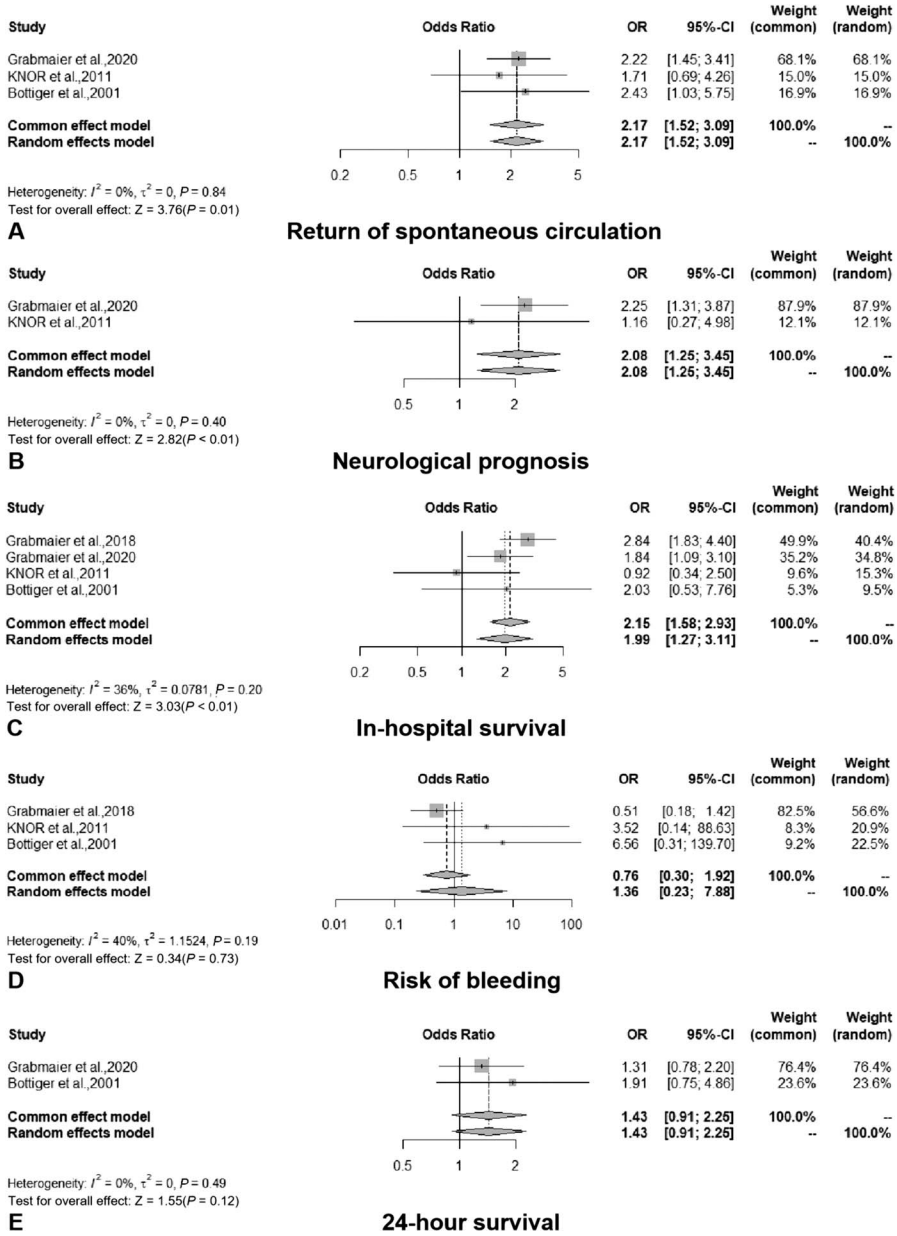

Figure 2. Forest plot for return of spontaneous circulation, neurological prognosis, in-hospital survival, risk of bleeding, and 24-hour survival in cardiac arrest. (A) Forest plot comparing anticoagulant with control groups for return of spontaneous circulation. (B) Forest plot comparing anticoagulant with control groups for neurological prognosis. (C) Forest plot comparing anticoagulant with control groups for in-hospital survival. (D) Forest plot comparing anticoagulant with control groups for risk of bleeding. (E) Forest plot comparing anticoagulant with control groups for 24-hour survival. CI, confidence intervals; OR, odds ratios.

hospital survival and neurological prognosis without significant association with bleeding risk or 24-hour survival. However, the studies we included were 1 RCT, 1 non-RCT, and 2 observational studies. The evidence was low-grade and imprecise. Further high-quality, large-scale studies are warranted to evaluate anticoagulation in patients with cardiac arrest.

