Critical Review Form
Therapy

Kudenchuk PJ, Brown SP, Daya M, et al; Resuscitation Outcomes Consortium Investigators. Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest. N Engl J Med. 2016 May 5;374(18):1711-22.

Objectives: **To compare "the effects of amiodarone, lidocaine, and placebo on survival to hospital discharge after out-of-hospital cardiac arrest due to shock-refractory ventricular fibrillation or pulseless ventricular tachycardia." (p. 2)**

Methods: **This multicenter randomized controlled trial was conducted at 55 emergency medical services at 10 North American sites from May 7, 2012 to October 25, 2015. Patients 18 years of age and older with nontraumatic out of hospital cardiac arrest (OHCA) and shock-refractory ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), defined as either nontermination or recurrence after one or more shocks, were eligible for inclusion. Patients who had already received lidocaine or amiodarone, or with known hypersensitivity to either drug, were excluded. Patients were excluded from the primary analysis (a per protocol analysis) if they did not receive any of the study drug, as were those patients in whom VF or VT was not the initial rhythm. A secondary intention to treat analysis was performed including these patients.**

Patients were randomized in a 1:1:1 fashion to receive amiodarone (150 mg per syringe), lidocaine (60 mg per syringe), or normal saline. Patients were given 2 syringes of trial medication as an initial dose (one syringe if estimated body weight was < 45.4 kg), followed by a 3rd syringe if VF or VT persisted after additional attempts at defibrillation.

The primary outcome was survival to hospital discharge. The secondary outcome was survival with favorable neurologic outcome, defined as a modified Rankin scale score of 3 or less. The authors also evaluated drug-related adverse events occurring within 24 hours of trial-drug administration, which included anaphylaxis, thrombophlebitis requiring intervention, seizure, and bradycardia requiring temporary cardiac pacing.

Out of 37,889 patients with nontraumatic OHCA during the study period, 7051 had shock-refractory VF or pulseless VT at some point and 4653 patients met all inclusion criteria and were included in the intention to treat population. Of these, 3026 patients received the study drug were included in the per protocol analysis (974 received amiodarone; 993 received lidocaine; and 1059 received placebo).

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Guide	Comments
Are the results valid?	
Did experimental and control groups being the study with a similar prognosis?	
Were patients randomized?	Yes. "Randomization was performed in permuted blocks of concealed size and was stratified according to participating site and agency." (p. 3)
Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be "randomized" to a particular group?	Likely yes. The authors report that kits and their contents were randomly distributed to EMS providers. In addition, the size of the blocks used in randomization was concealed, which would make it harder to subvert the randomization process. The authors did not, however, specify who prepared or distributed the kits.
Were patients analyzed in the groups to which they were randomized?	No. The authors chose for their primary analysis a per protocol analysis, in which patients who did not receive the study drug to which they were assigned were excluded. A secondary intention to treat analysis was performed including these patients.
Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to several key prognostic factors, including age, gender, witnessed arrest, bystander CPR, and time to EMS arrival. Patients were also similar with respect to time from arrest to first trial drug, and quality of EMS-performed CPR. The authors do not specify how many patients in each group had ventricular fibrillation or ventricular tachycardia as their initial rhythm.
Did experimental and control groups retain a similar prognosis after the study started?	
Were patients aware of group allocation?	No. These patients were suffering cardiac arrest and would have had no knowledge of the treatments they received.
Were clinicians aware of group allocation?	No. "Trial drugs were packaged in identically appearing, sealed kits each having three identically formulated syringes. Each syringe held 3 ml of color-less fluid containing 150 mg of amiodarone (totaling 450 mg in the amiodarone kit), 60 mg of lidocaine (180 mg in the lidocaine kit), or normal saline. Kits and their syringe contents were indistinguishable except by numerical code and were randomly distributed to EMS providers in a ratio of 1:1:1." (p. 3) Emergency unblinding could be requested by treating physicians but was only requested in 24 patients (0.8%) and was equally distributed across the groups.
Were outcome assessors aware of group allocation?	Likely no. Outcomes were obtained from the medical records, presumably by data collectors who remained blinded to treatment allocation, although this blinding is not specifically mentioned. The primary outcome, survival, is highly objective and not likely influenced by observer bias. The secondary outcome, a favorable neurologic outcome as measured by the modified Rankin scale, is less objective potentially a source of bias.
Was follow-up complete?	Mostly yes. For the per protocol analysis, outcome data was missing on a total of 15 patients, representing only 0.5% of the entire patient population.
What are the results?	
How large was the treatment effect?	In the per protocol population, survival to hospital discharge occurred in 24.4% of patients receiving amiodarone, 23.7% of patients receiving lidocaine, and 21.0% of patients receiving placebo. • There was no significant difference in survival between those receiving amiodarone compared to those receiving placebo (ARR 3.2%, 95% CI -0.4 to 7.0%).

