**Worksheet author(s)**

Michael Parr

**Date Submitted for review:** Revision 18.2.09, revised 15.9.09, revised 10.12.09

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**Clinical question.**

In adult cardiac arrest (asystole, pulseless electrical activity, pulseless VT and VF) (prehospital [OHCA], in-hospital [IHCA]) (P), does the use of fibrinolytics alone or combination with other drugs (I) compared with not using drugs (or a standard drug regimen) (C), improve outcomes (eg. ROSC, survival) (O)

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** Intervention: thrombolysis

**State if this is a proposed new topic or revision of existing worksheet.** Revision of W96A, W96B, W96C

**Conflict of interest specific to this question**

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

**Search strategy (including electronic databases searched).**

AHA EndNote 7 Master library [http://ecc.heart.org/]
MEDLINE, Embase, Cochrane database for systematic reviews and Central Register of Controlled Trials [http://ovidsp.ox.tx.ovid.com/spb/ovidweb.cgi]
Scopus [http://www.scopus.com/scopus/home.url]
Hand searches of journal references, review articles

**Search 1.** Heart Arrest / cardiac arrest AND (Thrombolytic Therapy <OR> Fibrinolysis <OR> Tissue Plasminogen Activator <OR> Streptokinase <OR> Urinary Plasminogen Activator <OR> thrombolysis

**Search 2.** Cardiopulmonary Resuscitation AND (Thrombolytic Therapy <OR> Fibrinolysis <OR> Tissue Plasminogen Activator <OR> Streptokinase <OR> Urinary Plasminogen Activator <OR> thrombolysis

**Search 3.** Heart Arrest / cardiac arrest AND Pulmonary Embolism AND (Thrombolytic Therapy <OR> Fibrinolysis <OR> Tissue Plasminogen Activator <OR> Streptokinase <OR> Urinary Plasminogen Activator <OR> thrombolysis

**Example search result (saved in OVID): Search 1**

1. heart arrest.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, nm]
2. cardiac arrest.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, nm]
3. 1 or 2
4. thrombolytic therapy.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, nm]
5. fibrinolysis.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, nm]
6. tissue plasminogen activator.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, nm]
7. streptokinase.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, nm]
8. urinary plasminogen activator.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, nm]
9. thrombolysis.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct, tn, dm, mf, nm]
10. 4 or 5 or 6 or 7 or 8 or 9
11. 3 and 10
12. limit 11 to humans
13. limit 12 to human
14. limit 13 to (clinical trial, all or controlled clinical trial or randomized controlled trial)
16. from 15 keep 1-10
17. from 15 keep 1-10
18. from 15 keep 1-10
19. from 15 keep 1-35

**State inclusion and exclusion criteria**

Inclusion: Human,
Exclusion: Animal, abstract only publications, non-peer reviewed, papers not answering the question.

**Number of articles/sources meeting criteria for further review:**

42 articles met the search criteria, some were duplicate and some were letters, after review 29 were selected for close review and are included in the bibliography.
10 publications (9 studies and 1 meta-analysis) sufficiently addressed the clinical question to be used as the basis of the consensus on science statement and treatment recommendation.
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td></td>
<td></td>
<td>(Bottiger BW 2001) AB</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>(Fatovich Dm 2004) A</td>
<td>(Bozeman Wp 2006) AB</td>
</tr>
<tr>
<td>Poor</td>
<td>(Li, Fu et al. 2006)ABCD</td>
<td>(Janata 2003) E</td>
<td>(Kurkciyan 2000) A</td>
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</tbody>
</table>

### Level of evidence:

- **A**: Return of spontaneous circulation
- **B**: Survival of event
- **C**: Survival to hospital discharge
- **D**: Intact neurological survival
- **E**: Other endpoint

**Italics = Animal studies**
### Evidence Neutral to Clinical question

<table>
<thead>
<tr>
<th></th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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</thead>
<tbody>
<tr>
<td>(Böttiger BW 2008) ABCDE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Fatovich Dm 2004) BC</td>
<td>(Stadlbauer, Krismer et al. 2006) C</td>
<td>(Kurkciyan 2000) C</td>
<td>(Janata 2003) AC</td>
</tr>
</tbody>
</table>

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<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
</table>

**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  

**Italics** = Animal studies

### Evidence Opposing Clinical Question

<table>
<thead>
<tr>
<th></th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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<th>1</th>
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</table>

**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  

**Italics** = Animal studies
REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Out-of-hospital cardiac arrest has a poor prognosis and it is estimated that up to 70% have underlying acute myocardial infarction or pulmonary embolism. Therefore, thrombolysis during cardiopulmonary resuscitation is a logical therapy and may result in improved survival.

