**Worksheet for Evidence-Based Review of Science for Emergency Cardiac Care**

**Worksheet author(s)**

| Steven Kronick | Date Submitted for review: January 19, 2010 |

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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/therapy**

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

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**Conflict of interest specific to this question**

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

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


Search Strategy: 
{ (cardiopulmonary arrest.mp. [mp=ti, tx, kw, hw, ab, ct, ot, sh, rw, tn, nm]) or (cardiac arrest.mp. [mp=ti, tx, kw, hw, ab, ct, ot, sh, rw, tn, nm]) or (cardiopulmonary resuscitation.mp. [mp=ti, tx, kw, hw, ab, ct, ot, sh, rw, tn, nm])} AND 
{ (thrombolytics.mp. [mp=ti, tx, kw, hw, ab, ct, ot, sh, rw, tn, nm]) or (fibrinolytics.mp. [mp=ti, tx, kw, hw, ab, ct, ot, sh, rw, tn, nm]) or (tissue plasminogen.mp. [mp=ti, tx, kw, hw, ab, ct, ot, sh, rw, tn, nm]) or (tissue plasminogen activator.mp. [mp=ti, tx, kw, hw, ab, ct, ot, sh, rw, tn, nm]) or (streptokinase.mp. [mp=ti, tx, kw, hw, ab, ct, ot, sh, rw, tn, nm]) or (urokinase.mp. [mp=ti, tx, kw, hw, ab, ct, ot, sh, rw, tn, nm])}

COS 2005 Worksheets reviewed for additional citations

- **State inclusion and exclusion criteria**

Search yielded 1179 citations which were hand searched. Citations not pertaining to the topic at hand were excluded (animal, abstract only, non-English, no pertinent to topic). The bibliographies of the citations that remained were searched by hand which yielded 52 total citations. Of these, 26 citations were papers for which a level of evidence could be assigned, 10 were letters or editorials, 9 were reviews, 5 speak to complications alone and 2 citations are not able to be located. Citations that referred to thrombolytic therapy for patient after cardiac arrest were excluded. Of the 26 for which LOE could be assigned 15 were single case reports or case series and excluded, but listed in the bibliography. All 54 citations are listed in the bibliography and divided into those cited with level of evidence found in the LOE tables, other related, but uncited papers and case reports/series.

- **Number of articles/sources meeting criteria for further review:** 11
# Summary of evidence

## Evidence Supporting Clinical Question

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<th>Good</th>
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<td></td>
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<td>Bottiger 2001, 1583 AB</td>
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<td></td>
<td>Fatovich 2004, 309A</td>
<td>Janata 2003, 49AC</td>
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<td>Lederer 2001, 71ABC</td>
<td>Bozeman 2006, 399AB</td>
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<td>Stadlbauer 2006, 305B</td>
<td>Li 2006, 31 ABCD</td>
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<td></td>
<td>Li 2006, 31 ABCD (Meta-analysis)</td>
<td>Kurkciyan 2000, 1529A</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: bleeding complications or multiple endpoints  

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

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<tr>
<th>Good</th>
<th>Bottiger 2008, 2651 ABCD</th>
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<td>Bozeman 2006, 399CDE</td>
<td>Li 2006, 31 E</td>
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<td>Kurkciyan 2000, 1529C</td>
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**Level of evidence**

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

Italics = Animal studies

### Evidence Opposing Clinical Question

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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = In tact neurological survival  
E = Other endpoint-bleeding complications

Italics = Animal studies
There is evidence although controversial demonstrating that survivors of cardiac arrest are more likely to have myocardial infarction or pulmonary embolus as the etiology of the cardiac arrest. Fibrinolysis is a well established treatment for patients with myocardial infarction and pulmonary embolus. Further, there is animal evidence and empiric evidence that demonstrates effects on microcirculation that might also lead to a survival benefit. Anecdotatal evidence in the form of case reports and case series is overwhelmingly positive showing a neurologically normal survival benefit in patients for whom the outcome was felt to be certainly dismal until fibrinolytic therapy was administered. In many of these patients, the suspected cause was pulmonary embolus or myocardial infarction. Despite this preponderance of anecdotatal evidence, randomized controlled trials have not been able to demonstrate a treatment effect that is as striking. The largest randomized controlled trial (Abu-Laban 2002,1522 – LOE1/good) failed to show a treatment benefit. A smaller randomized controlled trial (Fatovich 2004,309 – LOE1/poor) showed a trend toward the return of spontaneous circulation alone. Non randomized trials with concurrent controls (Janata 2003,49 – LOE3/poor and Lederer 2001,71 – LOE2/poor as well as Bozeman 2006,399 – LOE2/poor and Stadlbauer 2006,305 – LOE2/poor) demonstrated modest trends toward improved outcome.

