Comparative effectiveness of antiarrhythmics for out-of-hospital cardiac arrest
A systematic review and network meta-analysis

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Disclosure/Conflict of Interest

• Financial Disclosure: Zoll Medical Honorarium for Speaking on CPR Quality, Physio-Control sponsorship on CPR Quality
• AstraZeneca: Brilinta Advisory Board
• Unlabeled/Unapproved Uses Disclosure: None
• Conflicts of Interest: None

Traditional Meta-Analysis

• Is treatment A better than treatment B?
Traditional Meta-Analysis

- Is treatment A better than treatment B?

The Real Question...

- Which of the six treatments is the most effective?
- Is treatment B better than treatment F?

Network Meta-Analysis

- Which of the six treatments is the most effective?
- Is treatment B better than treatment C?
Network Meta-Analysis

- If you know the direct treatment effect from trials comparing A to B, and A to C, you can get an INDIRECT estimate of the treatment effect of B to C

Introduction

- There are ~400,000 out-of-hospital cardiac arrests (OHCA) each year in North America
- 20-25% are due to ventricular fibrillation or pulseless ventricular tachycardia (VF/VT)
- 1 in 5 survive to hospital discharge

Introduction

- Antiarrhythmic drugs (ie: amiodarone, lidocaine) used in hope of promoting the return of an organized rhythm and preventing relapses of VF/VT
- Despite their use, it remains unknown if antiarrhythmic agents impact survival following OHCA

Antiarrhythmics?
Research Question

Does the use of antiarrhythmic drugs improve the proportion of patients who survive following OHCA?

Inclusion Criteria

- **Study Design:** RCTs
- **Population:** Adult (≥ 18 years) patients suffering non-traumatic, OHCA
- **Intervention/Comparison:** Amiodarone, lidocaine, magnesium, sotalol, bretylium, and/or placebo
- **Outcomes:** ROSC, survival to hospital admission, survival to hospital discharge, and neurologically intact survival at hospital discharge (cerebral performance category score 1-2)

Search Strategy

- Electronic search of MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials
- 2 reviewers independently screened titles and abstracts to identify potentially eligible trials
  - Hand search of reference lists
  - Grey literature, clinicaltrials.gov
- No language restriction
Assessment of Risk of Bias

- Risk of bias independently assessed by two reviewers using a modified version of the Cochrane Collaboration’s tool
- Low, probably low, probably high, or high risk of bias
- Random-sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias
- Discrepancies resolved by consensus

Network Data Synthesis and Statistical Analysis

- Direct and indirect evidence were combined in a 6-node NMA
- Frequentist approach with fixed-effects models
- All network meta-analyses were performed using the package netmeta in R, v 3.3.1
- Network plots derived using the package mvmeta in Stata, v 14.1

Flow Diagram of Included Studies
“Table” of Included Studies

- 8 RCTs
- 6 treatments
- 4,464 patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>N</th>
<th>Treatment(s)</th>
<th>Placebo</th>
<th>MgSO₄</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>Allegra 2001</td>
<td>USA</td>
<td>116</td>
<td>Bretylium = 58</td>
<td>Placebo</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Dorian 2002</td>
<td>Canada</td>
<td>86</td>
<td>Amiodarone = 46</td>
<td>Placebo</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Hassan 2002</td>
<td>England</td>
<td>105</td>
<td>MgSO₄ = 52</td>
<td>Placebo</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Olson 1984</td>
<td>USA</td>
<td>91</td>
<td>Bretylium = 43</td>
<td>Placebo</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Kudenchuk 1999</td>
<td>USA</td>
<td>504</td>
<td>Amiodarone = 246</td>
<td>Placebo</td>
<td>258</td>
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<tr>
<td>Kudenchuk 2010</td>
<td>US/Canada</td>
<td>512</td>
<td>Amiodarone = 894</td>
<td>Placebo</td>
<td>538</td>
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<tr>
<td>Hassan 2002</td>
<td>England</td>
<td>105</td>
<td>MgSO₄ = 53</td>
<td>Placebo</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Kavoor 2005</td>
<td>Australia</td>
<td>129</td>
<td>Sotalol = 60</td>
<td>Placebo</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Haynes 1981</td>
<td>USA</td>
<td>146</td>
<td>Bretylium = 74</td>
<td>Placebo</td>
<td>72</td>
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</tr>
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<td>Olson 1984</td>
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<td>91</td>
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<td>48</td>
<td></td>
</tr>
</tbody>
</table>

Risk of Bias for Included Studies

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other bias

Evidence Network

- 5 RCTs; 1349 pts
- 2 RCTs; 117 pts
- 3 RCTs; 1400 pts
- 1 RCT; 60 pts
- 2 RCT; 150 pts
- 2 RCT; 140 pts
- 5 RCTs; 1428 pts
- 5 RCTs; 1428 pts
- 2 RCT; 60 pts
- 5 RCTs; 1428 pts
### ROSC and Survival to Hospital Admission

