The Circulation Improving Resuscitation Care Trial (CIRC)

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Representing the CIRC Investigators
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Conflict of Interest

- Dr. Herken employed by ZOLL Medical Corp.
- Trial funded by ZOLL
  - ZOLL and Principal Investigator developed the trial protocol with
    - Site Investigators
    - Staff at Data Coordinating Center
    - Statistical consultants
- Investigators’ institutions received funding from ZOLL
AutoPulse/LDB Research

• Shown to improve hemodynamics*
• Pre-hospital survival studies conflict
  – 3 retrospective studies found improved outcome ‡
  – 1 RCT (ASPIRE) stopped early#
    • No difference in 4 hour survival
    • Cerebral performance worse at discharge

*Ikeno F 2006; Duchateau FX 2010; Timerman 2004; Halperin 2004
‡Casner 2005; Ong 2006; Krep 2007;
#Hallstrom 2006
CIRC Trial Objectives

• Compare iA-CPR vs. M-CPR
  – Primary endpoint:
    • Survival to hospital discharge
  – Secondary endpoints:
    • ROSC to ED
    • 24 hour survival
  – Neurologic endpoint:
    • mRS score
Setting

The Fox Valley Region, WI
Vienna, Austria
Houston, TX
Nijmegen, The Netherlands
Hillsborough County, FL
High Quality CPR

• 4 hour standardized initial training
  – Pit Crew deployment strategy
  – Maximize CPR fraction
• Regular refresher training
Monitor CPR Quality

- CPR process monitored throughout trial
  - Accelerometer data
  - Transthoracic impedance data
- Reported to providers in aggregate
Trial Phases

• Three distinct study phases

- In-Field Phase
  Deployment and usage of the AutoPulse for every OHCA

- Run-In Phase
  Randomization and adherence to full study protocol for each OHCA

- Statistical Inclusion
  Randomization and adherence to full study protocol for each OHCA – Data included in analysis

*Transition based on predefined measures of protocol compliance according to monitoring of the CPR process
Randomization Procedure

- Confirm cardiac arrest
- Verify need for CPR
- Start manual compressions
- Determine trial eligibility
- Open randomization envelope
- Treat per randomization card
Subject Exclusion

- Known or apparent pregnancy
- Do Not Resuscitate orders
- Too big for the AutoPulse
- Prisoner or ward of the state
- Prior application of a mechanical chest compression device
- Randomizing EMS unit arrived >16 minutes after emergency call
Data Analysis

• Group Sequential Double Triangular Test

• Powered to determine superiority, inferiority, or equivalence
  – Two-sided significance level 5%
  – Power 97.5%

• Equivalence defined as OR 95%
  CI fully between 0.69 and 1.44
# General Characteristics by Arm

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>M-CPR n=2123</th>
<th>iA-CPR n=2099</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.6 ±16.0</td>
<td>65.7±16.4</td>
</tr>
<tr>
<td>Male gender</td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td>Public location of OHCA</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Bystander witnessed</td>
<td>37%</td>
<td>37%</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>49%</td>
<td>47%</td>
</tr>
<tr>
<td>Shockable initial rhythm</td>
<td>24%</td>
<td>21%</td>
</tr>
<tr>
<td>Response interval [min]</td>
<td>6.6 ± 3.0</td>
<td>6.7 ± 2.9</td>
</tr>
<tr>
<td>Prehospital epinephrine</td>
<td>91%</td>
<td>93%</td>
</tr>
<tr>
<td>Hospital hypothermia</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>PTCA/ PCI</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Time from arrival to termination/transport [min]</td>
<td>36.1 ± 14.1</td>
<td>37.3 ± 14.3</td>
</tr>
<tr>
<td>Initial rhythm VF/ VT average time from defib on to first shock [min]</td>
<td>3.5 ± 4.0</td>
<td>4.6 ± 4.8</td>
</tr>
<tr>
<td>Time from defib on to first recorded compression(s)</td>
<td>61 ± 127</td>
<td>65 ± 139</td>
</tr>
<tr>
<td></td>
<td>M-CPR (n=2,024)</td>
<td>iA-CPR (n=2,017)</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>CPR fraction</strong> (mean ± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 10 minutes</td>
<td>79.7% ± 10.1%</td>
<td>78.5% ± 9.4%</td>
</tr>
<tr>
<td>at 20 minutes</td>
<td>80.2 ± 9.1%</td>
<td>80.4% ± 8.3%</td>
</tr>
<tr>
<td><strong>Avg compressions per min</strong></td>
<td>89.2 ± 17.4</td>
<td>66.3 ± 10.7</td>
</tr>
<tr>
<td>(first 10 minutes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Avg ventilations per min</strong></td>
<td>8.8 ± 4.7</td>
<td>6.8 ± 3.4</td>
</tr>
<tr>
<td>(first 10 minutes)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Electronic Data available for 96% of study subjects*
Results: Primary Endpoint

