TAKE-HOME MESSAGE

Among out-of-hospital cardiac arrest patients with shock-refractory ventricular tachycardia or ventricular fibrillation, neither amiodarone nor lidocaine increases survival to hospital discharge or good neurologic outcome.

In Patients With Cardiac Arrest, Does Amiodarone or Lidocaine Increase Meaningful Survival?

EBEM Commentators
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METHODS

DATA SOURCES

The authors performed a search of the NHS Library Evidence tool and MEDLINE from inception through May 15, 2016. Full-text review was generally restricted to articles in English, French, Spanish, German, or Italian. The decision to obtain full articles in other languages was made after review of the abstract. The references of identified articles were also hand searched.

STUDY SELECTION

Articles eligible for primary analysis selection included randomized controlled trials of patients with out-of-hospital cardiac arrest who received amiodarone compared with either lidocaine or placebo. Survival to admission, survival to discharge, and favorable neurologic outcome (defined as a modified Rankin Scale score $\leq$3) were the endpoints of interest. A preplanned secondary analysis also included nonrandomized comparative studies and studies of patients with inhospital cardiac arrest.

DATA EXTRACTION AND SYNTHESIS

Four authors independently performed data abstraction and disagreements were resolved by discussion, but the methods of extraction were otherwise unclear. Quality of methodology was assessed with the Cochrane Collaboration tool and the

Results

Table 1. Primary meta-analysis results comparing amiodarone to lidocaine and placebo.

Outcome	Studies/ Patients	Comparisons		OR (95% CI)	I^2, %
		Amiodarone, n/N	Placebo, n/N		
Survival, hospital discharge	2/2,530	270/1,216	256/1,314	1.19 (0.98–1.44)	0
Survival with good neurologic outcome	2/2,526	200/1,213	192/1,313	1.16 (0.93–1.44)	0
		Amiodarone, n/N	Lidocaine, n/N		
Survival, hospital discharge	2/2,302	246/1,150	238/1,152	1.06 (0.87–1.30)	0

OR, Odds ratio; *CI*, confidence interval.

Three randomized controlled trials (n=3,677) and 4 observational studies (n=704) were included for meta-analysis out of 528 articles identified on the initial search. The results were driven by a single large (n=3,026) randomized controlled trial at low risk of bias. The 2 smaller randomized controlled trials had moderate risk of bias, and the observational studies were generally at low risk of bias. Both lidocaine and amiodarone resulted in increased odds of survival to admission but no difference in survival to discharge or favorable neurologic outcome compared with placebo. None of the endpoints were statistically different when amiodarone was compared with lidocaine. Secondary analyses including observational studies yielded similar results. The primary results are reported in Table 1 with 95% confidence intervals and heterogeneity statistics.

Commentary

Although the effect on long-term survival has been unclear,[1,2] advanced cardiac life support guidelines recommend amiodarone for patients with cardiac arrest caused by shock-refractory

Newcastle-Ottawa Scale for randomized controlled trials and observational studies, respectively. Statistical analysis was performed with the Mantel-Haenszel method, generating odds ratios. Heterogeneity was reported with the I^2 statistic. Meta-analysis was performed with a random-effects model unless I^2 was less than 25%, in which case a fixed-effects model was used.

Table 2. Key results from Kudenchuk et al.[4]

Outcome	Amiodarone (%)	Lidocaine (%)	Placebo (%)	*P* Value*
mRS ≤3, intention-to-treat analysis	221/1,539 (14.4)	207/1,541 (13.5)	217/1,573 (13.8)	.63
mRS ≤3, PPA	182/967 (18.8)	172/984 (17.5)	175/1,055 (16.6)	.19
Survival to discharge, bystander-witnessed subgroup of PPA	171/618 (27.7)	176/632 (27.8)	155/684 (22.7)	.04
Survival to discharge, EMS-witnessed subgroup PPA	22/57 (38.6)	10/43 (23.3)	9/54 (16.7)	.01

mRS, Modified Rankin Scale; *PPA*, per-protocol analysis.
**P* value as reported for comparison of amiodarone versus placebo.

ventricular tachycardia or ventricular fibrillation.[3] Early trial results suggested that amiodarone increased survival to hospital admission but did not result in increased survival to discharge or neurologically intact recovery, although they were underpowered for those outcomes.[1,2] An agent that increases hospital admission without increasing meaningful survival could have a negative overall effect by increasing costs and the proportion of patients receiving expensive critical care but never recovering.

Kudenchuk et al[4] published a landmark trial comparing amiodarone, lidocaine, and placebo for this indication. Table 2 summarizes key results. Because most would consider survival with modified Rankin Scale score greater than or equal to 4 a poor outcome (in which 4 represents moderately severe disability with inability to walk or tend to one's own bodily needs unassisted, 5 is bedridden and requiring constant care, and 6 is dead), the table focuses on neurologic recovery when possible. This trial of more than 4,500 patients was of high quality, with minimal risk of bias. Consistent with previous studies, there was no difference in hospital survival or favorable neurologic outcome between treatment arms, although both amiodarone and lidocaine increased survival to hospital admission. In the authors' primary analysis, each drug increased survival to discharge over placebo by approximately 3%, differences that were not statistically significant but would have clinical importance if reproduced in a larger trial. This systematic review and meta-analysis was thus undertaken to determine whether combining previous (lower-quality) studies with the results of the trial by Kudenchuk et al[4] might demonstrate benefit with antiarrhythmic drugs. The results of the meta-analysis, however, are dominated by the trial by Kudenchuk et al[4] and did not change the results or conclusions (Table 1).

Although the trial by Kudenchuk et al[4] was well designed and determined to be at low risk of bias, the results of their primary analysis represent a per-protocol analysis. The trial initially randomized 4,653 patients. The per-protocol analysis excluded 35% of the enrolled patients, mostly because the investigators determined post hoc that these patients had not actually met the inclusion criteria of the trial. When results of the intention-to-treat population are examined, the trend toward improved outcomes largely disappears. Most important, survival with modified Rankin Scale score less than or equal to 3 occurred in 14.4% of the patients treated with amiodarone, 13.5% of those treated with lidocaine, and 13.8% of those treated with placebo (Table 2).

Although this meta-analysis concluded that neither amiodarone nor lidocaine increased survival to discharge or favorable neurologic outcome, further research is justified. Kudenchuk et al[4] found that the subgroup of patients with emergency medical services (EMS)–witnessed arrest had improved survival with lidocaine or amiodarone compared with placebo (Table 2). These results require validation and should be viewed as exploratory because they represent a subgroup analysis of a per-protocol analysis. Neither amiodarone nor lidocaine has been proven to provide any meaningful patient benefit for patients with out-of-hospital cardiac arrest.

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals*' Systematic Review Snapshots (SRS) series. The source for this systematic review snapshot is: **Sanfilippo F, Corredor C, Santonocito C, et al. Amiodarone or lidocaine for cardiac arrest: a systematic review and meta-analysis. *Resuscitation*. 2016;107:31-37.**

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2. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitaiton after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med*. 1999;341:871-878.
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4. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med*. 2016;374:1711-1722.

Michael Brown, MD, MSc, Jestin Carlson, MD, and Alan Jones, MD, serve as editors of the SRS series.