Use of systemic thrombolytic therapy in patients with non-traumatic cardiac arrest: A systematic review and meta-analysis

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ABSTRACT

Objective: To better delineate the benefits and risks of systemic thrombolytic therapy in patients with cardiac arrest from non-traumatic etiologies.

Data sources: MEDLINE, EMBASE, and SCOPUS were systematically searched up to November of 2017.

Study Selection: All retrospective and prospective studies in which systemic thrombolytic therapy was used during the sequence of cardiopulmonary resuscitation (CPR) or shortly after achieving return of spontaneous circulation (ROSC) were included.

Data extraction: The following variable results were extracted from intervention and control groups if available: rate of ROSC, survival after 24 hours, survival at discharge, neurological performance at 6 months based on a favorable Cerebral Performance Categories Scale (1 or 2) and major bleeding events.

Data Synthesis: Eight retrospective studies and 6 prospective studies were included in the qualitative analysis. Research synthesis was conducted when at least 4 studies were available for an outcome, which limited the analysis of major bleeding events and neurologic outcomes. Benefit of thrombolytic therapy in survival to discharge showed a moderate beneficial effect (OR = 2.79, 2.11–3.69) in the retrospective study analysis while in the prospective study analysis no statistically significant benefit was found (OR = 1.27, 0.77–2.10). Benefit of thrombolysis in the rate of ROSC was not statistically significant in the prospective analysis (OR = 1.59, 0.92–2.76, p = 0.138) as well as survival at 24 hours (OR = 1.17, 0.72–1.71).

Conclusions: The widespread use of thrombolytics in patients with non-traumatic cardiac arrest does not seem to improve major outcomes, including survival to discharge. However, the modest benefit found in the retrospective study analysis suggests a subgroup of patients that may benefit from this therapy.

Keywords: Thrombolytic therapy, cardiac arrest, advanced cardiac life support, cardiopulmonary resuscitation, tissue plasminogen activator

INTRODUCTION

Although there are multiple causes of non-traumatic cardiac arrest (CA), pulmonary thromboembolism (PE) and acute coronary syndromes (ACS) explain more than 70% of the cases based on published autopsy series and postcardiac arrest coronary angiogram reports. In 1974, Renkes-Hegendorfer and Hermann reported the first patient treated with thrombolytics during CPR in a patient with PE diagnosed after a Cesarean section. Cardiac arrest continues to have a very poor prognosis with in-hospital survival rates ranging from 10.9 to 30%. Furthermore, out-of-hospital cardiac arrests usually have worse outcomes, with survival rates below 3%, which makes the development of innovative treatment strategies necessary.
The use of systemic fibrinolytic therapy (FT) during CA has two mechanisms of action that explain the logic of its use. First, the thrombolytic agent addresses the underlying potential cause of the majority of arrests (coronary or pulmonary arterial thrombosis). Second, thrombolytic therapy seems to enhance microcirculatory reperfusion by decreasing blood viscosity, thereby improving blood flow in the microcirculation. During and after cardiac arrest, there is a “no-reflow” phenomenon, in which the presence of diffuse/systemic micro thrombosis (driven by the slow and limited blood flow to small vascular beds) restricts the reperfusion of vital organs (especially the brain) after return of spontaneous circulation (ROSC) has occurred, explaining the poor neurologic outcomes of many patients. Additionally, there is a potential pro-thrombotic state after achieving spontaneous circulation driven by diffuse endothelial injury and subsequent abnormal fibrinolytic activity that exacerbates this process. Multiple studies conducted in animals have shown evidence for these events.

