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CAN SYSTEMIC THROMBOLYSIS IMPROVE PROGNOSIS OF CARDIAC ARREST PATIENTS DURING CARDIOPULMONARY RESUSCITATION? A SYSTEMATIC REVIEW AND META-ANALYSIS

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□ Abstract—Background: Cardiac arrests are caused in most cases by thromboembolic diseases, such as acute myocardial infarction (AMI) and pulmonary embolism (PE). Objective: We aimed to ascertain the associations of thrombolytic therapy with potential benefits among cardiac arrest patients during cardiopulmonary resuscitation (CPR). Methods: We searched PubMed, Embase, and Cochrane databases for studies that evaluated systemic thrombolysis in cardiac arrest patients. The primary outcome was survival to hospital discharge, and secondary outcomes included return of spontaneous circulation (ROSC), 24-h survival rate, hospital admission rate, and bleeding complications. Results: Nine studies with a total of 4384 cardiac arrest patients were pooled in the meta-analysis, including 1084 patients receiving systemic thrombolysis and 3300 patients receiving traditional treatments. Compared with conventional therapies, the use of systemic thrombolysis did not significantly improve survival to hospital discharge (13.5% vs. 10.8%; risk ratio [RR] 1.13; 95% confidence interval [CI] 0.92–1.39; p = 0.24, I^2 = 35%), ROSC (50.9% vs. 44.3%; RR 1.29; 95% CI 1.00–1.66; p = 0.05, I^2 = 73%), and 24-h survival (28.1% vs. 25.6%; RR 1.25; 95% CI 0.88–1.77; p = 0.22, I^2 = 63%). We observed higher hospital admission rates for patients receiving systemic thrombolysis (43.4% vs. 30.6%; RR 1.53; 95% CI 1.04–2.24; p = 0.03, I^2 = 87%). In addition, higher risk of bleeding was observed in the thrombolysis group (8.8% vs. 5.0%; RR 1.65; 95% CI 1.16–2.35; p = 0.005, I^2 = 7%). Conclusions: Systemic thrombolysis during CPR did not improve hospital discharge rate, ROSC, and 24-h survival for cardiac arrest patients. Patients receiving thrombolytic therapy have a higher risk of bleeding. More high-quality studies are needed to confirm our results.

□ Keywords—thrombolysis; cardiac arrest; cardiopulmonary resuscitation; pulmonary embolism; acute myocardial infarction

Yiwei Wang and Maoyun Wang contributed equally to this work.

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Each clinical trial included was approved by the corresponding institution's ethical committee.

Written informed consent was provided by participants of each study.

INTRODUCTION

Cardiac arrest is a life-threatening condition and a major cause of sudden death. Each year, it causes more than 3.7 million deaths worldwide (1). Studies show that 75–85% of out-of-hospital cardiac arrest cases have a primary

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cardiac cause, and respiratory diseases account for 8% of cardiac arrest (2,3).

Thromboembolic diseases, such as acute myocardial infarction (AMI) and pulmonary embolism (PE), are the most common causes of cardiac arrest (4–6). Thrombolytic therapy can reduce all-cause mortality and is recommended in guidelines for AMI and high-risk PE patients (presenting with shock or hypotension) (7–10). Dissolving blood emboli by administering fibrinolytic substances to re-establish circulation in cardiac arrest patients might work from a pathophysiological point of view. However, thrombolysis can increase bleeding risk and is one of the relative contraindications in patients receiving cardiopulmonary resuscitation (CPR) (11). Guidelines only suggest thrombolytic therapy for cardiac arrests secondary to PE, considering the life-threatening situation, and it is not routinely recommended for other etiologies (12,13).

Numerous studies have been published about thrombolytic therapy for cardiac arrest patients with inconsistent results. A retrospective study reported by Lederer et al. found that patients receiving recombinant tissue plasminogen activator (rt-PA) during CPR could improve return of spontaneous circulation (ROSC) and survival to hospital discharge (14). Bozeman et al. conducted a prospective cohort study in emergency departments and reported higher ROSC and hospital admission rates, but no difference was found for hospital discharge rate (15). The largest randomized controlled trial (RCT), conducted by Böttiger et al., did not detect any improvement in outcomes (16). Considering the clinical value and the current lack of evidence, we performed this systematic review and meta-analysis to identify the latest evidence on whether systemic thrombolysis has been shown to improve patient prognosis after cardiac arrest.

