ABSTRACT: Antiarrhythmic medications are commonly administered during and immediately after a ventricular fibrillation/pulseless ventricular tachycardia cardiac arrest. However, it is unclear whether these medications improve patient outcomes. This 2018 American Heart Association focused update on advanced cardiovascular life support guidelines summarizes the most recent published evidence for and recommendations on the use of antiarrhythmic drugs during and immediately after shock-refractory ventricular fibrillation/pulseless ventricular tachycardia cardiac arrest. This article includes the revised recommendation that providers may consider either amiodarone or lidocaine to treat shock-refractory ventricular fibrillation/pulseless ventricular tachycardia cardiac arrest.
BACKGROUND

Shock-refractoryVF/pVT refers to VF or pVT that persists or recurs after ≥1 shocks. An antiarrhythmic drug alone is unlikely to pharmacologically convertVF/pVT to an organized perfusing rhythm. Rather, the primary objective of antiarrhythmic drug therapy in shock-refractoryVF/pVT is to facilitate successful defibrillation and to reduce the risk of recurrent arrhythmias. In concert with shock delivery, antiarrhythmics can facilitate the restoration and maintenance of a spontaneous perfusing rhythm. Some antiarrhythmic drugs have been associated with increased rates of return of spontaneous circulation (ROSC) and hospital admission, but none have yet been demonstrated to increase long-term survival or survival with good neurological outcome. Thus, establishing vascular access to enable drug administration should not compromise the performance of CPR or timely defibrillation, both of which are associated with improved survival after cardiac arrest. The optimal sequence of ACLS interventions, including administration of antiarrhythmic drugs during resuscitation, and the preferred manner and timing of drug administration in relation to shock delivery are still not known.

For the 2018 ILCOR systematic review, the ALS Task Force considered new evidence published since the 2015 CoSTR. The review did not specifically address the selection or use of second-line antiarrhythmic drugs or different antiarrhythmic medications given in combination to patients who are unresponsive to the maximum therapeutic dose of the first administered drug, and limited data are available to direct such treatment. In addition, the optimal bundle of care for shock-refractoryVF/pVT has not been identified.

USE OF ANTIARRHYTHMIC DRUGS DURING RESUSCITATION FROM ADULTVF/pVT CARDIAC ARREST

2018 Evidence Summary

Amiodarone

Intravenous amiodarone is available in 2 approved formulations in the United States. One formulation contains the diluent polysorbate, which is a vasoactive solvent that can potentially cause hypotension. The other formulation contains capisol, which has no known vasoactive effects. In 2 out-of-hospital, blinded, randomized controlled trials in adults with shock-refractoryVF/pVT who received at least 3 shocks and epinephrine, paramedic administration of intravenous amiodarone improved survival to hospital admission. In 1 study, the ARREST trial (Amiodarone in the Out-Of-Hospital Resuscitation of Refractory Sustained Ventricular Tachyarrhythmias), amiodarone (300 mg) in polysorbate improved survival to hospital admission compared with a polysorbate placebo. In another study, the ALIVE trial (Amiodarone Versus Lidocaine in Prehospital Ventricular Fibrillation Evaluation), 5 mg/kg amiodarone in polysorbate improved survival to hospital admission compared with 1.5 mg/kg lidocaine with polysorbate. Survival to hospital discharge and survival with favorable neurological outcome were not improved by amiodarone, but neither study was powered for those outcomes.

In ROC-ALPS (Resuscitation Outcomes Consortium—Amiodarone, Lidocaine or Placebo Study), a large out-of-hospital randomized controlled trial that compared capitisol-based amiodarone with lidocaine or placebo for patients withVF/pVT refractory after at least 1 shock, there was no overall statistically significant difference in survival with good neurological outcome or survival to hospital discharge. In this study, ROSC was higher in patients receiving lidocaine compared with those receiving placebo but not for those receiving amiodarone compared with patients receiving placebo. Survival to hospital admission was higher in patients receiving ei-
ther amiodarone or lidocaine than in those receiving placebo, and this outcome did not differ between the 2 active drugs.