OHCA is one of the most serious medical events. Approximately only 11% of patients survived and were discharged following OHCA.[15,16] During CPR, early pharmacological intervention may improve clinical outcomes in patients with OHCA. Certain mechanisms of ischemia-reperfusion injury are activated as early as during CPR. Moreover, a significant increase in platelet and coagulation cascade activity is observed, but with no corresponding increase in fibrinolytic activity.[17] Wada et al. reported that the group of patients with noncardiogenic cardiac arrest exhibited higher thrombin activity, a lower survival rate, and a worse prognosis than the group of patients with cardiogenic cardiac arrest.[18] Following cardiac arrest, patients commonly demonstrate a spectrum of coagulation abnormalities, including dysfunction, enhancement, anticoagulation, and inhibition of the fibrinolytic pathway. These disturbances contribute to intravascular coagulation and intracirculatory thrombosis, ultimately leading to multiorgan dysfunction and a poor prognosis. Ames first described a microcirculatory disturbance following cardiac arrest leading to a localized area without blood flow, which is associated with PCAS brain injury, resulting in poor neurological prognosis in patients.[19] The reduced likelihood of spontaneous reperfusion

due to coronary thrombotic closure may contribute to this cascade,[20] resulting in decreased tissue oxygen supply, the emergence of PCAS, and subsequent organ dysfunction.[2,21] Theoretically, anticoagulant therapy holds promise for ameliorating this adverse condition.

Fischer et al. discovered that the combination of heparin and tissue plasminogen activators can enhance brain microcirculation perfusion, augment patient prognosis, and increase survival rates.[22] In a study involving rabbits as animal models, it was suggested that heparin could assist in restoring blood pressure following ischemia-reperfusion.[23] Several scholars have explored diverse approaches in various animal experiments to improve the phenomenon of "no-reflow." Among these, hypertension perfusion combined with heparin and dextran and dextran combined with streptokinase have demonstrated improvements in cerebral blood flow in laboratory animals, whereas protein C and antithrombin have been observed to be ineffective.[24] These experiments on animal models have shown that anticoagulation therapy can improve microcirculatory perfusion and benefit organ function after ischemia-reperfusion. Gianforcaro et al. reported that pre–cardiac arrest antiplatelet therapy improved survival at discharge and functional outcomes, whereas anticoagulation before cardiac arrest did not yield improved patient outcomes.[25] They suggested that this disparity may stem from the ability of antiplatelet agents to ameliorate a "sepsis-like" inflammatory response following cardiac arrest. In addition, regarding the timing of anticoagulation therapy, researchers argue that indiscriminately administering anticoagulation therapy to patients with cardiac arrest is not justified. Similar to the approach in sepsis management, patients with PCAS diagnosed with disseminated intravascular coagulation are better targets for physiological anticoagulants (eg, antithrombin and recombinant human thrombomodulin) than the entire patient cohort. Therefore, an accurate diagnosis of disseminated intravascular coagulation is crucial for patients with cardiac arrest.[26] Currently, animal experiments suggest that anticoagulation therapy is beneficial for organ perfusion following cardiac arrest, whereas clinical studies are mainly retrospective studies. Further prospective studies are warranted to prove the effectiveness of anticoagulation therapy. Only a limited number of studies have investigated the independent effects of anticoagulant therapy on the course of cardiac arrest and its results.[27–32] These studies typically involve experimental receptors. Trials assessing the clinical efficacy and/or safety of anticoagulants during cardiac arrest are scarce. Considering the proliferation of new and markedly effective anticoagulants, there remains ample opportunity to investigate their effects on patients with cardiac arrest.[33]

