

Comparing percutaneous coronary intervention and thrombolysis in patients with return of spontaneous circulation after cardiac arrest

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OBJECTIVE: To evaluate the effects of percutaneous coronary intervention and thrombolysis after restoration of spontaneous circulation in cardiac arrest patients with ST-elevation myocardial infarction using meta-analysis.

METHODS: We performed a meta-analysis of clinical studies indexed in the PUBMED, MEDLINE and EMBASE databases and published between January 1995 and October 2012. In addition, we compared the hospital discharge and neurological recovery rates between the patients who received percutaneous coronary intervention and those who received thrombolysis.

RESULTS: Twenty-four studies evaluating the effects of percutaneous coronary intervention or thrombolysis after restoration of spontaneous circulation in cardiac arrest patients with ST-elevation myocardial infarction were included. Seventeen of the 24 studies were used in this meta-analysis. All studies were used to compare percutaneous coronary intervention and thrombolysis. The meta-analysis showed that the rate of hospital discharge improved with both percutaneous coronary intervention ($p < 0.001$) and thrombolysis ($p < 0.001$). We also found that cardiac arrest patients with ST-elevation myocardial infarction who received thrombolysis after restoration of spontaneous circulation did not have decreased hospital discharge ($p = 0.543$) or neurological recovery rates ($p = 0.165$) compared with those who received percutaneous coronary intervention.

CONCLUSION: In cardiac arrest patients with ST-elevation myocardial infarction who achieved restoration of spontaneous circulation, both percutaneous coronary intervention and thrombolysis improved the hospital discharge rate. Furthermore, there were no significant differences in the hospital discharge and neurological recovery rates between the percutaneous coronary intervention-treated group and the thrombolysis-treated group.

KEYWORDS: Meta-analysis; Cardiac Arrest; Return of Spontaneous Circulation; St-Elevation Myocardial Infarction; Percutaneous Coronary Intervention; Thrombolysis.

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INTRODUCTION

Cardiac arrest (CA) is a major cause of death in adults both in and out of the hospital. The percentage of patients who survive to hospital discharge is approximately 5-10% at best (1). Cardiopulmonary resuscitation (CPR) is essential to prevent death and provide neuroprotection after CA.

However, the hospital discharge rates following in-hospital CPR remain as low as they were 50 years ago, at 15-20% (2).

Epidemiological studies have shown that coronary artery disease is the primary cause of CA, resulting in arrest within a short time due to acute myocardial infarction (AMI) or ischemia-related arrhythmias in 56-88% of clinical cases with CA (3,4). Autopsy studies have demonstrated that coronary arteries occluded by thrombi or ruptured atherosclerotic plaques have been identified in up to 95% of patients who die from sudden cardiac death (SCD) (5,6).

Clinical studies have shown that reperfusion therapy reduces the high mortality rate, particularly in patients with ST-elevation myocardial infarction (STEMI) (7). Some studies have demonstrated that percutaneous coronary intervention (PCI) is beneficial in patients with STEMI (8-10). Meanwhile, a meta-analysis also indicated that thrombolysis is an effective treatment for STEMI patients (11).

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However, a large-scale multicenter prospective study (TROICA) indicated that thrombolysis is ineffective in patients with CA after STEMI, and that study was stopped prematurely because of the convincing early-stage data (12). Therefore, the controversy still exists regarding the efficacies of PCI and thrombolysis in patients with CA after STEMI (12-17).

Both PCI and thrombolysis are efficacious in patients with STEMI. However, there is a significant difference between the efficacies of PCI and thrombolysis in patients with CA after STEMI. We assumed that most studies did not distinguish the condition of patients with STEMI. Thrombolysis may be used to treat patients without return of spontaneous circulation (ROSC) after CA. Therefore, the high mortality rate of patients with CA masked the benefit of thrombolysis. However, PCI can be used to treat patients with ROSC after CA. Herein, we assessed the efficacies of PCI and thrombolysis in patients with ROSC after CA in the presence of STEMI.

