TITLE: Thrombolytic Drugs for Cardiac Arrest: A Review of the Clinical Effectiveness

DATE: 28 January 2013

CONTEXT AND POLICY ISSUES

While out-of-hospital cardiac arrest is a relatively rare occurrence, with the median incidence estimated to be 52 people per 100,000 individuals in North America, cardiac arrest is associated with considerable mortality. While estimates vary, generally less than 10% of people who experience cardiac arrest will survive to hospital discharge.\(^1,2\)

There are a number of causes of cardiac arrest, and approximately 70% of cases of cardiac arrest are caused by acute myocardial infarction or pulmonary embolism.\(^3,4\) Other potential causes of cardiac arrest include non-traumatic bleeding, intoxication, trauma, and malignancy.\(^4\)

Treatment for cardiac arrest is focused on basic life support, which involves cardiopulmonary resuscitation (CPR) with chest compressions, with or without rescue breaths, defibrillation with an automated external defibrillator (AED) if the person has ventricular fibrillation or pulseless ventricular tachycardia, and access to emergency medical care as quickly as possible.\(^5\) Basic life support has been proven to improve survival in people with cardiac arrest, but even with administration of basic life support, likelihood of mortality due to cardiac arrest remains high.\(^1,5\)

Given that cardiac arrest is associated with considerable mortality, it is clear that strategies for preventing mortality in this population are necessary. Myocardial infarction and pulmonary embolism are two common causes of cardiac arrest,\(^3,4\) and thrombolytics can be used to treat these conditions in certain circumstances, including pulmonary embolism with hypotension and ST-elevation myocardial infarction (STEMI) with symptom onset within the previous 12 hours.\(^6,7\)

In addition, cardiac arrest itself initiates systemic coagulation due to ischemia.\(^8\) As a result, those who experience cardiac arrest may benefit from receiving thrombolytic therapy to dissolve blood clots and improve systemic circulation.

This purpose of this report is to determine the clinical effectiveness of thrombolytic drugs for the treatment of people experiencing cardiac arrest.
RESEARCH QUESTION

1. What is the clinical effectiveness of thrombolytic drugs for the treatment of adult patients experiencing cardiac arrest with a return of spontaneous circulation?

KEY FINDINGS

Higher quality controlled trials indicate that the use of thrombolytic drugs does not improve survival to hospital discharge and 30-day mortality, and increases the risk of bleeding for patients experiencing a cardiac arrest.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and December 19, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications for relevancy, and evaluated the relevant full-text publications for the final article selection based on the criteria listed in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults experiencing cardiac arrest with return of spontaneous circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Thrombolytics, including tissue plasminogen activator (t-PA) (alteplase, reteplase, and tenecteplase), anistreplase, streptokinase, and urokinase</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard care, placebo, or each other</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Improved clinical outcomes, mortality, or length of hospital stay</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and non-randomized studies</td>
</tr>
</tbody>
</table>

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, if they were duplicate publications or were included in a selected systematic review, or were published prior to January 1, 2007.

Critical Appraisal of Individual Studies

The Downs and Black checklist⁹ was used to critically appraise the observational studies included in this report, and the Assessment of Multiple Systematic Reviews (AMSTAR) tool was
used to critically appraise the systematic review. Summary scores were not calculated for the included studies, rather, a review of the strengths and limitations of each included study were described.

**SUMMARY OF EVIDENCE**

**Quantity of Research Available**

The literature search identified 254 citations. After screening titles and abstracts, 238 citations were excluded and 16 potentially relevant manuscripts were retrieved for full-text review. The grey literature search did not identify any additional relevant publications. Of the 16 potentially relevant manuscripts, 13 did not meet the selection criteria, and three publications were included in this review, as outlined in a PRISMA flowchart (Appendix 1). Among the three publications included, one was a systematic review of controlled trials, and two were observational studies.

**Summary of Study Characteristics**

Details on study design, critical appraisal, and study findings are located in Appendices 2, 3, and 4, respectively.

**Study Design**

One systematic review of controlled trials, and two observational studies were included in this review. Among the observational studies, both were retrospective cohort designs.

**Country of Origin**

One observational study was from Austria, and one study was from France. The systematic review originated in Canada, and included five controlled studies from Australia, Austria, Canada, and the United States. The fifth study in the systematic review was a multicentre study involving sites in Austria, Belgium, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and Switzerland.

**Patient Population**

The controlled trials from the systematic review included patients who failed to respond to advanced cardiac life support regardless of cause of cardiac arrest, or those with presumed cardiac causes of cardiac arrest. In the observational studies, Renard et al. included people with non-traumatic out-of-hospital cardiac arrest, and Richling included patients with cardiac arrest due to acute STEMI. Among the studies included, there were no studies that specifically looked at use of thrombolytics in people after return of spontaneous circulation (ROSC), rather, ROSC was an outcome measure in the five studies included in the systematic review.