Different case series have shown variable incidences of CA as the presentation of PE (from 5 to 20%); nonetheless, there seems to be consistency in the fatality of PE causing CA (mortality exceeds 60%). Fibrinolytic therapy in patients with PE and hemodynamic instability has shown mortality benefit (from 19% to 9%). The European Society of Cardiology guidelines of 2014 and the American Heart Association (AHA) guidelines of 2011 recommend the use of FT in this group of patients. The use of thrombolytic therapy has demonstrated a time dependent morbidity and mortality benefit in patients with ST segment elevation myocardial infarctions (STEMI) when used within 12 hours of symptom onset. For this reason, the AHA 2013 guidelines recommend its use in select patients with anticipated delay (above 120 minutes) in performance of primary percutaneous intervention. No benefit has been found from the use of thrombolytic therapy in patients with acute coronary syndromes without ST segment elevation. Advanced Cardiac Life Support (ACLS) guidelines do not recommend the use of systemic thrombolysis in cardiac arrest.

In 2005 Xin Li, et al. published a meta-analysis on this topic. Since then, multiple prospective and retrospective studies have been published, making a new systematic review and meta-analysis necessary.

**Methods**

**Search strategy**

A systematic review of literature was conducted in accordance with the recommended criteria provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). All available papers published up to November 2017 were identified in the MEDLINE, EMBASE, and SCOPUS databases. Selected keywords for the search were based on MeSH and EMTREE terminology in which “Heart Arrest” and “Thrombolytic therapy” were used initially to guide the search; then, further keyword combinations were applied using the following terms: “Advanced Cardiac Life Support”, “Tissue Plasminogen Activator”, “Tenecteplase”, “Reteplase”, “Streptokinase”, and “Urokinase”. The search was limited so that certain publications, like reviews, guidelines, letters, individual case reports, and editorials, were excluded; the search was limited to publications in humans and in English or Spanish. In addition, references cited by relevant papers were manually searched.

**Eligibility criteria**

All retrospective and prospective studies in which systemic thrombolytic therapy was used during the sequence of cardiopulmonary resuscitation (CPR) or shortly (3 hours) after achieving ROSC were included. Studies including thrombolytic strategies other than systemic thrombolysis (e.g., catheter guided or ultrasound accelerated thrombolysis) were excluded. Publications in which thrombolytic therapy was used before cardiac arrest were also excluded.

**Study selection**

Potentially relevant articles were selected by (1) screening the titles; (2) screening the abstracts; and (3) if abstracts did not provide sufficient data, the entire article was retrieved and screened to determine whether
it was in accordance with the eligibility criteria described above. The search results are detailed in Figure 1.

**DATA COLLECTION PROCESS**

The following qualitative and quantitative information was extracted from each included study: authors; publication year; baseline population characteristics; intervention and control procedures; study duration; and sample size per group. The following variable results were extracted from intervention and control groups if available: rate of ROSC, survival after 24 hours, survival at discharge, good neurological performance at 6 months based on a favorable Cerebral
Performance Categories Scale (1 or 2), and major bleeding events. Major bleeding events are defined as any intracranial bleeding complications, bleeding events requiring transfusion support or surgical intervention, or bleeding within in a third space cavity or a solid organ.

**Assessment of Risk of Bias**

Two reviewers ascertained individual study information as part of the quality control process. The prospective studies were assessed based on the Cochrane collaboration tool. Two authors performed the quality assessment independently, and their findings were compared until consensus was achieved. Six domains were reviewed and scored as −1 for high risk, 0 for unclear risk, and +1 for low risk. Scores were summed with a possible range of scores of −6 to 6. Detailed scoring for each domain on each study is provided in Supplementary Table 1. For retrospective studies we used the Newcastle-Ottawa Quality Assessment Form for Cohort Studies which assesses basic characteristics regarding selection, comparability, and outcome domains. Study quality was characterized as good, fair, or poor based on AHRQ standards. Detailed assessment of each retrospective study is provided in Supplementary Table 2.