■ METHODS

Study identification strategy

We searched for research papers indexed in the PUBMED, MEDLINE and EMBASE databases that were published from January 1995 to October 2012. The keywords used in the search were as follows: cardiac arrest or cardiopulmonary resuscitation or cardiopulmonary-cerebral resuscitation and thrombolysis or percutaneous coronary intervention and acute myocardial infarction. Furthermore, we manually reviewed the references for each article. The search was limited using the search terms ">19 years", "Publication Date from 1995/01/01 to 2012/10/01", "English", "Human", "PUBMED", "MEDLINE" and "EMBASE". We excluded research papers with the following keywords: "review", "review literature", "review of reported cases", "review, academic", "review, multicase", "review, tutorial", "case reports", "congresses", "interview", "overall", "comment", "letter", "practice guideline", "scientific integrity review", "news", "newspaper article" and "address". Some papers not included in the PUBMED, MEDLINE and EMBASE databases were also used in this meta-analysis.

Inclusion criteria

Eligible patients had experienced CA due to STEMI and achieved ROSC after CPR. The diagnosis of CA and whether CPR was used were determined based on the records in the respective studies. The diagnostic and management process that was followed was in accordance with the Utstein model. All the included articles were non-randomized comparative studies. Patients with ROSC after CA who then received PCI or thrombolysis treatment constituted the treatment groups. The types of PCI and the doses of thrombolytic agents used were not restricted. Patients in the control groups were those who underwent CA and achieved ROSC and who could be treated by CPR without PCI or thrombolysis. We compared the efficacies of PCI and thrombolysis between the treatment and control groups. We also compared the efficacies of PCI and thrombolysis in patients with ROSC after CA. The primary study endpoints were the rates of hospital discharge and neurological recovery.

Statistical analysis

We performed a meta-analysis using Review Manager 5.1 (The Cochrane Collaboration, Oxford, England). Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for each article using either the fixed-effects or the random-effects model. We used Cochran's χ^2 test and the I^2 test for heterogeneity to test the between-study heterogeneity, and a $p < 0.10$ and an $I^2 > 50\%$ were considered indicative of statistically significant heterogeneity. Between-group comparisons were performed using Pearson's χ^2 test for categorical variables. All of the analyses were performed using the SPSS 17.0 software package (SPSS, Inc., Chicago, IL, USA). P -values < 0.05 were considered statistically significant.

■ RESULTS

Eligibility of articles

In total, 127 articles were found by searching using the keywords mentioned in the methods section. Twenty-four of these articles were cohort studies and involved CA patients with STEMI who were treated with or without PCI or thrombolysis after ROSC. One hundred three articles were excluded because: ① they were reviews, case reports, or letters; ② they reported findings for CA patients with pulmonary embolisms (PEs) or for CA patients who had received reperfusion therapy during CPR without ROSC; or ③ the authors of the study did not present the details regarding the hospital discharge and neurological recovery rates. Because controlled studies are necessary for meta-analyses, the 17 cohort-controlled studies (8-10,18-31) were included in the meta-analysis to assess the efficacies of PCI and thrombolysis in patients with ROSC after CA. Fifteen studies (8-10,18-29) out of the total were used to analyze the efficacy of PCI. Four studies (26,27,30,31) were used to analyze the efficacy of thrombolysis. After the meta-analysis, we used all 24 studies (8-10,18-38) to compare the hospital discharge and neurological recovery rates between the PCI and thrombolysis groups among patients with ROSC after CA. The main features of these selected cohort studies are listed in Table 1.

Comparison of the hospital discharge rate between with- and without-PCI patients with ROSC after CA

We first compared the rate of hospital discharge between the with- and without-PCI patient groups using data from 15 articles (8-10,18-29). Overall, 1320 patients had ROSC after CA and then received PCI treatment. A total of 860 (65.15%, 95%CI, 62.58-67.72) of these patients survived to hospital discharge. In addition, 2152 patients with ROSC after CA did not receive PCI, and 1017 (47.26%, 95%CI, 45.15-49.37) of these patients were discharged from the hospital. In this meta-analysis, we used a random-effects model to take into account the effect of heterogeneity among studies ($\text{Tau}^2 = 0.33$; $\chi^2 = 54.25$; $p < 0.00001$; $I^2 = 74\%$). This meta-analysis indicated that PCI significantly improved the rate of hospital discharge in patients with ROSC after CA (OR, 1.92; 95% CI, 1.32-2.78, $p < 0.001$) (Figure 1).