**Interventions and Comparators**

Thrombolytics that were evaluated in the included studies were alteplase, reteplase, tenecteplase, and t-PA (type not specified). Placebo was the comparator in the randomized controlled trials included in the systematic review. One observational study compared
thrombolysis to percutaneous coronary intervention (PCI), and standard resuscitation care was used as the comparator in the other observational studies. Thrombolytics were administered by an out-of-hospital emergency physician or mobile intensive care unit prior to hospital arrival, immediately after admission to the emergency department, in those who failed to achieve ROSC after 15 minutes of standard advanced life support, or in those with pulseless electrical activity for at least one minute and no palpable pulse for more than 3 minutes during resuscitation.

Clinical Outcomes

A number of outcomes were assessed to identify the clinical effectiveness of thrombolytics in cardiac arrest, including best-achieved functional neurologic recovery within 6 months after cardiac arrest, mortality at 6 months after cardiac arrest, and survival to hospital admission. The studies included in the systematic review assessed 30 day survival, ROSC, survival to hospital admission, survival to 24 hours, length of hospital stay, survival to hospital discharge, neurologic outcome, risk of bleeding.

Summary of Critical Appraisal

Studies included in the systematic review were identified through a comprehensive literature search conducted up to August 2010, and the authors utilized duplicate data extraction to report data from each study. In addition, the authors stated they had no conflicts of interest to disclose. There were a number of limitations associated with the systematic review, including one reviewer to assess the search results for study relevancy and inclusion, no report of the number of studies identified in the literature search or after the relevancy assessment, lack of thorough reporting of the study characteristics, no assessment of individual study quality, and no assessment of publication bias.

Strengths of the study by Renard et al. included the reporting of a clear study objective, clear reporting of the outcome measurement, clear description of important demographic and clinical characteristics of the included patients, identification of controls and treated subjects from the same population, and appropriate statistical analyses with comparisons adjusted for differences in known confounding variables. Limitations included no randomization of individuals to thrombolysis or standard care, lack of blinding of outcome assessors to treatment group, and lack of reporting of potential side effects in those who receive thrombolytics compared to those who received standard care.

In the study by Richling et al., the study objective was clearly reported, controls and treated subjects were recruited from the same population, important demographic and clinical characteristics of the included patients were clearly described, and the statistical analyses were appropriate and comparisons were adjusted for differences in known confounding variables. The limitations included no randomization of individuals to thrombolysis or standard care, no report of potential side effects in those who received thrombolytics compared to those who received standard care, and the inclusion of individuals who had cardiac arrest due to an acute STEMI, therefore results likely are not generalizable to those with cardiac arrest not due to acute STEMI.
Summary of Findings

What is the clinical effectiveness of thrombolytic drugs for the treatment of adult patients experiencing cardiac arrest with a return of spontaneous circulation?

While three of the five studies included in the systematic review demonstrated an increased likelihood of ROSC, the studies also consistently demonstrated no survival difference between those who received thrombolytics compared to those who received placebo or standard care. The largest RCT included in the systematic review evaluated 1050 patients (525 in the treatment group and 525 in the placebo group) with cardiac arrest of presumed cardiac origin, and found no difference in likelihood of 24 hour or 30 day survival, but a significant increase in the likelihood of intracranial hemorrhage in those who received tenecteplase compared to placebo (2.7% vs. 0.4%, relative risk: 6.95; 95% CI: 1.59 to 30.41).

Renard and colleagues found that use of thrombolytic therapy increased the likelihood of surviving to hospital admission in those with non-traumatic out-of-hospital cardiac arrest (47.7% vs. 23.6%, adjusted odds ratio [OR]: 1.7; 95% confidence interval [CI]: 1.09 to 2.68). They found a statistically significant interaction between shock with an AED and thrombolytic therapy; in those who were not initially shocked with an AED, if a person received thrombolytic therapy, they were 3.6 times more likely to survive to hospital admission compared to those who did not receive thrombolytic therapy (adjusted OR: 3.61; 95% CI: 1.88 to 6.96). In those who were initially shocked with an AED, there was no significant difference in survival to hospital admission (adjusted OR: 1.08; 95% CI: 0.61 to 1.92).

In a population of people with cardiac arrest due to acute STEMI, no difference was found in functional neurologic recovery or survival at 6 months in those who received thrombolytics compared to those who received PCI. The authors concluded that thrombolytics may be an option for those with cardiac arrest due to acute STEMI in which PCI is not readily available.