In a prespecified subgroup analysis of patients with bystander-witnessed out-of-hospital cardiac arrest, a significant survival benefit (a 5% absolute improvement compared with placebo) was observed with either amiodarone or lidocaine. In these patients, time from collapse to drug administration was likely shorter than among patients with an unwitnessed arrest. This underscores the potential importance and effects of early recognition and treatment of out-of-hospital cardiac arrest on outcome. There was no statistically significant difference in survival between the 2 active drugs in this subgroup. Neurological status at discharge was not reported in the subgroup analysis. The captisol-based formulation of amiodarone used in this trial is currently marketed...
only as a premixed infusion and is not marketed in the concentrated form that was used for rapid injection in the study.

These randomized trials did not explore the timing or sequence of amiodarone versus epinephrine administration. No randomized trials were identified that address the use of amiodarone during in-hospital cardiac arrest.

**Lidocaine**

Intravenous lidocaine is an antiarrhythmic drug of long-standing and widespread familiarity. In the large ROC-ALPS out-of-hospital randomized controlled trial comparing captisol-based amiodarone with lidocaine or placebo for patients with VF/pVT cardiac arrest refractory after at least 1 shock, there was no overall statistically significant difference in survival with good neurological outcome or survival to hospital discharge.\(^\text{11}\) ROSC was higher in those receiving lidocaine compared with those receiving placebo. Survival to hospital admission was higher in patients receiving either amiodarone or lidocaine than in those receiving placebo, but there was no statistically significant difference between the 2 active drugs. A prespecified subgroup analysis of patients with bystander-witnessed arrest found that survival to hospital discharge was higher in patients receiving either amiodarone or lidocaine than in those receiving placebo. There was no statistically significant difference in patient survival between the 2 active drugs. This randomized trial did not explore the timing or sequence of lidocaine versus epinephrine administration.

No randomized trials were identified that assessed the efficacy of lidocaine for treatment of in-hospital cardiac arrest.

**Magnesium**

Magnesium acts as a vasodilator and is an important cofactor in regulating sodium, potassium, and calcium flow across cell membranes. In a total of 4 small randomized clinical trials, magnesium administration did not increase ROSC or survival to hospital discharge. Two of the trials compared magnesium with placebo for cardiac arrest with any presenting rhythm,\(^\text{12,13}\) and 2 trials compared magnesium with placebo for VF/pVT cardiac arrest.\(^\text{14,15}\) Although the 4 trials were underpowered to evaluate long-term outcomes, with a total of only 217 patients randomized to magnesium and 227 randomized to placebo across the 4 studies, the results were consistent in showing no benefit associated with magnesium administration.

Magnesium is commonly used to treat torsades de pointes (ie, polymorphic VT associated with long-QT interval), but it actually acts to prevent the reinitiation of torsades rather than to pharmacologically convert polymorphic VT. The use of magnesium for torsades de pointes is supported by only 2 observational studies.\(^\text{16,17}\) Magnesium administration was not beneficial in a series of 5 patients with polymorphic VT associated with normal-QT interval.\(^\text{16}\) The 2018 ILCOR systematic review identified no published randomized controlled trials of magnesium for torsades de pointes.

**2018 Recommendations for Use of Antiarrhythmic Drugs During Resuscitation From Adult VF/pVT Cardiac Arrest**

**Amiodarone and Lidocaine Recommendation—Updated**

1. Amiodarone or lidocaine may be considered for VF/pVT that is unresponsive to defibrillation. These drugs may be particularly useful for patients with witnessed arrest, for whom time to drug administration may be shorter (Class IIb; Level of Evidence B-R).

**Magnesium Recommendation—Updated**

1. The routine use of magnesium for cardiac arrest is not recommended in adult patients (Class III: No Benefit; Level of Evidence C-LD). Magnesium may be considered for torsades de pointes (ie, polymorphic VT associated with long-QT interval) (Class IIb; Level of Evidence C-LD). The wording of this recommendation is consistent with the AHA’s 2010 ACLS guidelines.\(^\text{7}\)