Comparison of neurological recovery between with- and without-PCI patients with ROSC after CA

We also compared the neurological recovery rate between the with- and without-PCI groups using data from 12



Table 1 - Characteristics of the studies included in the comparative analysis.

Author	Study Design	Type of reperfusion	Participants	Hospital discharge		CPC 1/2	
				with PCI	without PCI	with PCI	without PCI
Anyfantakis et al.*	Prosp	PCI	72	10/24	25/48	10/10	23/25
Cronier et al.*	Retro	PCI	111	29/46	31/65	29/29	25/31
Dumas et al.*	Retro	PCI	435	90/177	81/258	90/90	70/81
Garot et al.*	Retro	PCI	186	92/161	11/25	92/92	7/11
Hosmane et al.*	Retro	PCI	98	49/62	14/36	47/49	7/14
Kahn JK et al.*	Prosp	PCI	11	3/7	3/4	2/3	2/3
Koetha et al.*	Retro	PCI	736	114/143	248/593	103/114	208/248
Lettieri et al.*	Prosp	PCI	99	72/90	5/9	69/72	0/5
Merchant et al.*	Prosp	PCI	110	13/17	54/93		
Miloslav et al.*	Prosp	PCI	26	13/19	2/7	11/13	2/2
N.Nielsen et al.*	Retro	PCI	986	197/299	358/687	180/197	254/358
Tpmte et al.*	Prosp	PCI	248	71/111	80/137	71/71	69/80
V.Gorjup et al.*	Retro	PCI	135	79/108	13/27		
B.Bendz et al	Retro	PCI	40	29/40			
Knafelj et al	Retro	PCI	72	44/72			
Mager et al	Retro	PCI	21	18/21			
Markusohn et al	Retro	PCI	25	19/25			
Valente et al	Retro	PCI	31	23/31			
Keelan et al	Retro	PCI	15	11/15			
Richling et al.*	Retro	PCI	147	24/46	69/101	22/24	57/69
S.Bulut et al.*	Retro	PCI	72	4/10	23/62		
Total			3676	1004/1524	1017/2152	726/764	724/927
				with thrombolysis	without thrombolysis		
Richling et al.†	Retro	thrombolysis	147	69/101	24/46	57/69	22/24
S.Bulut et al. †	Retro	thrombolysis	72	3/7	24/65		
M.Ruiz-Bailén et al. †	Retro	thrombolysis	303	55/67	127/236		
W.Schreiber et al. †	Retro	thrombolysis	157	31/42	63/115	29/31	57/63
H.-R.Arntz et al	Retro	thrombolysis	50	23/50			
Total			729	181/267	238/462	86/100	79/87

Retro: retrospective study; Prosp: prospective study; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction. CPC: Cerebral Performance Categories; *Included in the meta-analysis for PCI; †Included in the meta-analysis for thrombolysis.

articles (8-10,18-23,25,26,28). Neurological recovery was described and recorded using the Cerebral Performance Categories (CPC) scale. Neurological recovery was

considered good for patients who could perform their normal activities independently (CPC 1 or 2). Neurological recovery was considered bad, poor or unfavorable for

