### WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

<table>
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<tr>
<th>Worksheet author(s)</th>
<th>Date Submitted for review: 2/12/08 Resubmitted 31/1/09 Revised and presented at Webinar 2/3/09 Revised and presented at Webinar 20/5/09 TASK FORCE WEBINAR DISCUSSION 20 MAY 09. Consensus on Science agreed at this webinar. Resubmitted 1/10/09</th>
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**Clinical question.**

In adult patients with ROSC after cardiac arrest diagnosed as PE, does the use of early fibrinolytic therapy as opposed to standard care, improve outcome e.g. survival

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

**State if this is a proposed new topic or revision of existing worksheet:** New topic

**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).**

Searches were performed of Pubmed (396 articles found), EMBASE (173 articles found) and Cochrane library in December 2008. Searches were repeated August 2009.

**Search terms:**

1. Cardiac arrest or heart arrest or cardiopulmonary resuscitation

   **AND**

2. Fibrinolytic therapy or thrombolysis or streptokinase or tissue plasminogen activator or urinary plasminogen activator or pulmonary embolism

In addition a hand search of references from relevant articles and the ATS, ESC and BTS guidelines on management of pulmonary embolism. Hand search of references from previous ILCOR worksheets on thrombolysis during cardiopulmonary resuscitation.

**State inclusion and exclusion criteria**

Inclusion criteria: Articles in English containing cases or series looking at thrombolysis following cardiac arrest where pulmonary embolism is thought to be the cause. Both animal and adult studies relating to the question were considered. Since there is so little available data, studies with indirect relevance were also considered.

Exclusion criteria: Thrombolysis commenced during attempts at resuscitation. Articles considering surgical treatment for pulmonary emboli. However, these were reviewed to look for cases where thrombolysis was commenced after CPR.

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

12 articles and 1 abstract (English with an article in German) were reviewed in more detail as below. All were LOE 5 as not directly related to the question. Of these 2 were animal studies which help provide a theoretical basis for treatment.
# Summary of evidence

## Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
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<tbody>
<tr>
<td><strong>Good</strong></td>
<td>Wan 2004 E Bottiger 2001 ABC</td>
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<tr>
<td><strong>Fair</strong></td>
<td>Lin 1978</td>
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<tr>
<td></td>
<td>Janata 2001 ABC</td>
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<tr>
<td></td>
<td>Jerjes-Sanchez 1995 C</td>
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<td>Schreiber 2002 D</td>
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<td>Fischer 1996</td>
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<td></td>
<td>Lederer 2001 ABC</td>
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<tr>
<td><strong>Poor</strong></td>
<td>Spohr 2003 ABC</td>
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**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

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<tr>
<td><strong>Good</strong></td>
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<td>Abu-Laban 2002 AB</td>
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<td>Thabut 2002 BC</td>
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REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

There are a number of theoretical reasons why fibrinolysis after return of spontaneous circulation in patients suffering cardiac arrest caused by pulmonary embolism would be effective. Firstly, the clot causing the cardiac arrest can be broken down much more quickly than by the body’s own fibrinolytic system. This could reduce the risk of further arrest and improve haemodynamic status. Data exists to demonstrate improved right ventricular function and increased clot resolution following thrombolysis although this was studied in more cardiovascularily stable patients. The relative improvement in haemodynamic state does not appear to be sustained and the two groups move close to each other in the first weeks following pulmonary embolism. (Dalla-Volta 1992, 520) Secondly, a reduction in microthrombi caused by activation of the clotting system during cardiac arrest could cause an improvement in survival and especially in neurological recovery. There are animal studies which show a reduction in microthrombi and improved cerebral circulation after thrombolysis during cardiac arrest and although the cardiac arrests were from a different cause it seems reasonable to extrapolate from these results. (Lin 1978, 340; Fischer 1996, 1214) Human studies show a trend towards improved neurological outcome after thrombolysis but have insufficient power currently to demonstrate whether or not a true difference exists. These possible advantages have to be weighed against the risks caused by thrombolysis and in particular the risk of major bleeding including intracranial bleeds.

There are no randomised controlled trials to look at whether or not thrombolysis after return of spontaneous circulation causes an improvement in outcome. Therefore the question can only be considered from reviewing isolated case reports, case series and considering studies that are indirectly related. Isolated case reports and case series show both long term survivors and those who initially do well but do not survive to hospital discharge.

