Resuscitation 121 (2017) 90–97

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

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

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ARTICLE INFO

*Article history:*
Received 3 August 2017
Received in revised form 4 October 2017
Accepted 13 October 2017

*Keywords:*
Network meta-analysis
Antiarrhythmics
Out-of-hospital cardiac arrest
Prehospital

ABSTRACT

*Background:* Despite their wide use in the prehospital setting, randomized control trials (RCTs) have failed to demonstrate that any antiarrhythmic agent improves survival to hospital discharge following out-of-hospital cardiac arrest.
*Objective:* To assess the use of antiarrhythmic drugs for patients experiencing out-of-hospital cardiac arrest (OHCA).
*Methods:* Electronic searches of Medline, EMBASE and Cochrane Central Register of Controlled Trials were conducted and reference lists were hand-searched. Randomized controlled trials (RCTs) investigating the use of antiarrhythmic agents administered during resuscitation for adult (≥18 years) patients suffering non-traumatic OHCA were included. Direct and indirect evidence were combined in a network meta-analysis (NMA) using a frequentist approach with fixed-effects models and reported as relative risks (RR) with 95% confidence intervals (CIs). For each pairwise comparison, the certainty of direct, indirect, and network evidence was assessed using the GRADE approach.
*Results:* 8 RCTs involving 4464 patients were combined to compare the effectiveness of 5 antiarrhythmic agents and placebo administered during resuscitation following OHCA. Lidocaine was associated with a statistically significant increase in ROSC compared to placebo (1.15; 95% CI: 1.03–1.28) and was also superior to bretylium (1.61; 95% CI: 1.00–2.60) for ROSC. When compared to placebo, both amiodarone (1.18; 95% CI: 1.08–1.30) and lidocaine (1.18; 95% CI: 1.07–1.30) were associated with a statistically significant increase in survival to hospital admission. However, no antiarrhythmic was statistically more effective than placebo for survival to hospital discharge or neurologically intact survival, and no antiarrhythmic was convincingly superior to any other for any outcome.
*Conclusions:* Amiodarone and lidocaine were the only agents associated with improved survival to hospital admission in the NMA. For the outcomes most important to patients, survival to hospital discharge and neurologically intact survival, no antiarrhythmic was convincingly superior to any other or to placebo.


## Introduction

Out-of-hospital cardiac arrest (OHCA) accounts for nearly 400,000 unexpected deaths each year in the United States and Canada, approximately 20% of which are specifically attributable to ventricular fibrillation or pulseless ventricular tachycardia (VF/VT) [1–3]. VF/VT is considered the most treatment-responsive presentation of cardiac arrest and is associated with the highest rate of survival [1,4]. However, clinical outcomes remain poor with approximately only 1 in 5 persons with VF/VT discharged alive from the hospital [1,5].

Resuscitation of VF/VT involves a sequence of interventions known as the "chain of survival," the cornerstone of which is defibrillation [6]. Although highly effective for its termination of VF/VT, defibrillation cannot prevent recurrences of VF/VT, which are com-

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https://doi.org/10.1016/j.resuscitation.2017.10.012
0300-9572/

mon during resuscitation and can become progressively resistant to repeated shocks [7,8]. To promote the return of an organized rhythm and prevent relapse of VF/VT, antiarrhythmic medications are frequently administered during cardiac arrest in the acute setting [9,10]. However, despite their wide use in the prehospital setting, randomized control trials (RCTs) have failed to demonstrate that any antiarrhythmic agent improves survival to hospital discharge following OHCA. A recent systematic review and meta-analysis by Sanfilippo et al., pooled the results from three RCTs and four small observational studies and found that compared to placebo, amiodarone and lidocaine showed similar improvements in survival to hospital admission, but neither agent increased survival to hospital discharge [11]. However, this review did not consider other antiarrhythmic drugs that have been used for OHCA.

One limitation of traditional meta-analyses is that they are restricted to head-to-head comparisons, and cannot inform the relative merit of candidate therapies that have not been compared directly. In response to the need to simultaneously evaluate all available treatments, new methods in meta-analysis, known as network meta-analysis (NMA), have emerged [12,13].

In brief, NMA use direct and indirect comparisons to quantify the relative effectiveness of three or more treatment options. NMA are complex studies that involve creating "networks" of three or more treatment options and then statistical methods are applied to these networks to estimate the treatment effects through direct comparisons (head-to-head trials, A versus B) and indirect comparisons (making inferences about A versus C by looking at how 'A' compares with common comparator 'B' and how 'C' compares with common comparator 'B'). Investigators then combine direct and indirect comparisons to provide an overall pooled treatment effect [14,15]. The objective of this systematic review and NMA was to assess the use of antiarrhythmic drugs for OHCA resuscitation.