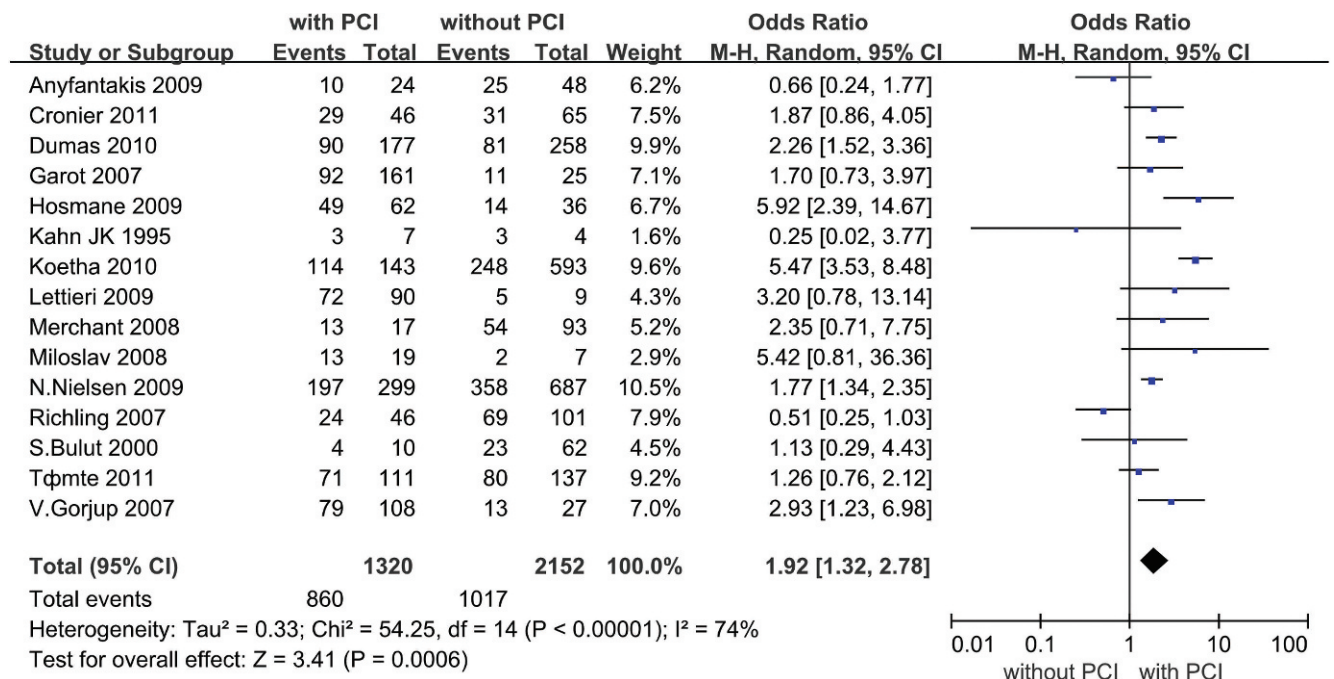


Figure 1 - Forest plot of the hospital discharge rates between the with- and without-PCI patients for the meta-analysis.