**Statistical Analysis**

Two different sets of data were collected for retrospective and prospective studies. Research synthesis was conducted when at least 4 studies were available for an outcome. From the set of retrospective studies only survival at discharge met the criteria. From the set of prospective studies, rate of ROSC, survival after 24 hours, and survival at discharge were included in the research synthesis. The random effects Mantel-Haenszel method was used to weight the studies and estimate the pooled odds ratios (OR) and 95% confidence intervals (CI). When using the Mantel-Haenszel method, we considered sample size and event rates. We chose odds ratios (OR) as effect measures owing to the small prevalence rates shown in some studies. Since at least one study presented a zero cell, the standard correction of 0.5 was used to perform the computation. Heterogeneity was assessed using Breslow-Day test for the odds ratios and I² statistic. Interpretation of variation attributable to heterogeneity was based on the suggested adjectives of low for I² values between 25%–50%, moderate for 50%–75%, and high for ≥75%. Statistical analysis was performed on Stata 13.1, and forest plots were done using R.

**Analysis of Publication Bias**

We assessed publication bias by visual inspection of asymmetry in funnel plots. We also carried out Begg and Mazumdar adjusted rank correlation test, and Egger regression asymmetry test for publication bias.

**Results**

**Retrospective Studies**

Eight studies were included in the qualitative analysis; their general characteristics are summarized in Table 1. The data synthesis of five retrospective studies, including data on survival at discharge, showed very low heterogeneity (I² = 0%, p = 0.528) and the funnel plot inspection showed a symmetric distribution of the studies (Figure not shown). Begg’s test was not statistically significant (p = 0.806) and Egger’s test showed no statistically significant coefficient for bias (p = 0.741). The pooled estimate for the five retrospective studies determined a moderate (OR = 2.79, 95% CI = 2.11-3.69) beneficial effect of thrombolytic therapy during CPR on survival at discharge (Figure 2).