## Methods

### *Data sources and search strategy*

In consultation with the review authors, a research librarian conducted the systematic literature searches in MEDLINE (1946 to March 2017) using both Ovid and PubMed search interfaces, EMBASE (1947 to March 2017), the Cochrane Central Register of Controlled Trials (March 2017), as well as electronic bibliographic databases. A comprehensive search strategy (Appendix A) included a combination of subject headings and free-text terms using various spelling and endings, such as, but not limited to the following terms: 'out-of-hospital', 'prehospital', 'ambulance', 'paramedic personnel', 'emergency medical services', 'emergency care', 'emergency treatment', 'antiarrhythmic agents', 'anti-arrhythmia', 'lidocaine', 'xylocaine', 'lignocaine', 'amiodarone', 'cordarone', 'heart ventricle fibrillation', 'ventricular tachycardia', 'sudden death', 'cardiac arrest', and 'heart arrest'.

We used an optimized hedges filter and keywords to refine search results to focus on RCTs and systematic reviews. The search strategies were modified for each database to include specific terms; search filters and fields. We also hand-searched reference lists of relevant articles and reviews; as well as the regulatory website "clinicaltrials.gov" to identify any unpublished trials.

### *Eligibility criteria and study selection*

Randomized controlled trials (RCTs) comparing the use of an antiarrhythmic agent administered in the prehospital setting to any other antiarrhythmic agent(s) or placebo during resuscitation for adult (≥18 years) patients suffering OHCA were eligible for inclusion. Studies investigating the use of antiarrhythmics for in-hospital cardiac arrest or post-arrest were excluded. There were no language restrictions. Two reviewers independently screened the search output to identify potentially eligible trials, the full texts of which were retrieved and assessed for inclusion (Fig. 1).

### *Patient involvement*

There was no patient involvement in framing the research question, choosing the outcome measures, or conducting the research. We plan to involve key stakeholders and interest groups in the dissemination of the research results by means of short, easy to read summaries of key results, infographics, and audio or video interviews that can be used by patients and caregivers.

### *Outcomes of interest*

Outcomes of interest included the proportion of patients who achieved return of spontaneous circulation (ROSC) at hospital arrival, survival to hospital admission, survival to hospital discharge, and survival to hospital discharge with favorable neurologic status (cerebral performance category score 1–2).

### *Assessment of risk of bias*

Risk of bias for the individual trials was independently assessed by two reviewers using a modified version of the Cochrane Collaboration's tool for assessing risk of bias and discrepancies in risk of bias judgments were resolved by discussion [16,17]. We judged each included study as having low, probably low, probably high, or high risk of bias for randomization-sequence generation, randomization concealment, blinding, incomplete data, selective reporting, and free of other bias (including intention-to-treat analysis).

### *Data synthesis and statistical analysis*

Using a standardized data collection form, two reviewers independently extracted data on patient demographics, sample size, intervention details, protocol used and outcome results. Direct comparisons were performed using Mantel-Haenszel fixed-effects models and reported as relative risks (RR) with 95% confidence intervals (CIs) using Review Manager 5.3.4 (Nordic Cochrane Centre, Copenhagen, Denmark) [18]. Statistical significance was defined as $p < 0.05$ or 95% CI of the RR that excluded unity. Statistical heterogeneity was assessed using the $I^2$ statistic.

We combined direct and indirect evidence using a frequentist (the approach most frequently used in conventional meta-analyses) rather than a Bayesian approach. We used fixed rather than random effect models. For three of the outcomes (ROSC, survival to hospital admission, and survival to hospital discharge), we considered 6 treatments plus placebo, and for 1 outcome (survival to hospital discharge with good neurologic status), we considered 5 treatments plus placebo. All estimates are reported as RR with 95% CIs. Global incoherence of the network was assessed using the design-by-treatment interaction model [19]. Local incoherence was assessed using a heat plot and a design-based decomposition of Cochran's Q [20]. There are a number of approaches available for separating direct and indirect estimates within the NMA. We used one of these, the technical term for which is a "node-splitting" approach. All network meta-analyses were performed using the package netmeta [21] in R, version 3.3.1. [22] The network plots were derived using the package mvmeta [23] in Stata, version 14.1. [24]