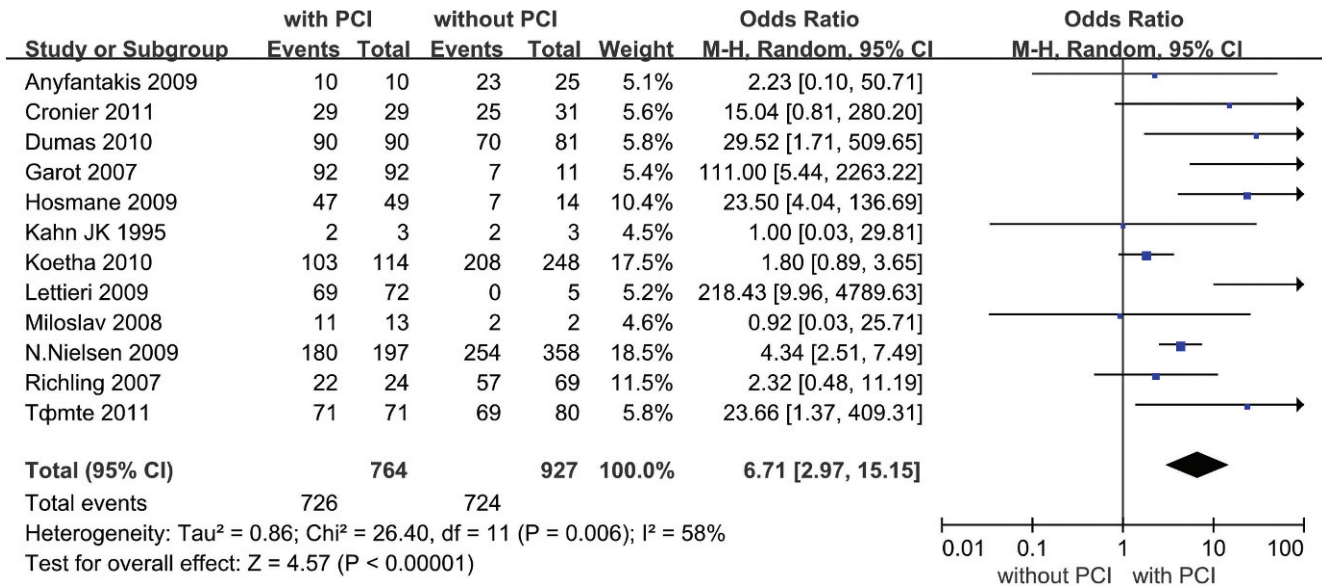


Figure 2 - Forest plot of the neurological recovery rates between the with- and without-PCI patients for the meta-analysis.

patients who were dependent on others, who were vegetative or who had died (CPC 3, 4 or 5).

The authors assessed the CPC score at the time of hospital discharge. The rates of good neurological recovery were 95.03% (726 of 764 patients; 95%CI, 93.49-96.57) and 78.10% (724 of 927 patients; 95%CI, 75.44-80.76) for the with- or without-PCI patient groups, respectively. To reduce the heterogeneity among these studies (Tau²=0.86; χ^2 =26.40; p =0.006; I²=58%), we used a random-effects model. PCI treatment significantly improved the rate of neurological recovery at the time of hospital discharge in patients with ROSC after CA (OR, 6.71; 95% CI, 2.97-15.15, p <0.001) (Figure 2).

Comparison of the hospital discharge rate between with- and without-thrombolysis patients with ROSC after CA

We also compared the rate of hospital discharge between the with- and without-thrombolysis patient groups using data from four articles (26,27,30,31). Thrombolysis was performed in 217 patients with ROSC after CA, and 158 (72.81%, 95%CI, 66.89-78.73) of these patients survived to hospital discharge. In addition, 462 patients with ROSC after CA were not treated with thrombolysis, and 238 (51.52%,

95%CI, 49.96-56.08) of these patients survived to hospital discharge. A fixed-effects model was used in this meta-analysis to account for the lack of heterogeneity among the included studies (χ^2 = 2.87, p = 0.41, I² = 0%), and the analysis indicated that thrombolysis could also significantly improve the rate of hospital discharge in patients with ROSC after CA (OR, 2.63, 95%CI, 1.77-3.90, p < 0.001) (Figure 3).

Comparison of neurological recovery between with- and without-thrombolysis patients with ROSC after CA

To compare the neurological recovery between the with- and without-thrombolysis patient groups, data from two articles were analyzed (26,31). The CPC scale was used. The homogeneity of the two studies was good (χ^2 = 1.17, p = 0.28, I² = 15%). Therefore, we used a fix-effects model for this meta-analysis. Overall, 86.00% (86 of 100 patients; 95% CI, 82.53-89.47) and 90.80% (79 of 87 patients; 95% CI, 84.73-96.87) of patients had a good neurological recovery in the patient groups with and without thrombolysis, respectively. Thrombolysis did not improve the neurological recovery status at the time of hospital discharge in patients with ROSC after CA (OR, 0.76, 95%CI, 0.27-2.17, p = 0.309) (Figure 4).

