Choosing Amiodarone or Lidocaine as First-Line Pharmacologic Agent for Pulseless Ventricular Tachycardia

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Editor's Note: *In this Clinical Controversies series, opposing authors present pharmacologic principles and clinical findings that underlie the use of amiodarone and lidocaine in treating pulseless ventricular fibrillation.*

LIDOCAINE AS FIRST-LINE TREATMENT FOR PULSELESS VENTRICULAR TACHYCARDIA AND VENTRICULAR FIBRILLATION

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[Ann Emerg Med. 2025;85:445-447.]

Antiarrhythmics are recommended after 3 defibrillation attempts for pulseless ventricular tachycardia or ventricular fibrillation (pVT/VF) cardiac arrest. Currently, either lidocaine or amiodarone are first-line options according to the American Heart Association Advanced Cardiovascular Life Support (ACLS) guidelines.[1] However, the absence of evidence for long-term survival or neurologically intact outcomes contributes to weaker recommendations for both agents. Lidocaine is a class Ib sodium-channel antagonist effective in ventricular arrhythmias, whereas amiodarone is a class III agent with multiple mechanisms of antiarrhythmic action.

We recommend lidocaine as the first-line agent for pVT/VF. It is supported not only by equivalent strength guideline recommendations but also by emerging literature, ease of administration, favorable pharmacokinetics, and the lack of significant drug interactions or short term adverse effects. Anecdotally, out-of-hospital systems and ACLS educators have de-emphasized the use of lidocaine in favor of amiodarone as the default agent for pVT/VF arrest. However, when examining the full body of literature, the rationale behind this preference remains unclear, aside from amiodarone's historical precedence and greater familiarity among decision makers and trainers.

In 2016, Kudenchuk et al[2] published the landmark resuscitation outcomes consortium - amiodarone, lidocaine, or placebo (ROC-ALPS) trial which included more than 3,000 patients experiencing out-of-hospital cardiac arrest with shock-refractory pVT/VF. Results showed no difference between amiodarone, lidocaine, and placebo for the primary outcome of survival to hospital discharge. The study was underpowered to detect a primary outcome difference, and antiarrhythmic administration was delayed by an average of nearly 20 minutes after initial emergency contact. However, in a secondary outcome, lidocaine resulted in significant return of spontaneous circulation on emergency department arrival (P=.01) compared with placebo, whereas amiodarone did not (P=.52).[2] This may suggest an improved survival benefit with lidocaine in the absence of adequate study power. In addition, nonshockable rhythms that turned shockable experienced increased return of spontaneous circulation with lidocaine compared with amiodarone (40.5% versus 31.9%; P<.05).[3] Another subanalysis found that longer time-to-amiodarone administration resulted in diminished rates of return of spontaneous circulation, whereas the relative effect of lidocaine appeared sustained at all timeframes of drug administration.[4] This may either highlight lidocaine's benefit in out-of-hospital cardiac arrest or amiodarone's adverse effect profile. Although we recognize that return of spontaneous circulation at emergency department arrival was once considered a practical outcome measure because of the limitations of earlier research, it is no longer regarded as a meaningful or optimal endpoint in contemporary resuscitation studies. Despite this, it can still

serve as a valuable interim indicator, particularly in the absence of large, adequately powered studies.

Inhospital cardiac arrest data may provide a best-case scenario considering earlier administration of medications while inherently controlling for other confounders (timing and quality of chest compressions, transport time, etc). Wagner et al[5] published an observational cohort in 2022 with more than 14,000 patients between 2000 and 2014 with inhospital cardiac arrest secondary to VT/VF who received at least one defibrillation and either lidocaine or amiodarone. After adjusting for baseline differences, treatment with lidocaine resulted in higher return of spontaneous circulation (adjusted odds ratio 1.15; 95% confidence interval [CI)] 1.03 to 1.30), 24-hour survival (adjusted odd ratio 1.16; 95% CI 1.05 to 1.28), survival to discharge (adjusted odds ratio 1.19; 95% CI 1.08 to 1.30), and favorable neurologic outcome at hospital discharge (adjusted odds ratio 1.18; 95% CI 1.07 to 1.30).[5] Although this observational, registry-level data have implicit limitations, there is a strong signal here that aligns with the aforementioned landmark ROC-ALPS trial.

At least 7 meta-analyses have been published with a variety of conclusions for amiodarone compared to lidocaine in pVT/VF cardiac arrest. Khan et al[6] reported a Bayesian analysis of 11 trials showing lidocaine as the most effective agent for survival to hospital discharge. A subsequent meta-analysis of 14 randomized controlled trials showed no difference in any patient-centered outcomes but lidocaine resulted in significantly more return of spontaneous circulation than amiodarone.[7]

Despite this evidence, lidocaine's broader adoption in clinical practice has been limited for several reasons. In 3 small cohorts of stable VT patients published prior to 1996, lidocaine did not demonstrate clear superiority over alternative treatments. That said, amiodarone was not a comparator in these trials. Second, the pivotal 2002 amiodarone versus lidocaine in prehospital ventricular fibrillation evaluation study in pVT/VF patients (n=347) favored amiodarone and secured its role in ACLS guidelines; however, more contemporary outcome measures such as long-term survival puts its results into question today, in addition to the existence of much larger available data sets.[8]