METHODS

We conducted this review in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement according to current guidelines (17). We registered the protocol of this systematic review with PROSPERO (International Prospective Register of Systematic Reviews; registration number: CRD42017069703).

Search Strategy

We searched PubMed, Embase, and Cochrane databases from inception to January 2019, and search strategies were adapted for each database, including medical subject headings and keywords for *heart arrest* or *cardiopulmonary resuscitation* and *thrombolysis* or *tissue plasminogen activator* without limitations on publication type or language.

Eligibility Criteria

We identified eligible comparative studies according to the following inclusion criteria: 1) exported data from original research studies, 2) human adults (≥16 years of age) suffering from sudden cardiac arrest, 3) studies focusing on systemic thrombolysis therapy during CPR, and 4) studies including at least one of the predetermined outcomes. We excluded studies published as conference abstracts in our meta-analysis.

Data Extraction and Quality Assessment

After removing duplications, two reviewers (YW-W and MY-W) independently assessed citation titles and abstracts using a “relevant,” “irrelevant,” or “unsure” designation. Disagreements were resolved by discussing with a third investigator (YN-N). The quality of the included studies was assessed by the Cochrane Risk of Bias Tool for RCTs and Newcastle-Ottawa Scale for observational studies (18,19).

Outcomes

The primary outcome was survival to hospital discharge. The secondary outcomes included ROSC, hospital admission, 24-h survival, and bleeding complications.

Heterogeneity and Sensitivity Analysis

We reported the overall effect size as well as the separate effect sizes for RCTs and observational studies. Studies were tested for heterogeneity using the I^2 statistic. An I^2 value > 50% suggested substantial heterogeneity (20). We used fixed-effects models to pool data with insignificant heterogeneity and the random-effects models for data with significant heterogeneity. We performed a sensitivity analysis by excluding one trial in each round to test the influence of a single study on the overall pooled estimate.

Statistical Analysis

We undertook this meta-analysis in Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK) using a random-effects model to incorporate covariate adjustment to mitigate overspecification. Meta-analysis results were presented in terms of risk ratio (RR) and 95% confidence interval (CI) for dichotomous outcomes. All statistical tests were two-sided, and statistical significance was defined as $p < 0.05$.

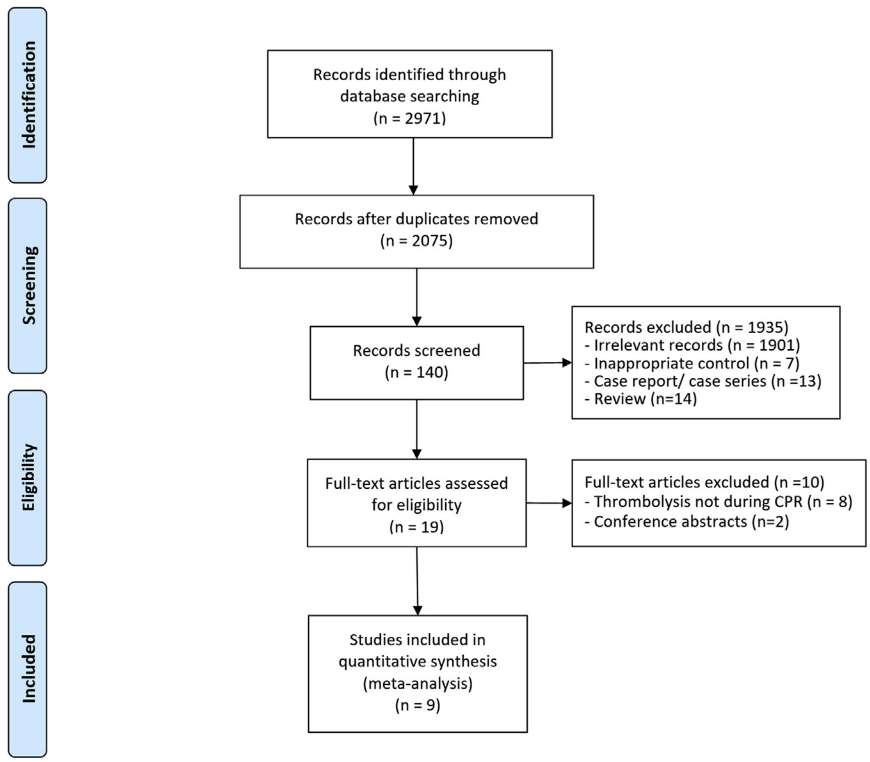

Figure 1. Flow diagram of primary study search process. CPR = cardiopulmonary resuscitation.