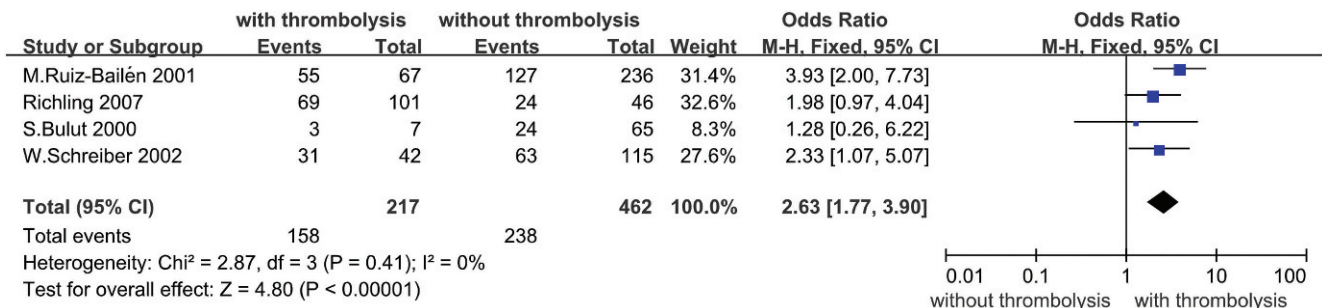


Figure 3 - Forest plot of the hospital discharge rates between the with- and without-thrombolysis patients for the meta-analysis.

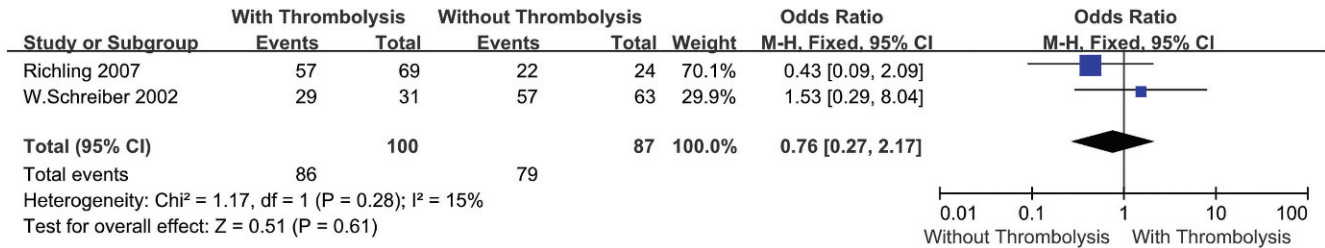


Figure 4 - Forest plot of the neurological recovery rates between the with- and without-thrombolysis patients for the meta-analysis.

Comparison of the hospital discharge rate between the PCI and thrombolysis groups among patients with ROSC after CA

There were 24 articles included in this comparison of the PCI and thrombolysis treatment groups. There were 21 articles (8-10,18-29,33-38) on PCI and 5 articles (26,27,30-32) on thrombolysis. Among the patients included in this analysis, 65.88% (1004 of 1524 patients, 95%CI, 63.50-68.26) survived to hospital discharge in the PCI treatment group. Similarly, 67.79% (181 of 267 patients, 95%CI, 62.18-73.40) of patients in the thrombolysis treatment group survived to hospital discharge. We found that the prognosis of patients treated with PCI was no better than that of patients treated with thrombolysis with respect to the hospital discharge rates ($p = 0.543$, Figure 5).

Comparison of neurological recovery between the PCI and thrombolysis groups among patients with ROSC after CA

This comparison between the PCI and thrombolysis groups was performed using 18 articles. There were 16 articles (8-10,18-23,25,26,28,34-37) on PCI and 3 articles (26,31,32) on thrombolysis. Among the patients included in this analysis, 856 patients with ROSC after CA who received PCI survived to hospital discharge, and 790 (92.29%, 95%CI, 90.50-94.08) patients had a good neurological recovery. In addition, 123 patients with ROSC after CA were treated

with thrombolysis and survived to hospital discharge, and 109 (88.62%, 95%CI, 83.01-94.23) patients had good neurological recovery. We noted that the PCI treatment group did not have a significantly better neurological recovery rate than the thrombolysis treatment group among patients with ROSC after CA ($p = 0.165$, Figure 5).