**Discussion**

The writing group recommends that amiodarone or lidocaine may be considered for VF/pVT that is unresponsive to defibrillation. Although no antiarrhythmic drug has yet been shown to increase long-term survival or to improve neurological outcome after VF/pVT cardiac arrest, the writing group also considered the small increase in the short-term outcome of ROSC in those treated with amiodarone in the 1999 ARREST study\(^\text{9}\) and in those treated with lidocaine in the most recent ROC-ALPS trial.\(^\text{11}\) In addition, the writing group considered the improved survival to hospital admission in patients receiving either amiodarone or lidocaine (compared with placebo) in the most recent ROC-ALPS trial, as well as the improved survival to hospital discharge among patients with witnessed cardiac arrest who received amiodarone or lidocaine.\(^\text{11}\) These considerations contributed to the weak recommendation for consideration of amiodarone or lidocaine in the context of a disease process for which there are limited therapeutic options other than CPR and defibrillation.

Lidocaine is now included with amiodarone in the ACLS algorithm for treatment of shock-refractory VF/pVT...
Panchal et al 2018 Focused Update on ACLS

The recommended dose of lidocaine is 1.0 to 1.5 mg/kg IV/IO for the first dose and 0.5 to 0.75 mg/kg IV/IO for a second dose if required. Although the most recent clinical trial of lidocaine used a standard-bolus dose for ease of execution, this 2018 recommended dose is made with a focus on patient safety through weight-based dosing. The recommended dose for amiodarone is unchanged, with randomized tri-
als supporting an initial IV/IO dose of 300 mg with a second IV/IO dose of 150 mg if required.\textsuperscript{10,11} Both the ROC-ALPS and ALIVE trials permitted dose reductions in lower-weight patients; however, higher cumulative bolus doses of amiodarone have not been studied in cardiac arrest. It is also important to note that the captoxol-based formulation of amiodarone is currently marketed only as a premixed infusion, not in concentrated form, making it impractical for rapid administration during cardiac arrest. The polysorbate-based formulation is currently available in concentrated form for rapid administration.

The writing group reaffirms that magnesium should not be used routinely during cardiac arrest management but may be considered for torsades de pointes (ie, polymorphic VT associated with long-QT interval). Unfortunately, these recommendations are based on low-quality evidence, representing a significant knowledge gap concerning the use of magnesium for VF/pVT. Future randomized studies are needed with rigorous evaluation of the impact of magnesium on survival and neurological outcomes to determine the importance of magnesium administration in this condition.

The writing group is aware of increased interest in and early studies of \(\beta\)-adrenergic–blocking drugs used during cardiac arrest.\textsuperscript{18,19} The question of the effectiveness of these drugs has been referred to ILCOR for future systematic review.

**ANTIARRHYTHMIC DRUGS IMMEDIATELY AFTER ROSC FOLLOWING CARDIAC ARREST**

The 2018 ILCOR systematic review sought to determine whether the prophylactic administration of antiarrhythmic drugs after successful termination of VF/pVT cardiac arrest results in better outcome. This prophylaxis includes continuation of an antiarrhythmic medication that was given during the course of resuscitation or the initiation of an antiarrhythmic after ROSC to sustain rhythm stability after VF/pVT cardiac arrest. Although improved survival is the ultimate goal of such treatment, other shorter-term outcomes (even
in the absence of a survival benefit) may still be important. For example, reducing the risk of recurrent arrhythmias with the use of arrhythmia prophylaxis can reduce the risk of recurrent cardiac arrest and its sequelae during transport, which may be particularly important when transport intervals are prolonged. Treatment for this indication is arguably beneficial even if there are as yet no studies showing long-term survival benefit, provided that the intervention itself is not harmful. The only medications studied in this context are β-adrenergic–blocking drugs and lidocaine. Although both drugs have precedent for use during acute myocardial infarction, the evidence for their use in patients immediately after resuscitation from cardiac arrest is limited. The fact that only 2 observational studies addressing this question have been performed to date underscores a sizeable knowledge gap and limits the conclusions that can be drawn from currently available information.