A number of studies have suggested improved outcomes such as increased rate of ROSC and admission to hospital following thrombolysis during cardiac arrest but poor methodology severely limits their interpretation (LOE1, poor (Fatovich Dm 2004), LOE2, poor,(Bozeman Wp 2006),(Stadlbauer, Krismer et al. 2006), LOE 3, poor, (Kurkciyan 2000), (Lederer, Lichtenberger et al. 2001).

There are 3 fair or good quality randomized studies from which valid conclusions and treatment recommendations can be formed.

In 2001 Bottiger published a randomized trial that showed improved ROSC and admission to hospital following thrombolysis after initially unsuccessful out-of-hospital CPR (LOE3, Fair. (Bottiger BW 2001)). There was no improvement in alive at 24 hours or hospital discharge. This trial used historical controls (1 year prior to the intervention group), and 90 patients were included. Heparin and rt-PA were given to 40 patients. There were no bleeding complications related to the CPR procedures. They concluded that thrombolytic therapy combined with heparin is safe and might improve patient outcome and this study provided the basis to justify the TROICA trial.

In 2002 Abu-Laban published a prospective randomized trial on adult cardiac arrest patients with pulseless electrical activity randomized to receive t-PA or placebo (LOE 1, Fair (Abu-Laban, Christenson et al. 2002)). There was no improvement in ROSC or survival to hospital discharge but the study had inadequate power, with only one survivor (in t-PA group who suffered a complication of pulmonary haemorrhage but had a full recovery) of 223 patients with out-of-hospital PEA.

The large, prospective, randomized clinical trial (“TROICA”) in Europe was terminated in 2006 and published in Dec 2008 (LOE1, good (Böttiger BW 2008)). The trial was terminated prematurely for futility after 1050 patients. There were no significant difference between tenecteplase and placebo in the 30-day survival, hospital admission, return of spontaneous circulation, 24-hour survival, survival to hospital discharge, or neurologic outcome. After blinded review of data from the first 443 patients, the data and safety monitoring board recommended discontinuation of enrollment of asystolic patients because of low survival. This protocol amendment results in a methodology limitation to interpretation and extrapolation to all cardiac arrest situations. There were significantly more intracranial hemorrhages (p=0.006) in the tenecteplase group. Four patients with intracranial hemorrhage (all in the tenecteplase group) were ‘symptomatic’ but definition of ‘symptomatic’ and impact on outcome are absent.

The study is notable for the short intervals from collapse to administration of study drug, relatively high survival rate and method that excluded patients where pulmonary embolism was thought to be the cause of the arrest (N=37), without defining how these were identified. This creates a potential selection bias in dealing with undifferentiated cardiac arrest situations. Likely PE cases were not excluded in the pilot study. The presented data does not include overall numbers of arrests during the study period, which may also reflect a selection bias.

Therefore evidence from randomized controlled trials in adults has failed to demonstrate a significant outcome benefit following the administration of thrombolytic agents during cardiac arrest, and this therapy appears to be associated with a significant increase in intracerebral haemorrhage. It is not clear if there are subgroups of patients who may benefit from thrombolysis during cardiac arrest or if the timing of administration is a factor in determining outcome.

Acknowledgements:
Citation List


Bibliography of papers used in worksheet with comments

   Comment: LOE 1, Fair. Neutral for survival to hospital discharge. But inadequate power, only 1 survivor (in t-PA group who suffered a complication of pulmonary haemorrhage but had a full recovery) of 223 patients (out-of-hospital, PEA) randomized to t-PA or placebo. No benefit in ROSC or hospital discharge.

   Comment: LOE3, Fair. Controlled trial but used historical controls (1 year prior to the intervention group). Pilot study basis of the TROICA trial. Improved ROSC and admission to hospital but not for alive at 24 hours and hospital discharge.

   Comment: LOE1, Good. The definitive, large, prospective, randomized clinical trial ("TROICA") in Europe which was terminated in 2006. The final results were published in NEJM in Dec 2008 (Böttiger BW 2008).
After blinded review of data from the first 443 patients, the data and safety monitoring board recommended discontinuation of enrollment of asystolic patients because of low survival. This protocol amendment results in a methodology limitation to interpretation and extrapolation to all cardiac arrest situations. The trial was terminated prematurely for futility after 1050 patients. No significant difference between tenecteplase and placebo in the 30-day survival, hospital admission, return of spontaneous circulation, 24-hour survival, survival to hospital discharge, or neurologic outcome. There were significantly more (p=0.006) intracranial hemorrhages in the tenecteplase group. Four patients with intracranial hemorrhage (all in the tenecteplase group) were 'symptomatic' but definition of 'symptomatic' and impact on outcome are absent.

Notable for short intervals from collapse to administration of study drug, relatively high survival rate and method excluded patients where pulmonary embolism (N=37) was thought to be the cause of the arrest (without defining how these were identified), which creates a selection bias in dealing with undifferentiated cardiac arrest situations. Likely PE cases were not excluded in the pilot study. Also data does not present overall numbers of arrests during the study period which may reflect a selection bias.

