Survival after IV/IO Amiodarone, Lidocaine or Placebo in Out-of-Hospital VF Cardiac Arrest

Resuscitation Outcomes Consortium Investigators

![Map of participating cities](image)

**a pre-specified analysis of**

... a prospective, randomized, multicenter trial comparing effects of amiodarone and lidocaine vs placebo on survival in shock-refractory OHCA

when given IV vs IO

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The Resuscitation Outcomes Consortium Investigators
Background
Out-of-Hospital Cardiac Arrest

• 400,000 out-of-hospital cardiac arrests/yr
• >100,000 caused by shockable rhythms (VF/VT)
• Most VF/VT episodes “shock-refractory” → drug therapy
• Optimal route drug administration in cardiac arrest?

Background
IO vs IV Vascular Access

Part 7.2: Management of Cardiac Arrest

“If access has not been established, the provider should insert a large peripheral venous catheter…”

*AHA Circulation 2005;112:IV-58.*

- Peripheral IV insertion heavily patient/operator dependent\(^1\)
- Variable success (18-98%)
- May require multiple attempts (30-50%)

Background
IO vs IV Vascular Access

Part 7.2: Management of Cardiac Arrest

“Intraosseous (IO) cannulation provides access to a non-collapsible venous plexus, enabling drug delivery … and is attainable in all age groups. Providers may establish IO access if IV access is unavailable (Class IIa).”


• Success of tibial IO (91%) exceeds peripheral IV (32%)¹
• IO access achieved faster than IV (1.5 min vs 3.6 min)²

Growing use of IO for primary access by EMS

Background

IO vs IV Clinical Effectiveness

“…route of vascular access may have differential physiological & clinical effects.”

“…IO access associated with lower survival & poor neurological recovery.”

Main Aim

Determine the effectiveness of amiodarone, lidocaine or placebo . . . given IV vs IO . . .

. . . on survival to hospital discharge after out-of-hospital cardiac arrest caused by shock-refractory VF/VT
Hypothesis

- A priori hypothesis
  - Effects of amiodarone and lidocaine attenuated by route of administration
  - Survival benefit from antiarrhythmic drugs most evident when given IV, not IO
Methods

Pre-specified analysis of RCT (ALPS) under EFIC

Patients

• Adults, non-traumatic out-of-hospital cardiac arrest
• Shock-refractory VF/VT after ≥ 1 shock(s)
• Known type of vascular access

Exclusion

• Protected populations (including opt-out)
• Amiodarone or lidocaine allergy
• Open label IV amiodarone or lidocaine
Study Outcomes

- **Primary - survival to hospital discharge**
- **Secondary**
  - Admission alive to hospital
  - Survival with favorable neurological status at discharge (modified Rankin scale ≤ 3)
- **Outcomes adjusted for …**
  - Age, gender, arrest location, witnessed status, bystander CPR, study site, **time** to … arrival ALS … receipt of study drug
**Results**

**Patient Screening, Stratification & Randomization**

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>No shock-refractory VF/VT</td>
<td>30,487</td>
</tr>
<tr>
<td>Initial rhythm not VF/VT</td>
<td>1,063</td>
</tr>
<tr>
<td>VF/VT terminated by 1 shock</td>
<td>1,318</td>
</tr>
<tr>
<td>Lost eligibility</td>
<td>270</td>
</tr>
<tr>
<td>Forgot study protocol</td>
<td>602</td>
</tr>
<tr>
<td>Study drug not given</td>
<td>257</td>
</tr>
<tr>
<td>Circumstantial issues</td>
<td>425</td>
</tr>
<tr>
<td>No vascular access</td>
<td>187</td>
</tr>
<tr>
<td>Prior IV amiodarone/lidocaine</td>
<td>75</td>
</tr>
<tr>
<td>Protected population</td>
<td>46</td>
</tr>
<tr>
<td>Advance directive</td>
<td>19</td>
</tr>
<tr>
<td>No advanced life support</td>
<td>19</td>
</tr>
<tr>
<td>Other ineligible</td>
<td>51</td>
</tr>
<tr>
<td>Other</td>
<td>44</td>
</tr>
</tbody>
</table>

**Analysis Population**

- **Total**: 3,026
- **Vascular access + study drug-eligible**: 3,026

**Drug Routes**

- **IV Drug Route**: 2,358 (78%)
  - 1,989 (84%) arm
  - 77 (3%) central
  - 10 (0.5%) leg
  - 190 (8%) unknown

- **IO Drug Route**: 661 (22%)
  - 614 (93%) tibial
  - 11 (2%) humeral
  - 36 (5%) unknown

**Drug Administration**

- **Amiodarone**
  - Total: 974 (32%)
  - IV: 762 (78%)
  - IO: 212 (33%)

- **Lidocaine**
  - Total: 993 (33%)
  - IV: 771 (33%)
  - IO: 220 (33%)