RESULTS

Study Selection

A total of 2971 records were identified through database searching. After removing duplicates, 1935 records were removed. The 140 remaining records were identified as being potentially relevant, and abstracts were assessed for eligibility. A total of 19 articles discussed thrombolytic therapy in cardiac arrest patients, and full articles were read carefully. Finally, nine studies discussing thrombolysis during CPR were identified and included in the meta-analysis (Figure 1) (14–16,21–26).

Table 1. Characteristics of Studies Included in the Meta-Analysis

First Author (Reference)	Year	Study Design	Etiology	Thrombolytic Agent	Patients, n, Thrombolysis/ Control	Outcomes
Abu-Laban (22)	2002	RCT	Non-traumatic	Alteplase	117/116	Discharge, 24-h survival, admission, ROSC, bleeding
Böttiger (21)	2001	Prospective cohort	Non-traumatic	Alteplase	40/50	Discharge, 24-h survival, admission, ROSC, bleeding
Böttiger (16)	2008	RCT	Presumed cardiac origin	Tenecteplase	525/525	Discharge, 24-h survival, admission, ROSC, bleeding
Bozeman (15)	2006	Prospective cohort	Non-traumatic	Tenecteplase	50/113	Discharge, 24-h survival, admission, ROSC, bleeding
Fatovich (23)	2004	RCT	Presumed cardiac or PE	Alteplase	19/16	Discharge, admission, ROSC, bleeding
Lederer (14)	2001	Retrospect cohort	Non-traumatic	Alteplase	108/216	Discharge, 24-h survival, ROSC, bleeding
Renard (25)	2011	Retrospect cohort	Non-traumatic	Alteplase, tenecteplase	107/1154	Admission
Stadlbauer (24)	2006	Post-hoc analysis	Non-traumatic	Tenecteplase, reteplase	99/1087	Discharge, admission
Yousuf (26)	2016	Retrospect cohort	PE	Alteplase	19/23	Discharge, 24-h survival, bleeding

AMI = acute myocardial infarction; PE = pulmonary embolism; RCT = randomized controlled trial; ROSC = return of spontaneous circulation.

Table 2. Quality Assessment of Included Studies

First Author, Year (Reference)	Selection: Representativeness of Exposed Cohort	Selection: Selection of Non-Exposed Cohort	Selection: Demonstration That Outcome of Interest Was Not Present at Start of Study	Selection: Ascertainment of Exposure	Comparability on Basis of Design and Analysis	Outcome: Assessment of Outcome	Outcome: Follow-Up Long Enough	Outcome: Adequacy of Follow-Up	Total Stars, n
Newcastle-Ottawa Scale for Assessing the Quality of Included Cohort Studies									
Böttiger, 2001 (21)	*	*	*	*	**	*	*	*	9
Bozeman, 2006 (15)	*	*	*	*	—	*	*	*	7
Lederer, 2001 (14)	*	*	*	*	*	*	*	*	8
Renard, 2011 (25)	*	*	*	*	—	*	*	*	7
Stadlbauer, 2006 (24)	*	*	*	*	*	*	*	*	8
Yousuf, 2016 (26)	*	*	*	*	**	*	*	*	9

Author, Year (Reference)	Random Assignment	Allocation Concealment	Blinding of Participants	Blind Evaluation For Outcomes	Incomplete Outcome Data	Selective Reporting	Other Bias
Quality Assessment of Included RCTs							
Abu-Laban, 2002 (22)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fatovich, 2004 (23)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Böttiger, 2008 (16)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

RCT = randomized controlled trial.