<table>
<thead>
<tr>
<th>Drug</th>
<th>ROSC Effect</th>
<th>95% CI</th>
<th>Survival to Hospital Admission</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>0.98</td>
<td>(0.74 to 1.33)</td>
<td>1.00</td>
<td>(0.91 to 1.09)</td>
</tr>
<tr>
<td>Bretylium</td>
<td>0.82</td>
<td>(0.51 to 1.32)</td>
<td>1.03</td>
<td>(0.80 to 1.32)</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>0.81</td>
<td>(0.10 to 1.30)</td>
<td>0.62</td>
<td>(0.38 to 1.00)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.81</td>
<td>(0.44 to 1.52)</td>
<td>1.13</td>
<td>(0.95 to 1.36)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.06</td>
<td>(0.96 to 1.18)</td>
<td>1.29</td>
<td>(0.49 to 4.02)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>0.90</td>
<td>(0.50 to 1.60)</td>
<td>0.81</td>
<td>(0.44 to 1.52)</td>
</tr>
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</table>

### Survival to Hospital Discharge

<table>
<thead>
<tr>
<th>Drug</th>
<th>ROSC Effect</th>
<th>95% CI</th>
<th>Survival to Hospital Discharge</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>0.81</td>
<td>(0.89 to 1.2)</td>
<td>0.56</td>
<td>(0.89 to 1.24)</td>
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<tr>
<td>Bretylium</td>
<td>0.81</td>
<td>(0.14 to 1.57)</td>
<td>0.81</td>
<td>(0.40 to 1.68)</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>0.81</td>
<td>(0.99 to 1.03)</td>
<td>0.81</td>
<td>(0.40 to 1.68)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.81</td>
<td>(0.19 to 3.84)</td>
<td>0.81</td>
<td>(0.40 to 1.68)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.06</td>
<td>(0.98 to 1.15)</td>
<td>1.29</td>
<td>(0.49 to 4.02)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>0.90</td>
<td>(0.50 to 1.60)</td>
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### 3-Phase Time-Sensitive Model of Cardiac Resuscitation

- Are the drugs being given too late?
- Median time from EMS call to drug administration ~23 min

- **Electrical Phase** 0-4 min
  - Early and rapid defibrillation is the most important intervention
  - Greatest possibility of ROSC

- **Circulatory Phase** 4-10 min
  - Increasing importance of high quality CPR and medications

- **Metabolic Phase** >10 min
  - Reperfusion injury, inflammatory cascade
  - Poor overall survival regardless of treatment

*Weisfeldt ML, JAMA 2002*
Possible Explanations

Cumulative burden of chronic health conditions?
- Patients with comorbidities (CHF, renal disease, liver disease) may respond to antiarrhythmics differently
- Medications (β-blockers, calcium channel blockers, diuretics) used to treat chronic conditions may limit the efficacy of antiarrhythmic agents

• These possible effect modifiers have not been adequately controlled for in any of the RCTs to date

Possible Explanations

• Is survival to hospital discharge an appropriate outcome?
• Given in the prehospital setting to terminate VF/VT, restore and stabilize an organized rhythm, promote ROSC
• Perhaps their role in the chain of survival is just to improve the likelihood of admission to hospital

Strengths

• Explicit eligibility criteria, comprehensive search, duplicate assessment of eligibility
• Incorporates the latest developments in NMA statistical analysis
• Applied the recently developed GRADE approach to NMA
  – assessment of transitivity assumptions for indirect evidence
  – assessed coherence for combining direct and indirect evidence
Limitations

- Substantial variability in:
  - CPR and defibrillation protocols
  - Differences in post-resuscitation hospital care (TTM, PCI)
- Unable to account for improvements in system care such as EMS response time, rates of bystander CPR, use of public access defibrillation
  - not able to assess their possible influence on treatment effect
- Indirect comparisons yielded only low or very low quality evidence

Conclusions

- No antiarrhythmic was superior to any other
- Compared to placebo, amiodarone and lidocaine were associated with improved survival to hospital admission
- For the outcomes most important to patients, survival to hospital discharge and neurologically intact survival, no antiarrhythmic was convincingly superior to any other agent or placebo

For Detailed review

Clinical trial
Comparative effectiveness of antiarrhythmics for out-of-hospital cardiac arrest: a systematic review and network meta-analysis
Shabab A. Al-Madani, Shilpa Prasad, Peter C. K. Chan, Andrew Tse, Ben Miller, Julia Wood, Nikole Blom, Gordon Gopinath, Shubhankar Choudhury
Thank You

Shelley McLeod
Lead Investigator

Andrew Worster
Co-Investigator

Gordon Guyatt
Co-Investigator

Romina Brignardello-Petersen
Co-Investigator

Alla Ianashchena
Co-Investigator

John You
Co-Investigator

Questions, Comments, Suggestions?

[Images of question marks, gears, a light bulb, and an exclamation mark]

[Images of smiling faces]