Clinical question.
In adult patients with ROSC after cardiac arrest (prehospital or in-hospital) (P), does the use of a specific strategy to manage blood glucose (eg. Target range) (I) as opposed to standard care (C), improve outcome (O) (eg survival)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention
State if this is a proposed new topic or revision of existing worksheet: Revision of existing worksheet

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).
PubMed, Cochrane, EMBase and AHA databases for MeSH keywords:
Cardiac arrest OR cardiopulmonary resuscitation OR heart arrest OR Ventricular Fibrillation AND Glucose
I also reviewed the references from the articles selected for review.

State inclusion and exclusion criteria
excluded studies involving:
1- Animal data
2- Studies lacking outcome data or intervention.
3- Letters to the editor, case reports, reviews of the literature or commentary articles.
4- Non-cardiac arrest studies (generally transplant literature evaluating solutions for organ preservation)
5- Pediatric data

<table>
<thead>
<tr>
<th>Table of Results by Research Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPR and Glucose (N=17)</td>
</tr>
<tr>
<td>Relevant</td>
</tr>
<tr>
<td>Non-human</td>
</tr>
<tr>
<td>Case report, LTE, Commentary</td>
</tr>
<tr>
<td>No outcomes/ No intervention</td>
</tr>
<tr>
<td>Not arrest</td>
</tr>
</tbody>
</table>

Number of articles/sources meeting criteria for further review:
299
5 met all criteria from the review
Additional 12 found by review of references in documents.
All 18 are reviewed in this document
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good</strong></td>
<td></td>
<td></td>
<td></td>
<td>van den Berghe 2001, p 1359 C</td>
<td></td>
</tr>
<tr>
<td><strong>Poor</strong></td>
<td></td>
<td></td>
<td>Mullner, 1997</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A = Return of spontaneous circulation  C = Survival to hospital discharge  E = Other endpoint  
B = Survival of event  D = Intact neurological survival  Italics = Animal studies
## Evidence Neutral to Clinical question

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Steingrub, 1996</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</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>NICE SUGAR 2009</th>
<th>Krinsley, 2007</th>
<th>Arabi, 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Optimal glucose level or interventional strategy to manage blood glucose during the post-cardiac arrest period has not been defined in the current literature.

Steingrub (1996) observed that an elevated initial blood glucose following either out-of-hospital or in-hospital cardiac arrest was associated with a worse outcome in patients with CPR lasting more than 5 minutes. A worse outcome was defined as a Cerebral Performance Category of 3-5.

Mullner (1997) observed that elevated blood glucose levels both initially and for the first 24 hours following either in or out-of-hospital cardiac arrest were associated with worse outcomes, defined as a Cerebral Performance Category of 3-5. This study was limited to ventricular fibrillation cardiac arrest victims.

Skrifvars (2003) observed that 6 month mortality increased with 72 hour mean blood glucose levels in a group of 98 witnessed ventricular fibrillation arrest victims. (Table)

<table>
<thead>
<tr>
<th>Mean blood glucose (mmol/L)</th>
<th>Number of patients</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.8-6.8</td>
<td>22</td>
<td>9%</td>
</tr>
<tr>
<td>6.9-7.9</td>
<td>22</td>
<td>23%</td>
</tr>
<tr>
<td>7.9-8.9</td>
<td>22</td>
<td>50%</td>
</tr>
<tr>
<td>9.1-27.9</td>
<td>22</td>
<td>64%</td>
</tr>
</tbody>
</table>

The initial survival model demonstrated that age, delay to return of spontaneous circulation, mean blood glucose, serum potassium and use of beta-blocking agents during post-resuscitation care were associated with survival. However, when patients with a do-not-resuscitate order were removed from the model, only mean blood glucose, potassium, and the use of beta-blocking agents were associated with survival. Some of the patients in this study received hypothermia as part of the HACA trial, but their results are not specifically reported.

Langhelle (2003) noted an odds ratio of 2.67 (95% CI 1.17-6.20) for survival in 459 patients with blood glucose levels <10.6 mmol/L. Fever was prevented, but therapeutic hypothermia was not delivered in these patients.

Losert (2007) performed a retrospective analysis from the HACA dataset. As part of the HACA protocol, patients with blood glucose levels >200mg/dL had an insulin infusion initiated as part of their care. The 12 hour blood glucose levels were separated into quartiles. In a multivariate analysis, they demonstrated an odds ratio of 4.55 (95% CI 1.28-16.12) for patients with blood glucose levels between 67-115mg/dL and an odds ratio of 13.02 (95% CI 3.29-49.90) for patients with 12 hour glucose levels of 116-143mg/dL. Glucose levels of 150-175mg/dL had an odds ratio of 1.37 (95% CI 0.38-5.64). The highest quartile of 207-292mg/dL was used as the reference group. The percentage of patients receiving therapeutic hypothermia was not different between these quartiles.

Oksanen (2007) randomized out-of-hospital ventricular fibrillation patients to strict glycemic control (glucose 72-108mg/dL) or moderate glycemic control (108-144mg/dL). Patients received therapeutic hypothermia and insulin infusions were guided by the bedside ICU nurse. The moderate glycemic control group tended to have glucose levels lower than targeted. Survival was similar in both groups (67% in strict glycemic control; 65% in moderate glycemic control). The study was stopped at the first interim analysis. Hypoglycemic episodes were more common in the strict glycemic group (7 v. 1, p<0.01).

The largest trials in the literature on glycemic control in critically ill patients come from van den Berghe and NICE-SUGAR. The work by van den Berghe (2001) in surgical patients suggested a mortality benefit in those patients with tight glucose control at a level of 4.4-6.1 mmol/L. However, subsequent trials by van den Berghe (2006), Arabi (2008), Preiser (2009), and Brunhorst (2008) failed to demonstrate a survival benefit of strict glucose control compared to norglycemic controls. In fact, the NICE-SUGAR trial found that intensive glucose control increased mortality (OR 1.14; 95% CI 1.02-1.28; p=0.02) when compared to normoglycemia. Many trials have demonstrated that intensive glycemic control has been associated with more frequent episodes of hypoglycemia (van den Berghe, 2001; van den Berghe, 2006; Oksanen, 2007; Arabi, 2008; Brunhorst, 2008; NICE-SUGAR 2009; Preiser, 2009). Hypoglycemia (blood glucose <2.2 mmol/L) has been associated with worse outcomes in several trials. (Krinsley, 2007; Arabi, 2009). This risk is not desirable during the post-cardiac arrest period.

Acknowledgements: Maureen Morgan for bibliographic work.
Citation List


LOE 5 (not target population, but RCT; no post arrest patients in study)


LOE 4 (observational). No comment on industry funding.


LOE 4 (observational). Funded by the Laerdal Foundation for Acute Medicine.


LOE 4 (no controls, correct population)


LOE 4 (observational). No industry funding.


LOE 4 (observational). No comment on industry funding.


LOE 1 (Randomized, controlled trial). Partial funding from Laerdal Foundation for Acute Medicine.


LOE 5 (not specific to ca patients, RCT, no report on post-ca patients)

LOE 5 (not post-ca patients, RCT)


LOE 5 (not post-ca patients, RCT)


LOE 5 (not post-ca patients, analysis of trials)


LOE 5 (not post-ca patients, analysis of RCT’s)


LOE 5 (not post-ca patients, RCT)


LOE 4 (observational). No comment on industry funding.


LOE 4 (post-ca patients, no controls, retrospective, no intervention studied)


LOE 5 (No post-ca patients, RCT)


LOE 5 (not post-ca patients, not randomized controls)

LOE 5 (not post-ca patients, nested cohort of patients)