Study or Subgroup	Thrombolysis Events	Thrombolysis Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abu-Laban 2002	1	117	0	116	0.4%	2.97 [0.12, 72.27]
Bottiger 2001	6	40	4	50	2.6%	1.88 [0.57, 6.19]
Bottiger 2008	78	517	90	514	66.2%	0.86 [0.65, 1.14]
Bozeman 2006	2	50	0	113	0.2%	11.18 [0.55, 228.64]
Fatovich 2004	1	19	1	16	0.8%	0.84 [0.06, 12.42]
Lederer 2001	27	108	33	216	16.1%	1.64 [1.04, 2.57]
Stadlbauer 2006	14	99	101	1087	12.4%	1.52 [0.91, 2.56]
Yousuf 2016	2	19	2	23	1.3%	1.21 [0.19, 7.80]
Total (95% CI)		**969**		**2135**	**100.0%**	**1.13 [0.92, 1.39]**
Total events	131		231			

Heterogeneity: Chi² = 10.80, df = 7 (P = 0.15); I² = 35%
Test for overall effect: Z = 1.17 (P = 0.24)

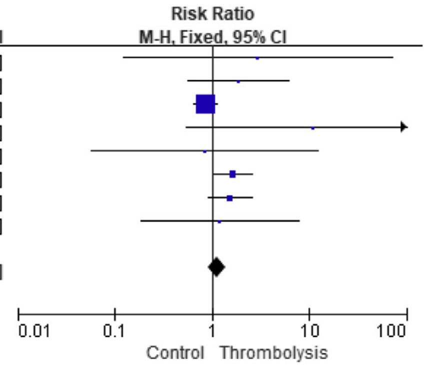

Figure 2. Effect of systemic thrombolysis on survival to hospital discharge. CI = confidence interval; M-H = Mantel-Haenszel.

Study Characteristics

Nine studies with a total of 4384 cardiac arrest patients were pooled in the meta-analysis, including 1084 patients receiving systemic thrombolysis and 3300 patients receiving traditional treatments. Of the nine studies included, three were RCTs, three were retrospective cohort studies, two were prospective cohort studies, and one was a post-hoc analysis. Details of each study included in our analysis are summarized in Table 1.

Quality Assessment

The Cochrane Risk of Bias Tool was used for RCTs, and the risk of bias was rated as "low," "unclear," or "high." The Newcastle-Ottawa Scale was used to assess the quality of observational studies with a maximum of 9 stars, and a study with final stars ≥ 6 was regarded as high quality. Overall, all of the included trials were considered high quality. The quality assessment results are presented in Table 2.

Survival to Hospital Discharge

Eight studies were pooled in this comparison, including 969 patients receiving thrombolysis and 2135 patients in the control group. The results showed that patients in both groups had survival rates similar to hospital discharge rates (13.5% vs. 10.8%; RR 1.08; 95% CI 0.92–1.39; $p = 0.24$, $I^2 = 35\%$) (Figure 2).

ROSC

We compared the rate of ROSC between the thrombolytic group and the control group. Six studies with a total of 1871 patients were enrolled, and we chose the random-effects model because of high heterogeneity. There was a trend for higher ROSC in the thrombolytic group, but the difference was not statistically significant (50.9% vs. 44.3%; RR 1.29; 95% CI 1.00–1.66; $p = 0.05$, $I^2 = 73\%$) (Figure 3).

Hospital Admission

Seven studies with a total of 4018 patients were pooled in this analysis. No study reported the admission time between emergency department and hospital ward, and we used the random-effects models for high heterogeneity. The result showed that patients in the thrombolytic group had higher hospital admission rates (43.4% vs. 30.6%; RR 1.53; 95% CI 1.04–2.24; $p = 0.03$, $I^2 = 87\%$) (Figure 4).

24-Hour Survival Rate

Six studies with 1883 patients analyzed the 24-h survival rate. No significant statistical difference was found

Study or Subgroup	Thrombolysis Events	Thrombolysis Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Abu-Laban 2002	25	117	27	116	14.7%	0.92 [0.57, 1.48]
Bottiger 2001	27	40	22	50	18.2%	1.53 [1.05, 2.24]
Bottiger 2008	283	515	279	511	29.2%	1.01 [0.90, 1.12]
Bozeman 2006	13	50	14	113	9.6%	2.10 [1.07, 4.13]
Fatovich 2004	8	19	1	16	1.6%	6.74 [0.94, 48.29]
Lederer 2001	76	108	110	216	26.8%	1.38 [1.16, 1.65]
Total (95% CI)		**849**		**1022**	**100.0%**	**1.29 [1.00, 1.66]**
Total events	432		453			

Heterogeneity: Tau² = 0.05; Chi² = 18.58, df = 5 (P = 0.002); I² = 73%
Test for overall effect: Z = 1.97 (P = 0.05)

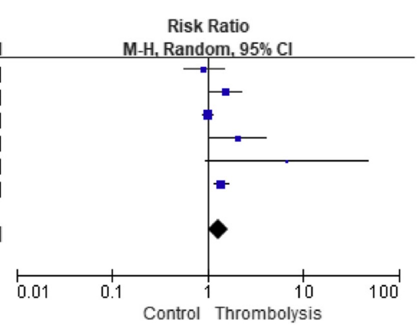

Figure 3. Effect of systemic thrombolysis on return of spontaneous circulation. CI = confidence interval; M-H = Mantel-Haenszel.