Most of the studies included patients with established PE or myocardial infarction. Lederer and Renard included patients with out-of-hospital CA without a clear etiology. In general, most of the studies reported benefit from thrombolytic therapy in the majority of outcomes. Renard, et al. included a significant control group which allowed a multivariate analysis based on a propensity score in which a statistically significant difference in survival at discharge, favoring the intervention group, was still present in
Table 1. Summary of retrospective studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Design</th>
<th>Thrombolytic therapy</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Campen</td>
<td>69 patients</td>
<td>Out of hospital CA (patients with presumptive MI)</td>
<td>Type of medication and regimen not specified, given during or shortly after ROSC</td>
<td>Increased 24h survival and discharge survival on IG</td>
</tr>
<tr>
<td>1994 [32]</td>
<td>(33 in the IG), prolonged CPR (over 20 minutes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schreiber</td>
<td>157 patients</td>
<td>In and out of hospital CA (patients with diagnosis of STEMI, only included patients that survived after first 24h)</td>
<td>Alteplase 100mg in infusion given after ROSC</td>
<td>Increased survival at 6 months in IG, better neurologic outcome (CPC 1-2) on IG at 6 months</td>
</tr>
<tr>
<td>2002 [39]</td>
<td>(42 in the IG) with VF-CA, short CPR (less than 4 minutes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruiz-Bailen</td>
<td>303 patients</td>
<td>In-hospital CA (patients with presumptive MI)</td>
<td>SK in 3%, alteplase infusion in 36%, alteplase in double bolus regimen in 28%, other agents in 3%. Given after ROSC</td>
<td>Increased discharge survival in IG, non-significant increase in major bleeding events in IG</td>
</tr>
<tr>
<td>2001[33]</td>
<td>(67 in the IG), subgroup of the ARIAM study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lederer</td>
<td>325 patients</td>
<td>Out of hospital CA (undetermined medical cause)</td>
<td>Alteplase given during CPR (Neuhaus regimen-1)</td>
<td>Increased rate of ROSC, 24h survival and discharge survival in IG Rate of ROSC of 70.4% in the IG vs 51% in controls (p 0.001). 24h survival of 48.1% in IG vs 32.9% in CG (p 0.003). Survival to discharge of 25% in IG vs 15.3% in CG (p 0.048)</td>
</tr>
<tr>
<td>2001[34]</td>
<td>(108 in the IG)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurkciyan</td>
<td>265 patients</td>
<td>Out of hospital CA (STEMI diagnosed after ROSC), patients treated with PCI were excluded</td>
<td>Alteplase (Neuhaus regimen) after ROSC</td>
<td>Increased 6m survival in IG, better neurologic outcome (CPC 1-2) on IG at 6 months</td>
</tr>
<tr>
<td>2003 [38]</td>
<td>(132 in the IG)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renard</td>
<td>1261 patients</td>
<td>Out of hospital CA (undetermined medical cause)</td>
<td>Alteplase (50mg bolus) or tenecteplase (100UI/kg in single bolus). Given during CPR</td>
<td>Increased discharge survival in IG (significant difference in patients with rhythms not amenable of defibrillation)</td>
</tr>
<tr>
<td>2011 [35]</td>
<td>(107 in the IG), propensity score matching</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Janata</td>
<td>66 patients</td>
<td>In and out hospital CA (confirmed PE before or after CA)</td>
<td>Alteplase bolus (weight based, up to 100mg)</td>
<td>24-hour survival 53% in the IG vs 23% in the control group (p 0.01). ROSC and survival to discharge favored IG (not statistically significant). Bleeding events more common in IG (not statistically significant).</td>
</tr>
<tr>
<td>2003 [36]</td>
<td>(36 in the IG)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kurkciyan</td>
<td>42 patients</td>
<td>In and out of hospital CA (with confirmed PE)</td>
<td>Alteplase (Neuhaus regimen or 2 separated boluses of 50mg)</td>
<td>ROSC incidence of 81% in intervention group vs 43% in the control group (p 0.03). Survival at 6 months was better in IG.</td>
</tr>
<tr>
<td>2000 [37]</td>
<td>(21 in the IG)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CA: Cardiac Arrest; IG: Intervention group; CG: Control Group; MI: Myocardial Infarction; CPR: Cardiopulmonary resuscitation; VF: Ventricular Fibrillation; CPC: Cerebral Performance Category; SK: Streptokinase; ROSC: Return of Spontaneous Circulation; Neuhaus Regimen: Alteplase given as 15mg bolus followed by 90mg in 90 minutes at 2 different infusion rates; PCI: Primary Coronary Intervention; PE: Pulmonary Embolism; PEA: Pulseless Electrical Activity, 24h: 24 hours.
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the matched analysis. This study also showed a significant difference in survival at discharge in the subgroup of patients who were not defibrillated during CA (48.8% in the intervention group vs 18.2% in the control group for a OR of 3.61, 95% CI = 1.88-6.96).

There were significant differences in definitions and reporting major bleeding complications and neurologic outcomes which prevented statistical analysis of these outcomes in the combined pool. Van Campen reported similar incidences of death by bleeding complications in both groups (despite prolonged cardiopulmonary resuscitation defined as more than 20 minutes); neurologic complications were similar in both groups (defined as coma, strokes, seizures or death secondary to neurological complication). Lederer, et al. found similar bleeding complications in his deceased patients at autopsy. Janata and Kurkiyian reported an increased rate of major bleeding complications in their intervention groups, although the difference was not statistically significant. Kurkiyian's study did not find any significant association between major bleeding events and duration of cardiopulmonary resuscitation (CPR) regardless of thrombolytic administration. In Ruiz-Bailen study there were no statistically significant differences in major bleeding complications between the intervention and control groups with a statistically significant difference in the incidence of anoxic encephalopathy in the intervention group. Kurkiyian and Schneider reported better neurologic outcomes in the intervention groups at 6 months using the cerebral performance category (CPC) scale; in both studies the results were statistically significant.

**PROSPECTIVE STUDIES**

Six studies were included in the qualitative analysis; their general characteristics are summarized in Table 2. Most of the studies had high mortality rates, regardless of the intervention, with low survival rates at discharge, which limited the reporting of neurologic outcomes and bleeding events. All the studies were conducted in patients with CA in an out-of-hospital setting with no established etiology of the arrest.