Comparison of the hospital discharge and neurological recovery rates in patients with ROSC after in-hospital CA (IHCA) or out-of-hospital CA (OHCA)

Even after excluding studies involving IHCA (20,21,24,29,30,36), results similar to those described above were obtained. Thus, PCI and thrombolysis had the same level of efficacy in patients with ROSC whether they experienced IHCA or OHCA.

DISCUSSION

Based on the 17 included studies (8-10,18-31), the meta-analysis indicated that both PCI and thrombolysis could improve the hospital discharge rate for patients with ROSC after CA, but only PCI could improve the neurological recovery rate. However, further analysis using a total of 24 studies (8-10,18-38) indicated that there were not significant differences in the hospital discharge and neurological recovery rates between the PCI and thrombolysis treatment groups.

PCI and thrombolysis are the two main reperfusion strategies currently in use. According to the recent AHA guidelines concerning CPR for ACS (acute coronary syndrome) patients (39), PCI may be considered for patients with ROSC after CA. Our data indicate that such a strategy improved the rate of hospital discharge and enhanced neurological recovery in patients with ROSC following CA. However, the efficacy of thrombolysis has been rarely mentioned in regard to CA patients. A recent randomized study (TROICA) reported that thrombolysis did not improve the hospital discharge and neurological recovery rates in patients with CA. The TROICA researchers reported that one possible reason might be the administration of antithrombin and antiplatelet agents during CPR. Another important reason might be the restriction of the perfusion of vital organs during CPR by blood clots in the coronary arteries, limiting the perfusion pressure and hindering the delivery of the thrombolytic agents to the location where they were to play their thrombolytic role (12). We concluded that one main possible reason for the lack of efficacy for thrombolysis might have been the lack of distinguishing patients with ROSC after CA from those without ROSC; when CA patients achieve ROSC, there may be suitable perfusion pressure in the coronary arteries, allowing

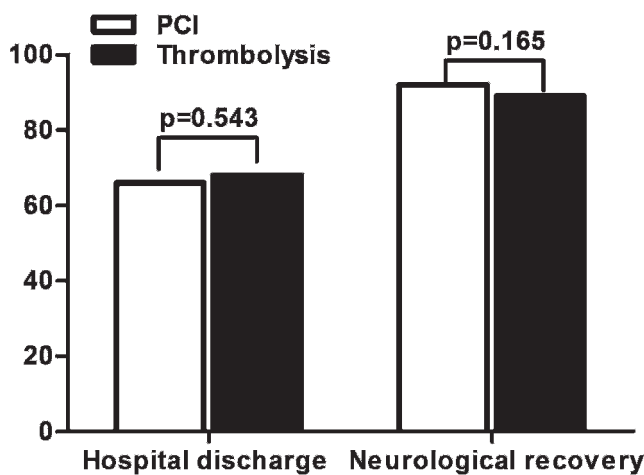


Figure 5 - Comparison of the hospital discharge and neurological recovery rates between the PCI and thrombolysis groups Left: Comparison of the hospital discharge rates between the PCI and thrombolysis groups ($p = 0.543$) Right: Comparison of the neurological recovery rates between the PCI and thrombolysis groups ($p = 0.165$).



thrombolysis could function effectively. In this study, we studied the efficacies of thrombolysis and PCI in patients with ROSC after CA, and we identified no differences in the hospital discharge and neurological recovery rates.

Plaque rupture, thrombus collapse and embolisms play key roles in the pathogenesis of SCD (5,6). Clinical studies have already identified disrupted atherosclerotic plaques or occlusive thrombi in CA survivors using coronary angiography (4). Therefore, early reperfusion therapy in patients with STEMI is an important cornerstone of the recommended therapy and is also recommended by the European Society of Cardiology (ESC) (40). Reperfusion treatment has been used to treat AMI patients for the past 20 years. As the two main reperfusion approaches for AMI, PCI and thrombolysis can recanalize the occluded artery, reduce the infarct size, minimize myocardial damage, enhanced left ventricular recovery, reduce the incidence of arrhythmias and decrease mortality (13). Because AMI is the main underlying cause of CA (3,4), therapeutic strategies for coronary reperfusion should be equally appropriate for CA patients. However, in clinical practice, there is still some controversy concerning the roles and efficacies of PCI and thrombolysis for the treatment of patients with CA caused by AMI (4,12,17,20,22).