Limitations

There are limitations in the currently available evidence that must be noted. The studies identified for this report did not look at the impact of thrombolytic administration after ROSC on patient outcomes, but most studies included ROSC as an endpoint. In addition, some of the studies used different study populations (for example, cardiac arrest due to presumed or confirmed cardiac causes) and different thrombolytic agents, making the results difficult to compare between studies. However, results were consistent across studies in terms of lack of benefit on survival, so this may indicate that thrombolytic agents as a class do not improve survival in different populations. Only one of the included studies involved patients from Canada, however, it is unlikely that the results of other studies included in this report would not apply to the Canadian population. Four of the studies, including two from the systematic review, did not randomize study participants to treatment or control, and are therefore subject to bias, including confounding by indication and residual confounding. Four of the studies had sample sizes of less than 200 people, limiting the power to detect differences in hard endpoints like survival.
CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Based on the evidence included in this review, it appears that while thrombolytics may increase the likelihood of ROSC and survival to hospital admission, they do not increase the likelihood of survival to hospital discharge or 30 days after cardiac arrest compared to placebo or standard care. In addition, use of thrombolytics increased bleed risk, including intracranial hemorrhage, compared to placebo.

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REFERENCES


APPENDIX 1: Selection of Included Studies

254 citations identified from electronic literature search and screened

238 citations excluded

16 potentially relevant articles retrieved for scrutiny (full text, if available)

0 potentially relevant reports retrieved from other sources (grey literature, hand search)

16 potentially relevant reports

13 reports excluded:
- irrelevant population (1)
- irrelevant outcomes (1)
- no control group (case series) (2)
- already included the selected systematic review (2)
- other (review articles, editorials) (7)

3 reports included in review
APPENDIX 2: Characteristics of Included Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design and Length</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Clinical Outcomes Measured</th>
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<tbody>
<tr>
<td><strong>Systematic Review</strong></td>
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<tr>
<td>Perrott, 2010, Canada</td>
<td>Systematic review</td>
<td>Included 5 controlled trials (2 were prospective observational studies; 3 were RCTs) involving 1,544 cases of cardiac arrest. Publication years were 2001, 2002, 2004, 2006, and 2008.</td>
<td>t-PA (type not specified) used in 2 studies, tenecteplase in 3 studies</td>
<td>RCTs: placebo Observational studies: standard resuscitation care</td>
<td>ROSC; survival to hospital admission; 24 hour survival; survival to hospital discharge; risk of bleeding events</td>
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<tr>
<td><strong>Observational Studies</strong></td>
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<td>Renard, 2011, France</td>
<td>Retrospective cohort study</td>
<td>19 month study period (2005 – 2007)</td>
<td>Non-traumatic OHCA, age &gt; 18 years Thrombolytic provided by an out-of-hospital emergency physician with EMS</td>
<td>Alteplase (50mg single bolus) or tenecteplase (100 IU/kg single bolus) (n = 107 combined without a description of who received each thrombolytic)</td>
<td>No thrombolytics (n = 1154)</td>
</tr>
<tr>
<td>Richling, 2007, Austria</td>
<td>Retrospective cohort study</td>
<td>13.5 year study period (1991 – 2003)</td>
<td>Witnessed cardiac arrest due to acute STEMI</td>
<td>Reteplase 100mg in a front-loaded regimen or tenecteplase in a weight-adjusted dosage after admission to emergency and a diagnosis of acute STEMI (n = 101 combined without a description who received each thrombolytic)</td>
<td>PCI (n = 46)</td>
</tr>
<tr>
<td>First Author, Publication Year, Country</td>
<td>Study Design and Length</td>
<td>Patient Characteristics</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Clinical Outcomes Measured</td>
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AED: automated external defibrillator; CPR: cardiopulmonary resuscitation; EMS: emergency medical services; OHCA: out of hospital cardiac arrest; PCI: percutaneous coronary intervention; RCT: randomized controlled trial; ROSC: return of spontaneous circulation; STEMI: ST-elevation myocardial infarction; tPA: tissue plasminogen activator