Comment: Level 2, Poor. Prospective, non random, observational. Improved ROSC but not survival to discharge.

5. Fatovich DM, Dobb GJ, Clugston RA
Comment: Level 1, Poor (because groups turned out to be not matched). Small prospective double blind RCT pilot study (n=35), but groups not matched (thrombolysis group were younger and more VF)

Comment: LOE3, Poor. Retrospective cohort study, non random contemporary controls. The methodology of this study is not entirely clear and it was not included in the previous worksheets. No benefit for ROSC and survival to discharge.

Comment: LOE3, Poor. Retrospective study, small number (n=60), a subgroup of which (n=21) received t-PA and were case matched to controls. Improved ROSC but not survival to discharge.

Comment: LOE3, Poor. Retrospective, not random, matched to concurrent controls. Complication rate based on autopsy in 43% of patients overall and 41% of rt-PA group. Improved ROSC and survival to 24 hours and discharge (p.048).

Comment: LOE1, Poor (because a mixture of methods). A meta-analysis, but a mixture of studies of thrombolytic administration during cardiac arrest and after ROSC. Not all thrombolysis during cardiac arrest studies (4 out of 8).
The "meta-analysis" by Li has an unclear LOE (LOE1 here as it is a "meta-analysis" which does include some RCTs, but it is poor quality and of mixed methods and poor initial studies (most retrospective) it includes 4 studies: - Kurkciyan I, Meron G, Sterz F, et al. Major bleeding complications after cardiopulmonary resuscitation: impact of thrombolytic treatment. J Intern Med 2003;253:128—35. Excluded because thrombolysis after cardiac arrest and
ROSC.
- van Campen LC, van Leeuwen GR, Verheugt FW. Safety and efficacy of thrombolysis for acute myocardial infarction in patients with prolonged out-of-hospital cardiopulmonary resuscitation. Am J Cardiol 1994;73:953—5. I don’t seem to have access to this (but I know I looked at a reprint..once upon a time) now but I am pretty sure same reason as above.


**Supplementary bibliography**


**Comment:** Prospective uncontrolled case series. First study on thrombolysis during CPR in a pre-hospital setting.


**Comment:** Response to Mysiak review 2007 and reports TROICA study results in some detail, as no difference in any outcome (ROSC through to discharge) compared to placebo in 1050 patients

Some of the data from the TROICA study had been previously been referred to in two publications: (Kozinski and Kubica 2007) (Spohr, Wenzel et al. 2008). Kozinski actually presents the results in a table form (below) which appears to be significantly different to the results in the NEJM.

**Table 1. Results of the TROICA trial.**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Tenecteplase [%]</th>
<th>Placebo [%]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day survival</td>
<td>18.2</td>
<td>20.2</td>
<td>0.512</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>59.0</td>
<td>59.5</td>
<td>0.931</td>
</tr>
<tr>
<td>Return of spontaneous circulation</td>
<td>59.6</td>
<td>59.2</td>
<td>0.977</td>
</tr>
<tr>
<td>24-hour survival</td>
<td>36.4</td>
<td>37.9</td>
<td>0.511</td>
</tr>
<tr>
<td>30-day survival or hospital discharge</td>
<td>18.8</td>
<td>21.0</td>
<td>0.481</td>
</tr>
<tr>
<td>Symptomatic intracranial haemorrhage</td>
<td>1.0</td>
<td>0.0</td>
<td>0.133</td>
</tr>
<tr>
<td>Major bleeds</td>
<td>8.9</td>
<td>7.4</td>
<td>0.528</td>
</tr>
</tbody>
</table>


**Comment:** Cohort descriptive. Not a controlled trial.


**Comment:** Response to Kozinski letter


**Comment:** Review


**Comment:** Retrospective. Thrombolysis administered after ROSC


**Comment:** Thrombolysis after ROSC


**Comment:** Review
27. Spohr F, Wenzel V, Bottiger B.W.
Thrombolysis and other drugs during cardiopulmonary resuscitation.
Comment: While this is a review paper it does announce the TROICA study result. Stating:
The study was stopped in 2006 owing to a missing additional therapeutic effect in the group of patients
receiving tenecteplase. Preliminary analyses of the study data showed no difference between tenecteplase
and placebo group regarding primary endpoints. Survival after 30 days was unexpectedly good in both the
groups. Detailed results of the TROICA study are expected to be published in 2008.

   Efficacy and safety of a new therapeutic approach." Minerva Anestesiol 69(5): 357-64.
Comment: Review

   International multicentre trial protocol to assess the efficacy and safety of tenecteplase during cardiopulmonary
Comment: This is a methodology description paper for the TROICA study, which has not been published to
date.