- **Placebo**
  - Total: 1,059 (35%)
  - IV: 825 (35%)
  - IO: 229 (35%)
IV vs IO Drug Administration by Study Site

At half of study sites ≥75% of established access was IV

Half of study sites contributed 89% of patients with IO access
## Pre-randomization Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>IV Route (n=2358)</th>
<th>IO Route (n=661)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) years</td>
<td>62.7 (14.3)</td>
<td>62.3 (14.4)</td>
<td>-</td>
</tr>
<tr>
<td>Male, %</td>
<td>82.1%</td>
<td>72.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Public location, %</td>
<td>31.4%</td>
<td>28.4%</td>
<td>-</td>
</tr>
<tr>
<td>Bystander witnessed, %</td>
<td>65.2%</td>
<td>62.4%</td>
<td>-</td>
</tr>
<tr>
<td>Bystander CPR, %</td>
<td>56.8%</td>
<td>58.1%</td>
<td>-</td>
</tr>
</tbody>
</table>
## Resuscitation Characteristics

<table>
<thead>
<tr>
<th></th>
<th>IV Route (n=2358)</th>
<th>IO Route (n=661)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression rate/min, mean (SD)</td>
<td>110 (10.9)</td>
<td>110 (11.3)</td>
<td>-</td>
</tr>
<tr>
<td>Compression depth mm, mean (SD)</td>
<td>51.7 (10.3)</td>
<td>49.7 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPR fraction %, mean (SD)</td>
<td>83% (10)</td>
<td>85% (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preshock pause secs, mean (SD)</td>
<td>10.3 (9.6)</td>
<td>9.8 (9.3)</td>
<td>-</td>
</tr>
<tr>
<td>Post-shock pause secs, mean (SD)</td>
<td>6.23 (32.4)</td>
<td>6.7 (37)</td>
<td>-</td>
</tr>
</tbody>
</table>
### Treatment Times

<table>
<thead>
<tr>
<th></th>
<th>IV Route (n=2358)</th>
<th>IO Route (n=661)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>911 Call to EMS arrival, min mean (SD)</td>
<td>5.8 (2.60)</td>
<td>5.4 (2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>911 to ALS arrival, min mean (SD)</td>
<td>8.3 (4.7)</td>
<td>6.8 (4.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>911 to IV/IO* min, mean (SD)</td>
<td>14.2 (5.6)</td>
<td>13.9 (5.8)</td>
<td>-</td>
</tr>
<tr>
<td>911 to Study Drug* min, mean (SD)</td>
<td>19.3 (7)</td>
<td>19.4 (7.3)</td>
<td>-</td>
</tr>
</tbody>
</table>

*non-EMS witnessed cardiac arrests
## Admission Alive to Hospital
### IV vs IO Drug Administration (n=3,019)

### Adjusted Absolute Difference (95% CI)*

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>IV (unadjusted %’s)</th>
<th>IO (unadjusted %’s)</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amiodarone vs Placebo</strong></td>
<td>48.6%</td>
<td>39.8%</td>
<td>9.1% (4.3, 13.8)</td>
</tr>
<tr>
<td><strong>Lidocaine vs Placebo</strong></td>
<td>48.2%</td>
<td>39.8%</td>
<td>9.4% (4.6, 14.2)</td>
</tr>
<tr>
<td><strong>Amiodarone vs Placebo</strong></td>
<td>35.4%</td>
<td>38.9%</td>
<td>-1.8% (-10.7, 7.1)</td>
</tr>
<tr>
<td><strong>Lidocaine vs Placebo</strong></td>
<td>43.2%</td>
<td>38.9%</td>
<td>7.4% (-1.5, 16.4)</td>
</tr>
</tbody>
</table>

*adjusted analysis confined to 2,860 patients with all known covariates
<table>
<thead>
<tr>
<th>Adverse Event within 24 hours</th>
<th>IV Route (n=2358)</th>
<th>IO Route (n=661)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IO complication, %</td>
<td>-</td>
<td>0.6%</td>
<td></td>
</tr>
<tr>
<td>Thrombophlebitis, %</td>
<td>0.3%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Cardiac pacing, %</td>
<td>3.6%</td>
<td>3.8%</td>
<td>-</td>
</tr>
<tr>
<td>Seizure, %</td>
<td>4.2%</td>
<td>3.2%</td>
<td>-</td>
</tr>
<tr>
<td>Anaphylaxis, %</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Any Adverse Event, %</td>
<td>7.8%</td>
<td>7.6%</td>
<td>-</td>
</tr>
<tr>
<td>Drug Comparison</td>
<td>IV (unadjusted %'s)</td>
<td>IO (unadjusted %'s)</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------</td>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Amiodarone vs Placebo</strong></td>
<td>25.9%  20.6%</td>
<td>19.3%  22.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Lidocaine vs Placebo</strong></td>
<td>24.6%  20.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted Absolute Difference (95% CI)*