Secondary outcome: mortality at 6 months after cardiac arrest
### APPENDIX 3: Critical Appraisal of Included Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systematic Review</strong></td>
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</table>
| Perrott, 2010 \(^{11}\) | - Duplicate data extraction.  
- Comprehensive literature search of three databases (MEDLINE, Embase, and Google Scholar) up to August 2010.  
- Authors reported no conflict of interest. | - No specific inclusion criteria were reported.  
- Only a list of the five included studies was reported, without mention of how many studies were identified from the original search or after the relevancy assessment.  
- No formal assessment of study quality.  
- No assessment of publication bias. |
| **Observational Studies** | | |
| Renard, 2011 \(^{12}\) | - Study objective clearly reported.  
- Outcome clearly reported in the methods section of the manuscript.  
- Important demographic and clinical characteristics of the included patients were clearly described.  
- Included all patients who presented with a non-traumatic out-of-hospital cardiac arrest from 2005 – 2007, therefore the patient population is likely generalizable.  
- Controls and treated subjects were recruited from the same population.  
- The main findings of the study are clearly described.  
- Statistical analyses were appropriate and comparisons adjusted for differences in known confounding variables. | - No mention of losses to follow up or if missing data existed, and how it was handled in the analysis.  
- No report of potential side effects in those who receive thrombolytics compared to those who received standard care.  
- No randomization of individuals to thrombolysis or standard care.  
- Outcome assessors were not blinded to treatment group. |
| Richling, 2007 \(^{13}\) | - Study objective clearly reported.  
- Controls and treated subjects were recruited from the same population.  
- Study endpoints clearly defined.  
- Important demographic and clinical characteristics of the included patients were clearly described.  
- The main findings of the study are clearly described.  
- Statistical analyses were appropriate and comparisons adjusted for differences in known confounding variables. | - Included individuals who had cardiac arrest due to an acute STEMI, therefore results are not generalizable to those with cardiac arrest not due to acute STEMI.  
- No randomization of individuals to thrombolysis or standard care.  
- No mention of losses to follow up or if missing data existed, and how it was handled in the analysis.  
- No report of potential side effects in those who received thrombolytics compared to those who received standard care.  
- Outcome assessors were not blinded to treatment group. |

STEMI: ST-elevation myocardial infarction
# APPENDIX 4: Results of Included Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
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<tbody>
<tr>
<td><strong>Systematic review</strong></td>
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</table>
| Perrott, 2010 ^1^              | - 3/5 studies demonstrated a significant increase in ROSC in those who received thrombolytics compared to those who received placebo/standard care.  
- 2/5 studies demonstrated a significant increase in likelihood of hospital admission in those who received thrombolytics compared to those who received placebo/standard care.  
- No significant difference was found between those who received thrombolytics compared to those who received placebo/standard care in 24 hour survival (evaluated in 3 studies) or survival to hospital discharge (evaluated in 5 studies).  
- A total of 94 bleeding events were reported in the 5 studies, 59 in the thrombolytics group and 35 in the placebo group. | “From a clinical decision-making perspective, controlled trials have shown that there is a lack of benefit and potential harm to administering thrombolysis in a patient with undifferentiated cardiac arrest…” (p. 2012)  
The authors suggest that those with a cardiac arrest due to pulmonary embolus may benefit from use of thrombolytics: “Clinicians should be cognizant of current evidence and not “write off” a potentially beneficial intervention in a patient who is part of a population that has not been adequately studied and who likely has a better than average chance of benefiting from this therapy.” (p. 2012) |
| **Observational Studies**      |                     |                      |
| Renard, 2011 ^2^              | Survival to hospital admission:  
- 51/107 (47.7%) who received thrombolysis  
- 272/1154 (23.6%) who did not receive thrombolysis | “This study showed that fibrinolytic therapy was associated with more frequent survival to hospital admission.” (p. 407)  
“In our study population, the influence of shock administration by first responder AED, the variables that influence the doctor’s decision to administer fibrinolytics and the choice of a pragmatic endpoint are three essential points that need further research.” (p. 408) |

Study authors performed a multivariate propensity score-matched logistic regression to estimate the impact of thrombolytic therapy on likelihood of hospital admission (47.7% in the thrombolytic group compared to 23.6% in the standard care group): Adjusted OR: 1.7; 95% CI: 1.09 – 2.68  
Adjusted for differences in age, gender, bystander presence and action, etiology, AED shock administration, and delay between alarm and AED switch on.  
Patients who did not receive external shock from an AED: thrombolytics associated with a greater likelihood of survival to hospital admission:  
Adjusted OR: 3.61; 95% CI: 1.88 – 6.96  
Patients who did receive external shock from an AED: survival to hospital admission was not impacted by administration of thrombolytics:  
Adjusted OR: 1.08; 95% CI: 0.61 – 1.92
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Authors’ Conclusions</th>
</tr>
</thead>
</table>
| Richling, 2007                | CPC 1 or 2 (56% in those who received thrombolysis compared to 48% in those who received primary PCI): Adjusted OR: 1.24; 95% CI: 0.58 – 2.62  
Survival at 6 months (68% in those who received thrombolysis compared to 55% in those who received primary PCI): Adjusted OR: 1.74; 95% CI: 0.80 – 3.80  
Comparisons were adjusted for differences in location of cardiac arrest, cooling, age, and sex. | “In patients with cardiac arrest due to acute STEMI, we found no evidence that PCI offers an important advantage compared with thrombolysis.” (p. 549)  
“Although the study was retrospective and too small to draw a definitive conclusion, it may be an acceptable option to use thrombolysis as a reperfusion strategy in such patients. This applies especially in hospitals where immediate PCI is not available.” (p. 549) |

AED: automated external defibrillator; CI: confidence interval; CPC: cerebral performance category; OR: odds ratio; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-elevation myocardial infarction; VF: ventricular fibrillation