Recent studies have focused on evaluating the prognosis of patients administered systemic thrombolysis during CPR.[34–39] Böttiger et al. conducted a randomized trial involving 1050 patients with OHCA suspected of cardiac origin, assigning them to receive either tenecteplase bolus or placebo during CPR. Their findings revealed no significant difference in 30-day survival between the 2 groups (14.7% vs. 17.0%, $P = 0.36$).[5] According to studies, patients with cardiac arrest have a high risk of bleeding when undergoing thrombolytic therapy, which has led to the discouragement of its use.[40,41] A recent meta-analysis investigating the efficacy of systemic thrombolysis during CPR in patients with cardiac arrest revealed no significant benefit in terms of discharge rate, ROSC, or 24-hour survival and patients receiving thrombolytic therapy have a higher risk of bleeding.[41]

Autopsies of patients who received CPR necessitating antithrombotic or anticoagulant therapy have revealed massive fibrin formation in the microcirculation of lung and renal tissues.[42] Therefore, it is necessary to maintain a balance between prothrombotic (acute ischemic event) and prohemorrhagic factors (eg, CPR, aggressive antiplatelet and anticoagulant therapy) in patients with cardiac arrest.[43] The effect of heparin on CPR success remains poorly studied, with only sporadic positive findings observed in animal experiments.[44,45] Clinical studies of heparin combined with systemic thrombolysis and reports of cardiac arrest treated solely with heparin remain limited.[36,46] The effect of heparin on the coagulation and fibrinolytic systems differs from thrombolytic, making it particularly valuable from a pathophysiological perspective in preventing thrombosis during cardiac arrest and microcirculatory dysfunction.[46] Moreover, heparin is an affordable and easy-to-use drug. All 4 studies included in our analysis used heparin. Although newer oral anticoagulants (eg, dabigatran, rivaroxaban, apixaban, and edoxaban) could potentially offer advantages, no clinical studies have yet been conducted on their use in patients with cardiac arrest.

Limitations

This meta-analysis was limited by the available data and bias associated with non-RCT and observational studies. Our results should be interpreted with caution as they are derived from 4 studies, with 2 being observational in design. Although anticoagulation may be worth considering for patients with low bleeding risks, the limited evidence underscores the necessity for more high-quality, large-scale clinical trials to evaluate the role of anticoagulation in patients with cardiac arrest. However, the ethical issues of refusing treatment or administering experimental treatments in lifesaving situations limit the conduct of large-scale RCTs. Moreover, obtaining the consent of the relatives is not appropriate in such critical situations. Conducting a clinical trial in a real-life clinical scenario involves a more careful assessment of a patient's bleeding risk, including a history of previous cerebral hemorrhage, gastrointestinal hemorrhage, hematologic disorders, and other medical conditions. Assessing hospitalized patients may provide a more suitable approach. Therefore, conducting studies focusing on a subset of patients with in-hospital cardiac arrest could be an initial step to further evaluate the efficacy and safety of anticoagulation therapy in this population.

Conclusion

This study found that anticoagulation during cardiac arrest was associated with achieving ROSC, enhancing survival to hospitalization, and potentially improving neurologic prognosis in patients. In addition, anticoagulation did not increase the incidence of bleeding events. In cases of cardiac arrest where myocardial ischemia or infarction is suspected as the underlying cause of circulatory failure, the potential benefit of anticoagulation may become apparent. However, further RCTs are required to validate the efficacy and safety of anticoagulation in patients with cardiac arrest.

Conflict of interest statement

Yuguo Chen, Editor-in-Chief of *Emergency and Critical Care Medicine*, confirms no involvement in any stage of this article's peer-review process, ensuring unbiased editorial decision-making. The authors declare no conflict of interest.

Author contributions

Zong M and Tian R conceived and designed the study and independently completed database search and screening and data extraction. Zhang J assessed the eligibility of unresolved studies between the 2 authors. Zong M and Zhang J inspected and verified the data. Zong M performed all statistical analysis on R 4.3.1. Zong M and Tian R wrote the manuscript, and Zhang J revised the finished manuscript. Li C and Chen Y provided suggestions on summarizations and statistical analysis. All authors read and approved the final version of the manuscript.

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Ethical approval of studies and informed consent

All studies included in this study followed the principles of the Declaration of Helsinki as revised in 2013.

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