

UNIVERSITY OF TORONTO | McMaster University | Mount Sinai Hospital | Sunnybrook Health Sciences Centre | London Health Sciences Centre

## Comparative effectiveness of antiarrhythmics for out-of-hospital cardiac arrest

### A systematic review and network meta-analysis

Dr. Sheldon Cheskes  
January 11, 2018

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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

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### Traditional Meta-Analysis

- Is treatment A better than treatment B?



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### Traditional Meta-Analysis

- Is treatment A better than treatment B?

```
graph LR; A --- B; D; C; E; F;
```

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### The Real Question...

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

```
graph LR; A --- B; D; C; E; F;
```

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### Network Meta-Analysis

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

```
graph LR; A --- B; A --- D; A --- C; B --- E; B --- F; E --- F; D; C; F;
```

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### 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

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### 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

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### 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?**

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### Research Question

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



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### 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)

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### 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



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### 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

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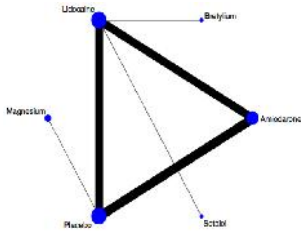
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### Network Data Synthesis and Statistical Analysis

- 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




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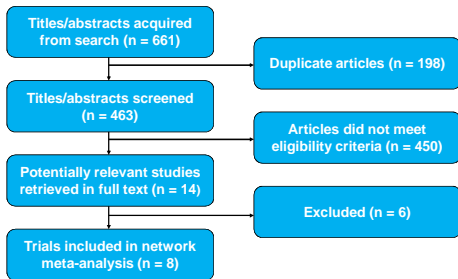
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### Flow Diagram of Included Studies




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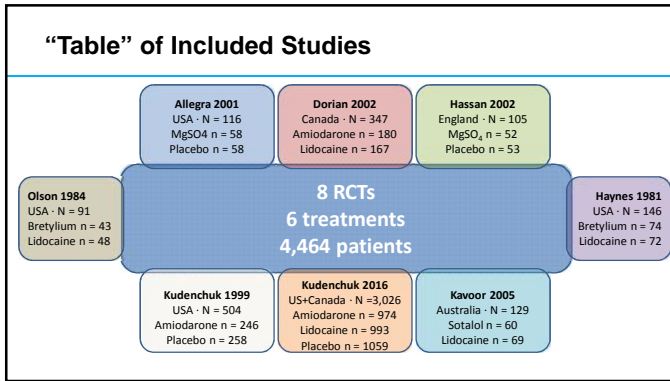
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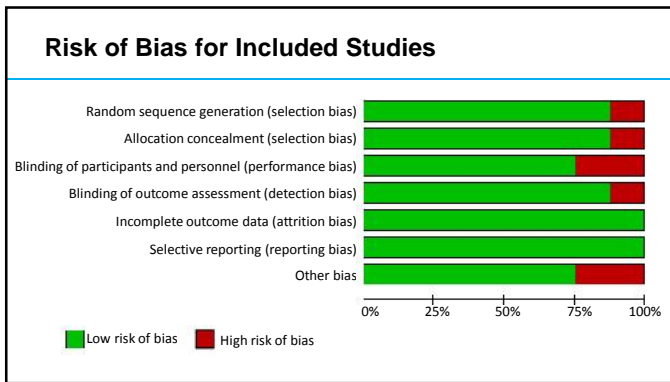
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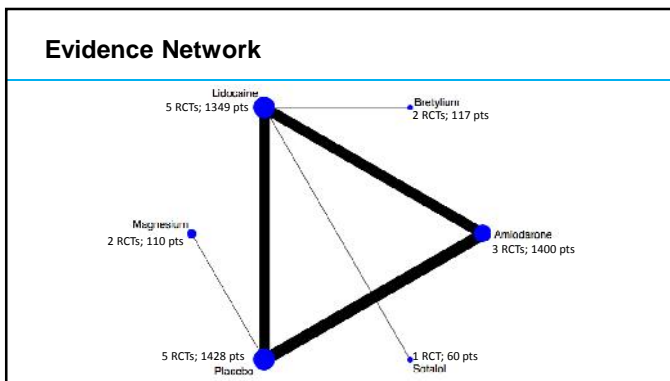
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### ROSC and Survival to Hospital Admission