Lidocaine rapidly distributes into cardiac tissue within a few minutes after an intravenous bolus with a serum half-life of 1.5 hours after a single dose.[9] This pharmacokinetic profile is desired in pVT/VF where the goal is immediate cardioversion followed by treatment of underlying causes. Conversely, amiodarone has a delayed onset of antiarrhythmic action, with an average cardioversion time of 8 hours compared with 1 to 4 hours of many other antiarrhythmics including lidocaine.[10] Amiodarone is lipophilic and has a half-life of more than 24 hours following a single IV dose and months after maintenance therapy.[11] Lidocaine has no significant drug interactions, whereas amiodarone is a strong inhibitor of CYP450 3A4, the enzyme responsible for a vast number of hepatic drug metabolism pathways. This suggests that many potential drug interactions may go unnoticed during hospitalizations following pVT/VF arrest in patients treated with amiodarone. Unfortunately, there is limited data on this issue. Amiodarone's extensive tissue distribution can adversely affect nearly every major organ, with early side effects appearing even after short courses due to its long half-life.[12] Ultimately, amiodarone's pharmacologic profile is reminiscent of less-utilized drugs such as digoxin, phenytoin, and warfarin. Lidocaine lacks significant adverse effects at doses used for pVT/VT. In fact, it is postulated that lidocaine has pleiotropic effects including anti-inflammatory and neuroprotective benefits relevant to cardiac arrest populations.[13]

The initial dose of lidocaine for pVT/VF is 1.5 mg/kg, which conveniently rounds to 100 mg for most patients. A prefilled 100 mg syringe formulation is widely available from several manufacturers and commonly used in clinical practice. This product facilitates swift assembly and administration, which is especially advantageous in resource-limited settings by minimizing the potential for errors and expediting treatment. Commercial forms of lidocaine are void of any excipients and often preservative free. Amiodarone's initial dose often requires multiple vials. All amiodarone vials and syringes currently manufactured in the United States contain polysorbate-80, a diluent linked to hypotension and negative inotropy. Notably, the ROC-ALPS trial used a proprietary amiodarone formulation void of any diluent, limiting applicability of results until amiodarone void of polysorbate-80 is available for widespread use.[2] Both amiodarone and lidocaine intravenous formulations are similar in cost and typically less than $10 per total dose for ACLS.

In conclusion, lidocaine should be the preferred agent over amiodarone for pVT/VF due to its more favorable evidence, desirable pharmacokinetics, fewer drug interactions, and convenient dosage form.

Funding and support: By *Annals'* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

https://doi.org/10.1016/j.annemergmed.2024.11.018

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AMIODARONE SHOULD BE THE FIRST-LINE ANTIARRHYTHMIC TREATMENT FOR PULSELESS VENTRICULAR TACHYCARDIA AND VENTRICULAR FIBRILLATION

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[Ann Emerg Med. 2025;85:447-448.]

Sudden cardiac death occurs in more than 350,000 individuals annually in the United States.[1] Pulseless ventricular tachycardia and ventricular fibrillation (VF) are potentially treatable arrhythmias necessitating advanced cardiovascular life support (ACLS). Recommended treatments for cardiac arrest caused by pulseless ventricular tachycardia/VF include high-quality chest compressions, defibrillation, epinephrine, and antiarrhythmic agents.[2] Antiarrhythmics can facilitate the restoration and maintenance of a spontaneous perfusing rhythm, typically by increasing likelihood of successful defibrillation and reducing the risk of recurrent arrythmias. They have been associated with increased rates of return of spontaneous circulation (ROSC) and survival to hospital admission, but none have consistently demonstrated increased long-term survival or survival with a good neurologic outcome.[2] The American Heart Association ACLS guidelines recommend that either amiodarone or lidocaine may be considered for pulseless ventricular tachycardia/VF that is refractory to defibrillation, particularly for witnessed cardiac arrest with shorter downtime.[2] We propose that amiodarone should be used as the first-line antiarrhythmic for treatment of pulseless ventricular tachycardia/VF because it has robust data supporting its use for pulseless ventricular tachycardia/VF to facilitate ROSC, especially if used early, and it has broader receptor targets relative to lidocaine.

Amiodarone has been recommended by American Heart Association ACLS guidelines since 2000. It was historically preferred based on the Amiodarone versus Lidocaine in Prehospital Ventricular Fibrillation Evaluation study, which included 347 patients with out-of-hospital cardiac arrest.[3] This study enrolled patients with refractory VF (not pulseless ventricular tachycardia) who were resistant to 3 shocks, had received intravenous epinephrine and a further shock, or had recurrent VF after initially successful defibrillation. More patients who received amiodarone were significantly more likely to survive to hospital admission (22.8% amiodarone versus 12.0% lidocaine), especially if given less than 24 minutes from dispatch to administration.[3] However, there was no difference in long-term survival and neurologic recovery was not assessed.

Current ACLS guidelines are based on the Resuscitation Outcomes Consortium–Amiodarone, Lidocaine or Placebo study. A total of 3,026 patients refractory to defibrillation were randomly assigned to amiodarone 300 mg (plus 150 mg if needed; n=974), lidocaine 120 mg (plus 60 mg if needed; n=993), or placebo (n=1,059).[4] There was no