2018 Evidence Summary

β-Adrenergic–Blocking Drugs

β-Adrenergic–blocking drugs blunt the heightened catecholamine activity that can precipitate cardiac arrhythmias. These drugs also reduce ischemic injury and may have membrane-stabilizing effects. Conversely, intravenous β-blockers can cause or worsen hemodynamic instability, exacerbate heart failure, and cause bradyarrhythmias, making their routine administration after cardiac arrest potentially hazardous. There are no new studies that address this topic. In 1 observational study that was evaluated for the ACLS guidelines in the 2015 guidelines update, oral or intravenous metoprolol or bisoprolol administration during hospitalization after VF/pVT cardiac arrest was associated with a significantly higher adjusted survival rate in recipients compared with nonrecipients at 72 hours after ROSC and at 6 months.20 This study was not considered by ILCOR in the 2018 evidence review because predefined criteria for the evaluation of post-ROSC prophylactic antiarrhythmic drugs included only drug administration within 1 hour (as opposed to within 72 hours) after ROSC. There is no evidence addressing the use of β-blockers after cardiac arrest precipitated by rhythms other than VF/pVT.

Lidocaine

Early studies in patients with acute myocardial infarction found that lidocaine suppressed premature ventricular complexes and nonsustained VT, rhythms that were believed to presage VF/pVT. Later studies noted a disconcerting association between lidocaine and higher mortality after acute myocardial infarction, possibly resulting from a higher incidence of asystole and bradyarrhythmias; thus, the routine practice of administering prophylactic lidocaine during acute myocardial infarction was abandoned.21,22 One observational study with propensity-matched cohorts23 found that lidocaine was not associated with increased survival when administered prophylactically after ROSC in adults with VF/pVT cardiac arrest, although it decreased the recurrence of VF/pVT. Thus, evidence supporting a potential role for prophylactic lidocaine after VF/pVT arrest is relatively weak, limited to short-term outcomes, and nonexistent for cardiac arrest presenting with nonshockable rhythms.

2018 Recommendations for Antiarrhythmic Drugs Immediately After ROSC Following Cardiac Arrest

β-Blocker Recommendation—Updated

1. There is insufficient evidence to support or refute the routine use of a β-blocker early (within the first hour) after ROSC.

Lidocaine Recommendations—Updated

1. There is insufficient evidence to support or refute the routine use of lidocaine early (within the first hour) after ROSC.

2. In the absence of contraindications, the prophylactic use of lidocaine may be considered in specific circumstances (such as during emergency medical services transport) when treatment of recurrent VF/pVT might prove to be challenging (Class IIb; Level of Evidence C-LD).

Discussion

Evidence supporting the prophylactic use of lidocaine or β-blockers on ROSC after VF/pVT cardiac arrest is insufficient to support or refute their routine use. However, the writing group acknowledges that there are circumstances (eg, during emergency medical services transport of a resuscitated patient after VF/pVT arrest) when recurrence of VF/pVT might prove logistically challenging to treat; in such situations, the use of lidocaine may be considered to prevent recurrence. There is insufficient evidence to recommend for or against the routine initiation or continuation of other antiarrhythmic medications after ROSC following cardiac arrest. For example, no study has considered or evaluated amiodarone for this indication.

SUMMARY

As noted in the ACLS portion of the 2010 guidelines,7 CPR and defibrillation are the only therapies associated with improved survival in patients with VF/pVT. In this
2018 ACLS guidelines focused update, the updated treatment recommendations include consideration of either amiodarone or lidocaine for shock-refractory VF/pVT, whereas previous guidelines favored amiodarone as the first-line therapy. Because no antiarrhythmic drug has yet been shown to increase long-term survival or survival with good neurological outcome, these treatment recommendations are based primarily on potential benefits in short-term outcomes (such as ROSC or survival to hospital admission) and on a potential survival benefit in patients with witnessed arrest, for whom time to drug administration may be shorter.

Finally, the optimal sequence of ACLS interventions for VF/pVT cardiac arrest, including administration of a vasopressor or antiarrhythmic drug, and the timing of medication administration in relation to shock delivery are not known. The sequence and timing of interventions recommended in the current ACLS Adult Cardiac Arrest Algorithms (Figures 1 and 2) will be affected by the number of providers participating in the resuscitation, their skill levels, and the ability to secure intravenous/intraosseous access in a timely manner.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on September 5, 2018, and the American Heart Association Executive Committee on September 17, 2018. A copy of the document is available at http://professional.heart.org/statement by using either “Search for Guidelines & Statements” or the “Browse by Topic” area. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.


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Disclosures

Writing Group Disclosures

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*Modest.
†Significant.

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