- **IV**
  - Amiodarone vs Placebo: 5.5% (1.5, 9.5)
  - Lidocaine vs Placebo: 4.7% (0.7, 8.8)

- **IO**
  - Amiodarone vs Placebo: -1.8% (-9.2, 5.6)
  - Lidocaine vs Placebo: 0.3% (-7.4, 7.9)

*p for interaction = 0.23

*adjusted analysis confined to 2,860 patients with all known covariates
Favorable Functional Survival at Discharge (mRS ≤ 3) IV vs IO Drug Administration (n=3,019)

Adjusted Absolute Difference (95% CI)*

**IV** (unadjusted %’s)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Favorable Survival (%)</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone vs Placebo</td>
<td>20.1%</td>
<td>4.3% (0.6, 8)</td>
</tr>
<tr>
<td>Lidocaine vs Placebo</td>
<td>18.6%</td>
<td>2.9% (0.8, 6.6)</td>
</tr>
</tbody>
</table>

**IO** (unadjusted %’s)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Favorable Survival (%)</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone vs Placebo</td>
<td>14.2%</td>
<td>-1.5% (-8.1, 5.2)</td>
</tr>
<tr>
<td>Lidocaine vs Placebo</td>
<td>13.8%</td>
<td>-0.8% (-7.5, 5.8)</td>
</tr>
</tbody>
</table>

*p for interaction = 0.32

*adjusted analysis confined to 2,860 patients with all known covariates
Summary of Outcome Measures
IV Drug Administration (n=2,358)

Adjusted Absolute Difference (95% CI)*

**IV Drugs** (unadjusted %’s)

### Admission Alive to Hospital

- **Amiodarone vs Placebo**
  - 48.6% vs 39.8%
  - 9.1% (4.3, 13.8)

- **Lidocaine vs Placebo**
  - 48.2% vs 39.8%
  - 9.4% (4.6, 14.2)

### Discharged Alive

- **Amiodarone vs Placebo**
  - 25.9% vs 20.6%
  - 5.5% (1.5, 9.5)

- **Lidocaine vs Placebo**
  - 24.6% vs 20.6%
  - 4.7% (0.7, 8.8)

### mRS ≤ 3 at Discharge

- **Amiodarone vs Placebo**
  - 20.1% vs 16.6%
  - 4.3% (0.6, 8)

- **Lidocaine vs Placebo**
  - 18.6% vs 16.6%
  - 2.9% (0.8, 6.6)

*adjusted analysis confined to patients with all known covariates*
Summary of Outcome Measures
IV vs IO Drug Administration (n=661)

Adjusted Absolute Difference (95% CI)*

**IO Drugs** (unadjusted %’s)

**Admission Alive to Hospital**
- Amiodarone vs Placebo
  - 35.4% vs 38.9%
- Lidocaine vs Placebo
  - 43.2% vs 38.9%

**Discharged Alive**
- Amiodarone vs Placebo
  - 19.3% vs 22.5%
- Lidocaine vs Placebo
  - 20.6% vs 22.5%

**mRS ≤ 3 at Discharge**
- Amiodarone vs Placebo
  - 14.2% vs 16.3%
- Lidocaine vs Placebo
  - 13.8% vs 16.3%

*adjusted analysis confined to patients with all known covariates

p for interaction (IV vs IO)
- **p = 0.08**
  - Amiodarone vs Placebo: 35.4% vs 38.9%, difference: -1.8% (-10.7, 7.1)
  - Lidocaine vs Placebo: 43.2% vs 38.9%, difference: 7.4% (-1.5, 16.4)

- **p = 0.23**
  - Amiodarone vs Placebo: 19.3% vs 22.5%, difference: -1.8% (-9.2, 5.6)
  - Lidocaine vs Placebo: 20.6% vs 22.5%, difference: 0.3% (-7.4, 7.9)

- **p = 0.32**
  - Amiodarone vs Placebo: 14.2% vs 16.3%, difference: -1.5% (-8.1, 5.2)
  - Lidocaine vs Placebo: 13.8% vs 16.3%, difference: -0.8% (-7.5, 5.8)
Summary

Given IV, amiodarone and lidocaine vs placebo were associated with significantly higher . . .

- Hospital admission rate
- Survival to hospital discharge
- Favorable functional survival at hospital discharge

No obvious clinical benefit over placebo seen with IO-administered antiarrhythmics
Limitations

- Vascular access prespecified, but not randomized
- Hospital care not standardized
- Adjusted analysis may not fully correct for imbalances
- Proportion IO:IV recipients relatively small – underpowered to assess statistical interactions
- Did not address anatomic access site or mechanism(s)
Conclusions

• Amiodarone and lidocaine associated with improved clinical outcomes in cardiac arrest given IV but not IO
• Effectiveness of antiarrhythmic drugs in resuscitation may be dependent on route of vascular access
• Findings may explain inconclusive results of drug trials
• Role of IV vs IO drug administration during cardiac arrest merits prospective investigation