Five prospective studies were suitable for a research synthesis on survival at 24 hours, and the data presented low heterogeneity ($I^2 = 46\%$, $p = 0.113$). Although the funnel plot (Figure not shown) showed that the study by Bozeman was out of confidence limits, neither Beggs nor Egger’s tests found statistically significant bias. However, the pooled estimate showed no statistically significant effect of thrombolytic therapy on survival at 24 hours ($OR = 1.17$, 95% CI = 0.72-1.71) (Figure 3).

Six prospective studies were included in the research synthesis on survival at discharge, and the data presented low heterogeneity ($I^2 = 50\%$, $p = 0.077$). Similar to the outcomes on survival at 24 hours, the funnel plot (Figure not shown) showed that the study by Bozeman was out of confidence limits, but neither Beggs nor Egger’s tests found statistically significant bias. Similarly, the pooled estimate of the six studies showed no statistically significant effect of thrombolytic therapy on survival at discharge ($OR = 1.27$, 95% CI = 0.77-2.10) (Figure 4).

Five prospective studies were considered for research synthesis of the rate of ROSC. The data
Table 2. Summary of prospective studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Design</th>
<th>Thrombolytic therapy</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottiger 2001 [40]</td>
<td>90 patients (40 in the IG), nonrandomized</td>
<td>Out of hospital (undetermined medical cause), observational</td>
<td>Tenecteplase 50mg bolus during CPR, repeated after 15 minutes if no ROSC</td>
<td>Increased ROSC, 24h survival and discharge survival in IG. Non-significant increase in major bleeding events in IG</td>
</tr>
<tr>
<td>Bottiger 2008 (TROICA study) [41]</td>
<td>1050 patients (525 in the IG)</td>
<td>Out of hospital (undetermined medical cause), randomized</td>
<td>Tenecteplase in one bolus (weight based) during CPR</td>
<td>No significant difference in ROSC, 24h survival, discharge survival and favorable CPC (1-2) at 6 months. Increased intracranial hemorrhage in IG. Stopped after futility analysis</td>
</tr>
<tr>
<td>Abu-Laban 2002 [42]</td>
<td>233 patients (117 in the IG), only patients with PEA rhythm during CA. Autopsies (18% patients) revealed MI in 21% and PE in 2.4%</td>
<td>Out of hospital (undetermined medical cause), randomized. Canada</td>
<td>Alteplase 100mg in 15-minute infusion</td>
<td>No significant differences in ROSC, 24h survival and discharge survival (only 1 patient survived in the IG)</td>
</tr>
<tr>
<td>Stadlbauer 2006 [43]</td>
<td>1186 patients (99 in the IG)</td>
<td>Out of hospital CA (undetermined medical cause)</td>
<td>Tenecteplase or ralteplase (different regimens) during or shortly after ROSC (not specified)</td>
<td>Increased discharge survival in IG. Statistically significant in patients with suspected MI</td>
</tr>
<tr>
<td>Bozeman 2006 [45]</td>
<td>163 patients (50 in the IG), nonrandomized, witnessed CA more common in IG</td>
<td>Out of hospital (undetermined medical cause), observational</td>
<td>Tenecteplase in one bolus (weight based) during CPR</td>
<td>Increased ROSC, 24h survival and discharge survival in IG (no survivors in the CG)</td>
</tr>
<tr>
<td>Fatovich 2004 (TICA study) [46]</td>
<td>35 patients (19 in the IG), VF more common in IG, PEA more common in CG</td>
<td>Out of hospital (undetermined medical cause), randomized. Australia</td>
<td>Tenecteplase 50mg bolus during CPR</td>
<td>Increased ROSC in IG, no differences in 24h survival or discharge survival. No difference in major bleeding complications.</td>
</tr>
</tbody>
</table>

CA: Cardiac Arrest; IG: Intervention group; CG: Control Group; MI: Myocardial Infarction; CPR: Cardiopulmonary resuscitation; VF: Ventricular Fibrillation; CPC: Cerebral Performance Category; SK: Streptokinase; ROSC: Return of Spontaneous Circulation; PE: Pulmonary Embolism; PEA: Pulseless Electrical Activity.