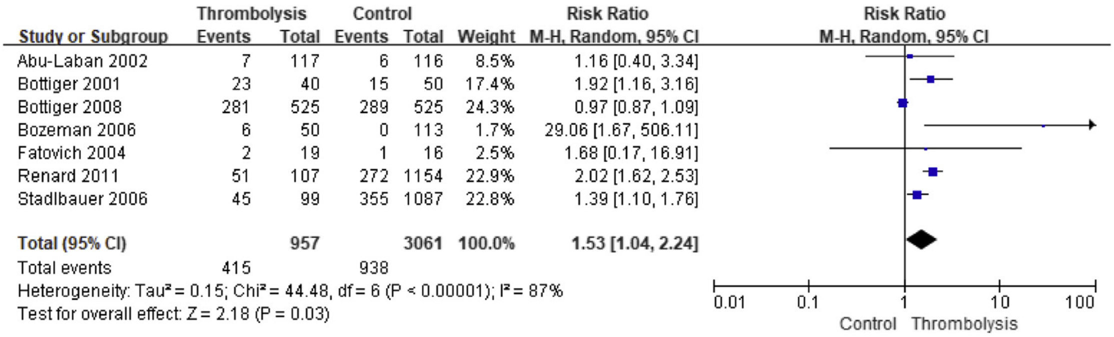

Figure 4. Effect of systemic thrombolysis on hospital admission. CI = confidence interval; M-H = Mantel-Haenszel.

between the thrombolytic group and the control group (28.1% vs. 25.6%; RR 1.25; 95% CI 0.88–1.77; $p = 0.22$, $I^2 = 63\%$) (Figure 5).

Bleeding Complications

Seven studies with a total of 1686 patients reported bleeding complications. Compared with non-thrombolytic therapy, patients receiving systemic thrombolysis showed a significantly higher risk of bleeding (8.8% vs. 5.0%; RR 1.65; 95% CI 1.16–2.35; $p = 0.005$, $I^2 = 7\%$) (Figure 6).

Publication Bias

No obvious publication bias was observed by a visual inspection of the funnel plots in our meta-analysis (Figure 7).

DISCUSSION

Our study suggested that, compared with conventional therapies for cardiac arrests, patients receiving systemic thrombolysis during CPR did not show any improvements in survival to hospital discharge, ROSC, and 24-h survival. A higher hospital admission rate was observed. In addition, more bleeding events were reported for patients receiving thrombolytic therapy.

Thromboembolic diseases, such as AMI and PE, are the main causes of non-traumatic cardiac arrests. Obstruction of the coronary artery and pulmonary trunk can affect systolic function of the heart and causes hemodynamic instability or even cardiac arrest. Based on the pharmacologic properties of thrombolytic agents, systemic thrombolysis can dissolve blood clots, thus helping reperfusion of important organs. However, our meta-analysis did not find any improvement in hospital discharge, ROSC, and 24-h survival rates. The cause of these results may be related to the restriction of organ perfusion during chest compression, which may hamper the delivery of thrombolytic drugs to blood clots.

ROSC is the sustained perfusing cardiac activity and respiratory activity after cardiac arrest. It is regarded as an earlier achievement of CPR that may indirectly decrease mortality. In our meta-analysis, higher ROSC was observed in patients receiving thrombolysis, but the difference was not statistically significant. This finding might suggest that thrombolytic drugs have the potential to improve circulation, or it may be related to the small sample size of our study. Further increasing the number of articles may make this result more obvious. Approximately half of the cardiac arrest patients achieved ROSC in our meta-analysis, but only slightly more than 10% of patients survived to hospital discharge. According to some large studies, approximately 70% of ROSC patients died of complications (27,28). The survival rate remains poor, even after achieving ROSC, and post-cardiac arrest syndrome (PCAS) is the most common