		Survival to Hospital Admission					
		Amiodarone	Bretlyium	Lidocaine	Magnesium	Placebo	Sotalol
ROSC	Amiodarone	-----	0.98 (0.74 to 1.28) VERY LOW	1.00 (0.91 to 1.10) LOW	1.06 (0.56 to 1.97) VERY LOW	1.18 (1.08 to 1.30) HIGH	1.67 (0.90 to 3.08) VERY LOW
	Bretlyium	1.49 (0.91 to 2.43) VERY LOW	-----	1.03 (0.80 to 1.32) LOW	1.08 (0.55 to 2.13) VERY LOW	1.21 (0.92 to 1.59) VERY LOW	1.71 (0.89 to 3.30) VERY LOW
	Lidocaine	0.92 (0.83 to 1.03) LOW	0.62 (0.38 to 1.00) MOD	-----	1.05 (0.56 to 1.97) VERY LOW	1.18 (1.07 to 1.30) HIGH	1.67 (0.91 to 3.06) LOW
	Magnesium	0.81 (0.44 to 1.47) VERY LOW	0.54 (0.25 to 1.17) VERY LOW	0.87 (0.48 to 1.59) VERY LOW	-----	1.12 (0.60 to 2.08) LOW	1.58 (0.66 to 3.78) VERY LOW
	Placebo	1.06 (0.95 to 1.18) MOD	0.71 (0.43 to 1.16) VERY LOW	1.15 (1.03 to 1.28) HIGH	1.31 (0.73 to 2.36) LOW	-----	1.41 (0.76 to 2.61) VERY LOW
	Sotalol	1.13 (0.78 to 1.63) VERY LOW	0.76 (0.42 to 1.37) VERY LOW	1.22 (0.86 to 1.74) LOW	1.40 (0.70 to 2.80) VERY LOW	1.07 (0.74 to 1.54) VERY LOW	-----

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### Survival to Hospital Discharge

		Neurologically Intact Survival					
		Amiodarone	Bretlyium	Lidocaine	Magnesium	Placebo	Sotalol
Survival to Hospital Discharge	Amiodarone	-----	-----	1.08 (0.89 to 1.30) MOD	0.49 (0.07 to 3.28) VERY LOW	1.13 (0.95 to 1.36) MOD	8.43 (0.46 to 154.32) VERY LOW
	Bretlyium	0.89 (0.54 to 1.47) VERY LOW	-----	-----	-----	-----	-----
	Lidocaine	1.04 (0.89 to 1.21) MOD	1.16 (0.72 to 1.88) LOW	-----	0.45 (0.07 to 3.06) VERY LOW	1.05 (0.87 to 1.27) MOD	7.83 (0.43 to 142.58) LOW
	Magnesium	0.86 (0.19 to 3.84) VERY LOW	0.96 (0.20 to 4.66) VERY LOW	0.83 (0.18 to 3.72) VERY LOW	-----	2.33 (0.35 to 15.54) LOW	17.30 (0.54 to 557.82) VERY LOW
	Placebo	1.15 (0.99 to 1.34) MOD	1.29 (0.78 to 2.14) VERY LOW	1.11 (0.95 to 1.30) MOD	1.34 (0.30 to 5.97) LOW	-----	7.44 (0.41 to 136.26) VERY LOW
	Sotalol	2.10 (0.56 to 7.84) VERY LOW	2.36 (0.59 to 9.50) VERY LOW	2.03 (0.55 to 7.50) LOW	2.45 (0.33 to 17.97) VERY LOW	1.83 (0.49 to 6.82) VERY LOW	-----

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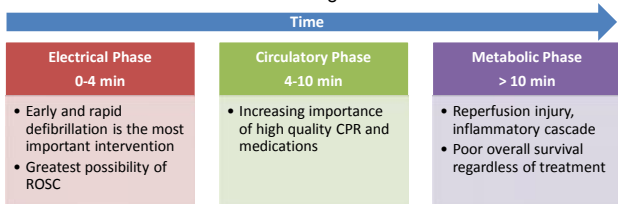
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### 3-Phase Time-Sensitive Model of Cardiac Resuscitation

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



Weisfeldt ML, JAMA 2002

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**Possible Explanations**

**Cumulative burden of chronic health conditions?**

- Patients with comorbidities (CHF, renal disease, liver disease) may respond to antiarrhythmics differently
- Medications ( -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

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**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




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**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




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### 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

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### 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

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### For Detailed review


Resuscitation 127 (2018) 18–27

Contents lists available at ScienceDirect



## Resuscitation


Journal homepage: [www.elsevier.com/locate/resuscitation](http://www.elsevier.com/locate/resuscitation)



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Clinical paper

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



Shelley L. McLeod<sup>a,b,c,d</sup>, Romina Brignardello-Peterson<sup>e</sup>, Andrew Worster<sup>a,d</sup>, John You<sup>a,d</sup>, Alia Iansavichene<sup>a</sup>, Gordha Guyatt<sup>a,d</sup>, Sheido J. Chaskas<sup>a,b</sup>

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### Thank You



**Shelley McLeod**  
Lead-Investigator



**Gordon Guyatt**  
Co-Investigator



**Romina Brignardello-Petersen**  
Co-Investigator



**Andrew Worster**  
Co-Investigator



**Alla Iansavichene**  
Co-Investigator



**John You**  
Co-Investigator

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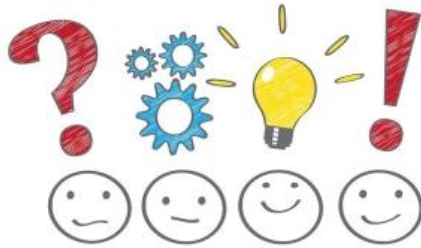
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### Questions, Comments, Suggestions?



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