• Equivalent survival to hospital discharge
  – OR 1.06, 95% CI 0.83 - 1.37
    • Adjusted for covariates (age, witnessed arrest, initial cardiac rhythm, and enrollment site) and interim analyses
    • Within pre-defined equivalence region (0.69 - 1.44)
  – Non-inferiority test iA-CPR vs. M-CPR p=0.0003
  – Non-inferiority test M-CPR vs. iA-CPR p=0.008
## Results: Effectiveness Endpoints

<table>
<thead>
<tr>
<th></th>
<th>M-CPR (2132)</th>
<th>iA-CPR (2099)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Partially Adjusted OR (95% CI)</th>
<th>Fully Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival to Hospital Discharge</strong></td>
<td>11.0%</td>
<td>9.4%</td>
<td>0.84 (0.69 – 1.02)</td>
<td>0.89 (0.72 – 1.10)</td>
<td>1.06 (0.83 - 1.37)</td>
</tr>
<tr>
<td><strong>Survival to 24h</strong></td>
<td>25.1%</td>
<td>21.8%</td>
<td>0.84 (0.72 – 0.96)</td>
<td>0.86 (0.74-0.998)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Sustained ROSC</strong></td>
<td>32.3%</td>
<td>28.6%</td>
<td>0.84 (0.74 – 0.96)</td>
<td>0.84 (0.73-0.96)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Results: Neurologic Endpoint

- No difference in mRS scores ≤3
  -Adjusted OR 0.80, 95% CI 0.47 - 1.37 (n.s.)

<table>
<thead>
<tr>
<th>Discharge mRS</th>
<th>M-CPR (n=233)</th>
<th>iA-CPR (n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score of 0 -3</td>
<td>48.1%</td>
<td>44.4%</td>
</tr>
<tr>
<td>Score of 4 -5</td>
<td>26.2%</td>
<td>25.5%</td>
</tr>
<tr>
<td>Unknown score</td>
<td>25.8%</td>
<td>30.1%</td>
</tr>
</tbody>
</table>
Highest CPR Fraction Reported

CPR Fraction for Manual Compressions Reported in Prospective, Multi-Center Data Sets (> 500 patients)

- Christenson 2009: 54.0%
- Cheskes 2011: 63.0%
- Stiell 2011 Control Arm (5 min): 66.0%
- Stiell 2011 Experimental Arm (5 min): 71.0%
- Vaillancourt 2011 (5 min): 71.0%
- CIRC 2011 Manual arm (20 min): 80.2%
Subgroup Analysis

- Witnessed VF/VT Arrests
- Survival higher for iA-CPR if CPR fraction <78%
- No survival difference with higher CPR fractions.
- Example: CPR fraction 70% OR 3.4, 95% CI: 2–7.4
Discussion

- **Equivalence**
  - Powered to show true statistical equivalence
  - At least as good as high-quality M-CPR
- **iA-CPR may solve practical problems**
  - CPR in confined spaces
  - CPR with limited number of rescuers
  - CPR during transport
    - Rescuer safety
    - Compression efficacy
Discussion

• CPR fraction
  – ~80% CPR Fraction in both arms
    • Higher than most CPR fractions reported for other large RCTs.
  – High CPR fraction hard to achieve and maintain
  – Secondary analysis: at typical “clinical” CPR fractions iA-CPR better than M-CPR
Conclusions

• CPR quality good in both arms
• It is possible to achieve high-quality manual CPR
• Compared to high-quality M-CPR:
  – iA-CPR statistically equivalent survival to hospital discharge
  – No difference in neurologic status at discharge
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