PCI can directly open the occluded coronary artery and stabilize hemodynamics. Many clinical studies on reperfusion therapy have indicated that immediate PCI after CA is a safe procedure and is associated with a good prognosis (4,8,20,22,27,29,33,37). A series of large-scale clinical studies demonstrated that PCI has pronounced efficacy for treating CA patients with STEMI (8-10), a result that was confirmed by our meta-analysis. We know that thrombolysis is able to improve the prognosis of STEMI patients and has an efficacy comparable to that of PCI. However, it is not clear why there is such a large difference between these treatments in CA patients. After carefully analyzing the relevant articles (4,12,17,20,22), we found that this difference may be the result of the selection of the study populations. PCI was used to treat patients with STEMI without CA. In contrast, thrombolysis was most often used to treat patients with STEMI with CA because of its convenience and rapid action. The high mortality rate of CA patients masked the benefit of thrombolysis for the treatment of AMI (41-43). With the development of CPR, medical scientists have realized the importance of neuroprotection after CPR, especially in patients with ROSC after CA. Our meta-analysis and comparative analysis aimed to evaluate the benefits of PCI and thrombolysis for patients with ROSC after CA.

In this study, we found that both PCI and thrombolysis improved the hospital discharge rates of patients with ROSC after CA. There were no significant differences in the hospital discharge and neurological recovery rates of CA patients. We also found that thrombolysis could improve the hospital discharge rate, but it could not improve the neurological recovery rate. However, several studies have demonstrated that thrombolysis also results in good neurological recovery in CA patients. Hemodynamic studies indicate that thrombolysis can decrease microthrombosis, improve microcirculation metabolism and further promote neurological recovery (30,31). Therefore, we concluded that the previous studies are insufficient to demonstrate the benefit of thrombolysis in neurological recovery.

Reperfusion therapy can open the occluded artery and rescue dying myocardium in patients with ROSC after CA. PCI is used to treat patients with STEMI but without CA, preventing many deaths. Thrombolysis is used to treat patients with STEMI during CPR. However, patient hemodynamics are unstable during that time. This instability may be the reason why the results were so dismal. Our results indicate that the first step should be the selection of patients with ROSC after CA; then, the decision between PCI and thrombolysis can be made. In developing countries, the mortality rate for ischemic heart disease is expected to increase by almost 120-137%, compared with 29-48% in developed countries, between 1990 and 2020; however, developing countries cannot afford the widely used expensive PCI techniques (44,45). Compared with PCI, thrombolysis is convenient and rapid, has a similar efficacy and is relatively simple, making it especially suited for use in clinics that cannot perform PCI. Our findings provide information to guide the resuscitation of patients with ROSC after CA. Of course, these results require validation by additional randomized control trials.

In conclusion, our comparative analysis demonstrated that thrombolysis had an efficacy similar to that of PCI in patients with ROSC after CA. Our results indicate that there is still a need to conduct large-scale randomized clinical trials to confirm the benefits of thrombolysis in patients with ROSC after CA and in the presence of STEMI.

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■ AUTHOR CONTRIBUTIONS

Li YQ, Sun SJ and Liu N contributed equally to this study. Li X conceived the study, designed the trial and obtained the research funding. Li YQ, Sun SJ, Liu N and Hu CL collected the data. Wei HY and Li H collected the data. Liao XX analyzed the output data with advice from Li X. Li YQ and Liu N drafted the manuscript. Li YQ, Liao XX, Liu N and Li X discussed the results and implications and commented on the manuscript at all stages.

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