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

## Worksheet author(s)

| Morten Pytte | Date Submitted for review: December 10, 2009 |

## Clinical question.

LS-SAM-063A - In adult cardiac arrest (prehospital or in-hospital) (P), does an alternate timing for drug delivery (eg. early or delayed) (I) as opposed to standard care (standard position in algorithm) (C), improve outcome (O) (eg. ROSC, 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).


COCHRANE: (heart arrest [MESH] OR cardiopulmonary resuscitation) [MESH]; epinephrine [MESH] OR vasopression [MESH] OR amiodarone [MESH] OR fibrinolytic agents [MESH]) AND (early [text] OR delayed [text] OR timing [text])

Clinical Trials.gov

Review of related articles in Pubmed.

Search in the ILCOR endnote database.

## State inclusion and exclusion criteria

Inclusion: Clinical and experimental studies of cardiac arrest and resuscitation, which include assessable information regarding time of drug delivery and outcome.

Exclusion: abstract only studies, not peer reviewed, not answer worksheet question

## Number of articles/sources meeting criteria for further review: Performed January 2009.

Pubmed: 132 (22 reviews, 11 clinical trials)

Embase: 54

Cochrane: 34 (reviews 2, clinical trials 34, economic evaluation 6)

Clinical Trials.gov: 0
# Summary of evidence

## Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Evidence Supporting Clinical Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>Rittenberger 2007, A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<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 Neutral to Clinical question

<table>
<thead>
<tr>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</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 Opposing Clinical Question

<table>
<thead>
<tr>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</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*
REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

The search identified one experimental study primarily addressing the timing of drug delivery in the treatment algorithm of cardiac arrest (LOE 5: Wenzel 1999, 1379) reporting lower coronary perfusion pressure when drug delivery (epinephrine or vasopressin) was delayed (4 minutes vs. 12 minutes).

Three clinical studies reporting secondary findings related to the timing of drug delivery were identified (LOE 4: Dorian 2002, 884; Kudenchuk 1999, 871), reporting worsened survival for every minute drug delivery was delayed. The time to drug administration included the time from dispatch and the finding is likely to be biased by a concomitant delay in onset of ALS. In one study (LOE 4: Dorian 2002, 884) the interval from the first shock to the administration of the drug was a significant predictor of survival.

Secondary finding of improved outcome related to timing of drug administration was identified in four experimental studies (LOE 5: Menegazzi 1993, 235; Menegazzi 2000, 31; Menegazzi 2003, 261; Rittenberger 2007, 154). A retrospective analysis of 271 swine cardiac arrest concluded that time to drug administration was a predictor of ROSC, with a 50% likelihood of ROSC when the drug cocktail was administered after 14.1 minutes of CPR (Rittenberger 2007, 154). The studies (Menegazzi 1993, 235; Menegazzi 2000, 31; Menegazzi 2003, 261) were not designed to compare early vs. late drug administration and the observed difference in outcome may be a drug effect or related to differences in CPR performance; early chest compression CPR vs. shock first CPR (Menegazzi 1993, 235).

Acknowledgements: none

Citation List


LOE 4. Clinical study not directly related to the worksheet assignment. Shorter interval from the dispatch of the crew to the administration of the study drug was associated with increased survival to hospital admission, and the interval from the first shock to the administration of the drug was a significant predictor of survival (odds ratio for survival for each minute of delay, 0.87; 95% CI 0.8 to 0.96, p=0.003).


LOE 4. Clinical study with secondary findings related to timing of drug. Numerically fewer patients were admitted to hospital with increasing time from dispatch to intravenous administration of amiodarone.


LOE 5. Randomized, open, swine study comparing early administration of a drug cocktail "experimental algorithm" with "standard algorithm". There was improved survival to one hour when drugs were administered early. The study was not designed to compare early vs delayed drug delivery. In addition to different timing of drug delivery, CPR was started early in only one group and only one
group received propranolol. Thus, the differences between the groups may not be related to the timing of drug delivery.


LOE 5. Randomized and blinded swine study comparing combination pharmacotherapy and delayed countershock with standard ACLS. The study was not designed to address early vs delayed drug administration alone and the observed difference between early drug administration and delayed countershock compared to standard treatment, may be a drug effect.


LOE 5. Randomized, open, swine study not primarily assessing the work sheet assignment. Secondary finding of numerically higher frequency of ROSC in animals treated with high dose epinephrine at 8 minutes of VF compared to 11 minutes. The study was not powered to detect differences between the HD-8 and HD-11 groups.


LOE 5. Retrospective study of swine cardiac arrest. Logarithmic analysis of time to first drug and treatment group were predictors for ROSC. There was a 50% likelihood of ROSC when the drug cocktail was administered after 14.1 minutes of CPR. The likelihood of ROSC declined when drug administration was delayed.


LOE 5. Random comparison of coronary perfusion pressure (CPP) after early (4 min) and delayed (12 min) administration of epinephrine and vasopressin in a swine model of cardiac arrest and resuscitation. CPP was lower in the groups with delayed drug administration compared to early administration, 66% and 35 % of the CPP achieved with early administration for vasopressin and epinephrine, respectively.