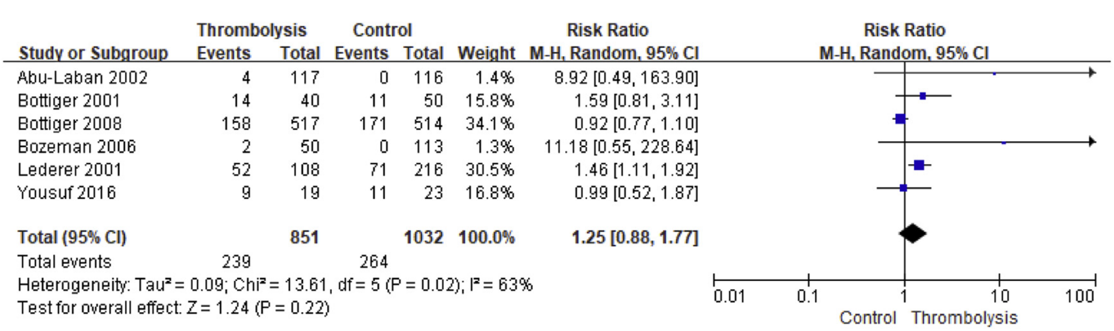

Figure 5. Effect of systemic thrombolysis on 24-hour survival. CI = confidence interval; M-H = Mantel-Haenszel.

Study or Subgroup	Thrombolysis Events	Thrombolysis Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abu-Laban 2002	3	117	1	116	2.2%	2.97 [0.31, 28.18]
Bottiger 2001	2	40	0	50	1.0%	6.22 [0.31, 125.98]
Bottiger 2008	54	518	35	514	78.6%	1.53 [1.02, 2.30]
Bozeman 2006	3	50	0	113	0.7%	15.65 [0.82, 297.38]
Fatovich 2004	0	19	0	16		Not estimable
Lederer 2001	6	45	7	46	15.5%	0.88 [0.32, 2.41]
Yousuf 2016	3	19	1	23	2.0%	3.63 [0.41, 32.13]
Total (95% CI)		**808**		**878**	**100.0%**	**1.65 [1.16, 2.35]**
Total events	71		44			

Heterogeneity: Chi² = 5.39, df = 5 (P = 0.37); I² = 7%
Test for overall effect: Z = 2.78 (P = 0.005)

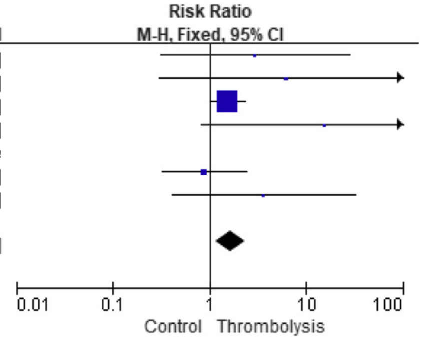

Figure 6. Effect of systemic thrombolysis on bleeding complications. CI = confidence interval; M-H = Mantel-Haenszel.

cause (29). PCAS refers to a series of abnormalities that develop after resuscitation, including post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathology. The most common causes of death during the first 24 h after ROSC are refractory shock and multi-organ system failure, while later deaths result from neurologic injury (30).

In our meta-analysis, patients receiving systemic thrombolysis had higher hospital admission rates. None of the articles included mentioned the admission criteria, and very high heterogeneity was observed. It is difficult to assess whether this heterogeneity was related to the potential role of thrombolytics. Compared with the 24-h survival rate, we hypothesized that hospital admission was not representative to assess short-term survival. However, a higher admission rate also means more opportunities for treatment, and we should not ignore the potential benefits for patients.

Bleeding is one of the complications of thrombolytic therapy, resulting from systemic activation of plasmin outside the thrombus that leads to systemic fibrinolysis (31). Some studies we examined reported the total number of bleeding events, while other studies only reported major bleeding, or divided bleeding events into minor bleeding and major bleeding. Given the inconsistent definition and inclusion criteria, we analyzed all types of

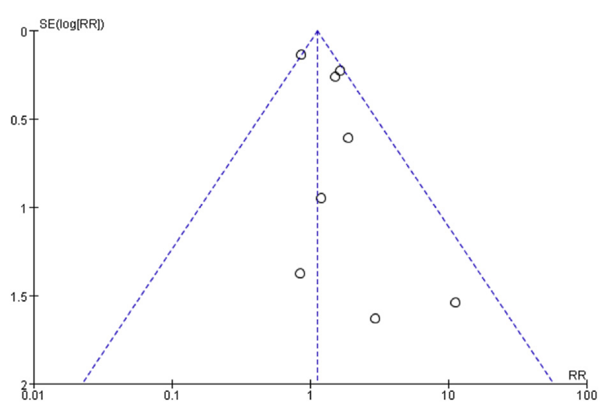

Figure 7. Funnel plots for publication bias. RR = risk ratio; SE = standard error.

bleeding events without classification. In our meta-analysis, an increase in bleeding complications was observed, but there was not sufficient evidence to prove that thrombolysis would increase bleeding-related mortality from the studies examined.