Presented moderate and statistically significant heterogeneity ($I^2 = 70\%$, $p = 0.01$), and the funnel plot (Figure not shown) showed that the study by Fatovich was clearly out of pseudo 95% confidence limits. Although Egger's test failed to find statistically significant bias ($p = 0.071$). Even without this study, the analysis of heterogeneity did not show any improvement ($I^2 = 63\%$, $p = 0.043$). The pooled estimate on the rate of ROSC was not statistically significant (OR = 1.59,
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The study reported a difference, though not statistically significant, in survival to discharge (the difference was statistically significant only when patients with suspected myocardial infarction were included). Bozeman conducted a non-randomized trial that reported a statistically significant difference in the rate of ROSC favoring the intervention group. There were only 2 survivors, both from the FT group, from the 163 patients selected, and both had favorable neurologic outcomes at 6 months based on the CPC scale. Fatovich conducted a randomized trial with a limited sample (due to funding limitations) that reported a statistically significant difference in the rate of ROSC favoring the intervention group.

**DISCUSSION**

There is significant variability between retrospective and prospective studies. We found a statistically significant variability between retrospective and prospective studies.
significant benefit of FT in survival at discharge in our retrospective study analysis but did not find any significant benefit with the use of FT in multiple outcomes in the prospective study analysis, with the majority of the patient sample coming from the TROICA trial. Most of the retrospective studies were done in patients with established etiologies of CA (PE or STEMI), and there was significant variability between intervention and control groups (e.g., age, comorbidities, type of CA rhythm) due in part to selection bias, with only one of the studies using a propensity score for analysis. In some retrospective studies defibrillation rhythms were more prevalent; hence, the prognosis at baseline was potentially better, which may mask a real benefit from FT. There was also inconsistency in the regimens used for thrombolysis and additional medications provided during ACLS (e.g., aspirin, heparin). This variability was also found in the prospective studies.

Cardiac arrest has a very high mortality; this fact correlates better with the findings reported by most of the prospective studies compared to variable mortality rates in the retrospective studies (even in the control groups). It is important to note that because most of the patients included in the retrospective studies had myocardial infarctions (mainly STEMI) or PE their prognosis at baseline was potentially better (versus other etiologies of CA). In addition, knowing the cause of the CA makes the decision of using FT more selective, thus making this therapy potentially more effective. Compared to the retrospective studies, the prospective studies included patient with non-traumatic cardiac arrest from non-established etiologies, to the point that the study of Abu-Laban seemingly included a small percentage of patients with PE (less than 3% of the autopsies even when only patients with CA and PEA rhythms were included in the study) which could have contributed to the high mortality rates of many of these studies.42

Based on the TROICA trial, it is unlikely that a new prospective study with similar characteristics will be conducted. Nonetheless, based on the result discrepancies noted above between retrospective and prospective cohorts, it would be useful to have new prospective studies conducted in in-hospital settings in patients diagnosed with STEMI or PE (or with very high likelihoods based on objective scoring systems) who develop CA in order to clarify the benefits and safety of this therapy in this selected group of patients.

**Conclusion**

Based on the prospective studies we analyzed, the widespread use of thrombolytics in patients with non-traumatic cardiac arrest does not seem to improve major outcomes, including survival to discharge, and, more significantly, it raises safety concerns (i.e., increased risk of major bleeding events). However, based on retrospective studies, there seems to be a benefit to thrombolytic use when patients are adequately selected based on their likelihood or confirmation of having a STEMI or PE as the cause of their CA. To truly determine the benefit of thrombolytic therapy in the patient population of interest, more prospective studies utilizing objective stratification strategies for these diagnoses are required to help place patients into appropriate treatment groups.

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**Figure 5.** Odds ratio for return of spontaneous circulation in prospective studies.
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Conflicts of interest: none

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21. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI
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