	• There was also no significant difference between those receiving lidocaine vs. placebo (ARR 2.6% 95% CI -1.0 to 6.3%) or between those receiving amiodarone vs. lidocaine (ARR 0.7%, 95% CI -3.2 to 4.7%). • Rates of favorable neurologic outcomes were also similar between the amiodarone (18.8%), lidocaine (17.5%), and placebo groups (16.6%). • In subgroup analysis, survival to hospital discharge in those patients with witnessed OHCA was higher among patients receiving amiodarone vs. placebo (ARR 5.0%, 95% CI 0.3 to 9.7%) and among those receiving lidocaine vs. placebo (ARR 5.2%, 95% CI 0.5 to 9.9%). • There was no significant difference between the groups with regards to adverse events. In the intention to treat analysis, which included those patients who did not actually receive the study drug and those patients without VF or VT as the initial rhythm, there was still no significant difference in either the primary or secondary outcomes between the groups.
How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?)	See above. This was a fairly large trial and hence confidence intervals were quite narrow.

How can I apply the results to patient care?	
Were the study patients similar to my patient?	Yes. This study included adult patients enrolled at several sites in North America and utilized our existing EMS systems to administer the study medications. While none of the patients was enrolled directly from the ED, it also seems likely that these results would apply to patients suffering cardiac while already admitted to the ED.
Were all clinically important outcomes considered?	No. While authors considered survival to hospital discharge and survival with good neurologic outcomes, they did not consider more long term outcomes. While some groups have recommended 90-day neurologic outcomes as a better measure in cardiac arrest (Research Working Group of the American Heart Association Emergency Cardiovascular Care Committee) such outcomes are more difficult and more expensive to measure. The authors also do not report hospital length of stay, ICU length of stay, or cost.
Are the likely treatment benefits worth the potential harm and costs?	No. Based on this study alone, administration of lidocaine or amiodarone to patients presenting with shock-refractory VF or pulseless VT did not improve survival to hospital discharge or discharge with a good neurologic outcome compared to placebo. These results confirm previous evidence regarding the use of amiodarone in cardiac arrest (Laina 2016).

Limitations:

1. **The authors chose to perform a per protocol analysis rather than the traditionally recommended intention to treat analysis as their primary outcome. While some have recommended using a per protocol analysis in pragmatic studies, this practice does remain controversial. As a result, only about two-thirds of patients enrolled in this study were actually included in the primary analysis.**

2. **Although the trial's focus was on patients whose initial presenting OHCA rhythm was VF or pulseless VT, in actuality those patients with shock-resistant VF/VT at any time during**

resuscitation were eligible for randomization, even though they would later be excluded.

3. **There were some issues with incomplete reporting, including failure to specify who prepared and delivered study packets to EMS personnel, how abstraction of outcome data was performed, and the initial rhythm of patients included (VF vs. pulseless VT).**

4. **The assessment did not include long-term neurologically intact survival, as previously recommended.**

5. **While this study was fairly large, it was not sufficiently powered to detect a possible 3.2% difference in the primary outcome between thos receiving amiodarone and those receiving placebo.**

Bottom Line:

This methodologically sound randomized, controlled trial detected no difference in either survival to hospital discharge or survival with a good neurologic outcome between those patients receiving amiodarone, lidocaine, or placebo for an initial rhythm of shock-refractory VF or pulseless VT in OHCA. While the authors used a controversial per protocol analysis as their primary analysis, they did perform a secondary intention to treat analysis, which still demonstrated no significant difference in outcomes.