Systemic thrombolytic therapy is widely used in the treatment of coronary and pulmonary thrombosis. Current approaches for AMI patients aim to restore the blood flow to myocardial cells, and guidelines recommended thrombolysis for patients who have no access to percutaneous coronary intervention within 120 min (32,33). For PE, systemic thrombolytic therapy is recommended for patients with hemodynamic instability, and greatly improves their prognosis (10). For patients with clear-onset cardiac arrest, thrombolysis might improve outcomes according to some observational studies, but the results have yet to be verified by high-quality RCTs (34,35). For sudden cardiac arrest, physicians often do not have sufficient time to determine the cause of cardiac arrest. The results of our meta-analysis indicate that there is no survival benefit for systemic thrombolysis during CPR in cardiac arrest patients with unclear etiologies.

It is controversial whether thrombolysis could improve prognosis of cardiac arrest patients. Prior to our study, a meta-analysis with eight studies on cardiac arrest patients receiving thrombolytic therapy was published in 2004 (36). The meta-analysis showed that thrombolysis could improve survival to hospital discharge, ROSC, hospital admission, and 24-h survival, and was associated with better long-term neurologic function. After carefully reading all of the articles, only two studies met our inclusion criteria. Other studies were excluded for enrolling subjects receiving thrombolysis after CPR. All of the studies included in our review focused on subjects receiving systemic thrombolysis during CPR. The difference between our study and the conclusions of previous articles may be attributed to the research object itself. Despite the inconsistent results, systemic thrombolysis is still used for the rescue of patients with cardiac arrest. To ascertain the associations of thrombolytic therapy with potential benefits among cardiac arrest patients, we conducted this systematic review and meta-analysis by focusing on systemic thrombolysis during CPR.

Limitations

This meta-analysis summarizes the most recent evidence available on systemic thrombolysis therapy in cardiac arrests, but some limitations should be noted. First, our research consists of nine articles. Of these studies, only three are RCTs, and the others are post-hoc analysis and observational studies. More high-quality studies are needed to evaluate the efficacy of systemic thrombolysis in the future. Second, heterogeneity was inevitable in many aspects, such as different etiologies for cardiac arrest, inconsistent baseline levels, and various supportive treatments. In addition, varying doses and types of thrombolytic drugs were used, and different anticoagulant therapies were employed in the studies. These differences potentially affect the evaluation of the thrombolytic treatment.

CONCLUSIONS

Systemic thrombolysis does not improve survival to hospital discharge, ROSC, and 24-h survival rates, and is associated with more bleeding events for cardiac arrest patients. More large RCTs are needed to confirm our results.

Acknowledgments—Authors' contributions: YW-W designed the study, conducted the literature search, performed data analysis, and drafted the manuscript. MY-W conducted the literature search and revised the manuscript. YN-N helped in the design of the study and data analysis. BM-L helped in data analysis and revised the manuscript. ZA-L participated in modifying the important knowledge content and provided the final version for publication. All authors read and approved the final manuscript.

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ARTICLE SUMMARY

1. Why is this topic important?

The mortality rate of cardiac arrest patients is very high and limited measures can be taken in addition to cardiopulmonary resuscitation (CPR). Many studies reported systemic thrombolytic therapy during CPR with inconsistent results.

2. What does this review attempt to show?

We aim to ascertain associations of thrombolytic therapy with potential benefits among cardiac arrest patients during CPR with the latest evidence.

3. What are the key findings?

Systemic thrombolysis during CPR did not significantly improve survival to hospital discharge, return of spontaneous circulation, and 24-h survival rate. A higher hospital admission rate and more bleeding events were reported for patients receiving thrombolytic therapy.

4. How is patient care impacted?

Systemic thrombolysis does not improve hospital survival during CPR and can cause more bleeding events. Clinicians should be cautious in choosing thrombolytic therapy for cardiac arrest patients with unknown etiology.