The Thrombolysis in Cardiac Arrest (TROICA) trial is the largest randomized trial to attempt to answer the question of what role fibrinolytics play in the treatment of patients with cardiac arrest. The trial stopped enrolling patients due to the inability to demonstrate a difference after 1050 of the planned 1300 patients were enrolled because no difference was detected (Bottiger 2009, LOE1/good).

Numerous studies have demonstrated the feasibility and safety of administering fibrinolytics in this cohort of patients. Many fibrinolytics have been used in these trials and case reports/series (including streptokinase, urokinase, alteplase and tenecteplase) without clear evidence that one has any benefit over the others despite some theoretical advantages of individual agents.

Although an appealing therapy with theoretical advantages and face validity to its use, there has been insufficient evidence to recommend the routine use of fibrinolytics for the patient in cardiac arrest. Because of the plethora of anecdotatal evidence and the theoretical considerations, the use of fibrinolytics while not recommended, cannot, however, be condemned.

Acknowledgements:

Citation List

CITATIONS CITED IN SUMMARY OF EVIDENCE


Notes: LOE 1 Quality Good. Neutral. Randomized controlled trial of 233 patients that showed no evidence of improved outcome in patients with PEA arrest with treatment of tPA over 15 minutes during CPR.


Notes: LOE 3 Quality Good Supporting. Prospective trial of 90 patients who received rt-PA and heparin. Showed therapy to be safe and outcome (ROSC: 68% vs 58%, admitted to ICU: 44% vs 30%, survival at 24h 35% vs 22% and discharge from the hospital15% vs 8%).

Notes: LOE 1 Quality Good, Neutral. Randomized control trial of 1050 patient (525 each arm) of TNK vs placebo. Did not show any significant improvement in any outcome.


Notes: LOE 2, Quality Fair, supporting. Case control trial of 50 patients receiving TNK and 113 controls. Showed improvement in ROSC (26% vs 12.4%), survival to admission (12% vs 0%), and survival to hospital discharge (4% vs 0%). All survivors had good neurological outcome.


Notes: LOE 1 Quality Good, supporting. Randomized controlled pilot of TNK vs placebo in 35 patients (19 receiving TNK). ROSC in 42% (8 patients) vs 6% (1 patient). Two TNK patients survived to leave ED and one placebo patient survived to leave the ED.


Notes: 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.


Notes: LOE 5, Quality Good. Opposing. Trend to increase in major bleeding complications in patients receiving fibrinolysis. Only in patients with arrest due to massive pulmonary embolism. LOE 5 due to different patient population.


Notes: LOE 2, Quality Good, supporting. A retrospective chart review of 401 patients with cardiopulmonary resuscitation over a 6 year period. 108 of these patients received rt-PA. Patients receiving rt-PA had a higher ROSC (70.4% vs 51%), survival first 24h (48.1% vs 32.9%),

Notes: Contains studies of LOE 1/2/3 (as a meta analysis – listed in table as 3) Quality Good, supporting. Meta analysis of 8 papers showing improved ROSC, survival to 24h, survival to discharge and long term neurological functioning. Four of the papers (Kurkciyan 2003, 128; Ruiz-Ballen 2001, 1050; Schreiber 2002, 63; Van Campen 1994, 953) are primarily patients who received fibrinolytics after CPR and are therefore not included as separate citations in this analysis.


Notes: LOE 3, Quality Good, Opposing. A post hoc analysis of an originally designed RCT. Fibrinolysis did not lead to improved outcome even when adjusting for those with higher likelihood of suspected myocardial infarction as the etiology of cardiopulmonary arrest.

ADDITIONAL CITATIONS


   The authors present three case reports retrospectively casting doubt on the benefit of thrombolysis after external cardiac massage.


CASE REPORTS AND CASE SERIES


Notes: Long term follow up. Does not answer clinical question.