A meta-analysis looking at whether or not thrombolysis improves outcome in patients with pulmonary embolism does not show a benefit in unselected patients. However, sub-group analyses of those trials including patients with massive pulmonary embolism (defined as a pulmonary embolism causing cardiovascular instability) do indicate that there is a reduction in the combined end point of recurrent pulmonary embolism and death with a trend towards a reduction in both as separate end points. There is however a trend towards an increase in major haemorrhage and a significant increase in non-major haemorrhage. (Wan 2004, 744) There is only one small randomised controlled trial in thrombolysis in massive pulmonary embolism (8 patients) which showed 100% survival in the thrombolysis arm and 100% mortality in the heparin alone arm. There are a number of flaws in this study. (Jerjes-Sanchez, 1995, 227) This has led to a recommendation that patients with massive haemorrhage are thrombolysed. Since those who have suffered a cardiac arrest are haemodynamically unstable it could be argued that they fall into this sub group.

A review of case series showing results from patients thrombolysed after return of circulation shows an excellent initial survival rate in these patients and a trend towards improved neurological recovery. However, only 5 of these patients had a presumed diagnosis of pulmonary embolism and a difference between patients who have return of spontaneous circulation following cardiac arrest from acute myocardial infarction and those from pulmonary embolism cannot be excluded. (Spohr 2003, 357)

The recent study from the TROICA group looked at thrombolysis during cardiac arrest. They excluded those with a presumed diagnosis of pulmonary embolus from the trial but approximately 8% of patients recruited had probable pulmonary embolism as a cause of their arrest. These were not analysed separately. This study was stopped prematurely for futility as no difference in outcome was seen between those thrombolysed and those not. There were more intracranial haemorrhages in the thrombolysed group. (Böttiger 2008, 2651)

Acknowledgements:
I would like to thank Prof P Morley, Prof I Jacobs and Dr J Nolan for their advice.
Citation List


Comment: LOE 5, Good randomised controlled trial. Neutral as to whether fibrinolysis during CPR improved outcome in patients. 223 patients (out-of-hospital, PEA, unknown or cardiovascular cause) randomized to t-PA or placebo. No benefit in ROSC or hospital discharge.


Comment: LOE 5, prospective trial. Well conducted trial but used historical controls and non-random allocation. Improvement in ROSC and admission to intensive care unit. Trend towards 24 hour survival and hospital discharge being improved. This was a basis for performing the TROICA trial.


Comment: LOE 5, well conducted randomised controlled trial. Out-of –hospital cardiac arrest patients of presumed cardiac origin enrolled. Asystolic patients excluded after an interim analysis. Stopped for futility. Heparin and aspirin not used which could explain difference to previous work.


Comment: LOE 5, well conducted experimental trial in cats. This showed that in cats thrombolytic therapy during cardiac arrest improves microcirculatory reperfusion post arrest. It is unclear how closely this relates to neurological recovery in humans.


Comment: LOE5, Retrospective cohort study. Since the decision whether or not to thrombolys was left to the attending physician this study was very open to recruitment bias. The study showed a trend towards increased major bleeding complications in thrombolysed patients. It also showed increased ROSC and 24hr survival. Survival to discharge was not statistically different but again showed a trend towards improvement.


Comment: LOE 5, Randomised controlled trial. Originally planned to have 40 patients enrolled but stopped by safety committee after 8 patients as all in thrombolysis arm survived and all in heparin alone died. There were some important differences between these 2 groups of patients including the time from onset of symptoms to treatment (2.5 hours versus 34.75 hours) ie patients who had already had a PE and then went on to have further PEs causing their deterioration. Another problem is the small sample size.


Comment: LOE 5. Experimental study in dogs. This showed that thrombolysis improved cortical and hippocampal blood flow after cardiac arrest when given during the arrest. It is unclear how well these results can be generalised to humans and what impact these improvements would have on neurological recovery.


Comment LOE 4. Retrospective case series. Two patients successfully thrombolysed after return of circulation.


Comment: LOE 5. Retrospective case controlled study. After multivariate regression analysis there was a non-significant trend towards good neurological recovery.


Comment: LOE 4. This review contains many of the case series that have been conducted following thrombolysis after cardiopulmonary resuscitation. Only one of these case series contained patients with suspected PE, therefore 5 patients with PE were included.


Comment LOE 5. Reasonably conducted meta-analysis. It covers essentially the same material as Wan et al (2004) but omits 2 studies. One of these was published after this metanalysis. It shows no significant effect on mortality but an increase in major haemorrhage.


Comment LOE 5. This meta-analysis is well conducted. Although it does not directly address the question it does look at thrombolysis for massive pulmonary embolism and suggests that there is a significant reduction in recurrent pulmonary embolism or death but only a trend to either of these outcomes separately.