Out-of-hospital cardiac arrest accounts for approximately 356,000 deaths per year in the United States, with many patients having ventricular fibrillation or pulseless ventricular tachycardia as the presenting rhythm. In an effort to reduce mortality, the American Heart Association (AHA) developed the “Chain of Survival,” including early cardiopulmonary resuscitation (CPR), rapid defibrillation, and “effective advanced life support” as central links in management. However, the rate of survival of out-of-hospital cardiac arrest with good neurologic function remains poor, averaging just 8.5%. Geographic variation exists, and higher rates of survival are reported in specific locations such as aircraft and casinos.

Defibrillation is effective at terminating most sustained ventricular fibrillation or pulseless ventricular tachycardia, but the arrhythmia persists in some patients, and many have immediate recurrence. Antiarrhythmic medication, typically intravenous amiodarone or lidocaine, is often used with the goal of restoring and maintaining a stable rhythm. Both agents have a class IIb recommendation in the 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, which states that these drugs “may be considered” for ventricular fibrillation or pulseless ventricular tachycardia that is unresponsive to CPR, defibrillation, and a vasopressor therapy. The uncertainty in these recommendations is based on previous trials that were not powered to make comparisons with respect to overall survival and that showed no survival benefit. Furthermore, all previous trials of intravenous amiodarone were potentially undermined by a formulation that included a solvent that causes hypotension; thus, the effect purely of the drug had not been evaluated. In this context, the Resuscitation Outcomes Consortium (ROC) conducted a trial to address an important question: are drugs the answer? The results of this trial are now reported by Kudenchuk et al. in the Journal.

The ROC is a network of regional centers across North America, supported by the National Institutes of Health and other organizations, that allows for well-powered randomized studies of out-of-hospital cardiac arrest and trauma. The trial is the first randomized, multicenter, double-blind comparison of intravenous saline placebo versus amiodarone versus lidocaine, along with standard care, in patients with out-of-hospital cardiac arrest and ventricular fibrillation or pulseless ventricular tachycardia that recurs or persists after one or more electrical shocks. Although the lidocaine preparation is standard, the formulation of amiodarone with a solvent that does not cause hypotension (Nexterone, Baxter Healthcare) is novel and allows for isolated evaluation of the pharmacologic effect of the drug.

In the trial, neither amiodarone nor lidocaine resulted in a significantly higher rate of survival to hospital discharge (the primary outcome) or favorable neurologic function at discharge (the secondary outcome) than the rate with placebo among the 3026 patients studied. On the other hand, there were nonsignificant differences between each drug and placebo in the survival rate (a difference of 3.2 percentage points for amiodarone vs. placebo and 2.6 percentage points for lidocaine vs. placebo). Further evidence of an antiarrhythmic effect was the significant benefit of both drugs over placebo in several measures: fewer shocks were administered after the first...
dose of the trial drug; fewer patients received rhythm-control medications during hospitalization; and fewer patients required CPR during hospitalization.

How might we explain the negative results of the trial? One possibility, as the authors suggest, is that the trial was underpowered for the smaller-than-predicted drug effect. A further possibility is that drug delivery was provided too late to overcome the metabolic consequences of prolonged arrest. Rates of conversion to sinus rhythm and survival rates are highest immediately after out-of-hospital cardiac arrest, with up to 74% survival among patients with ventricular fibrillation or pulseless ventricular tachycardia if a shock is administered within 3 minutes. This brief “electrical phase” is followed by a “hemodynamic phase”; however, after 10 minutes, the “metabolic phase” dominates and the chances of survival are reduced.

For the vast majority of the trial patients (for whom emergency medical services [EMS] personnel were not present at the time of arrest), the mean time to drug treatment was 19.3 minutes — well into the metabolic phase. What if the drug therapy were administered sooner, as we might presume would occur for the substantial subgroup (66%) whose arrest was witnessed by a bystander? For these patients, the rate of survival to hospital discharge was significantly higher with amiodarone (27.7%) or lidocaine (27.8%) than with placebo (22.7%) — a clinically important difference of 5 percentage points.

What can we conclude from the current trial, and how might we modify care for out-of-hospital cardiac arrest with ventricular fibrillation or pulseless ventricular tachycardia that either recurs or persists despite electrical shock? The data do not support the use of amiodarone or lidocaine for all patients, but, although they are not absolutely conclusive, the data suggest that EMS personnel should consider these agents when the arrest is witnessed. There is no signal from the data as to which drug might be preferable, however.

We commend the ROC investigators for their efforts to provide scientific evidence to support emergency care, and we agree with the Institute of Medicine recommendations that research must continue, with efforts to coordinate emergency care and quickly implement best practices on the basis of contemporary data. Finally, we emphasize the benefit of bystander-initiated CPR, for which the current trial showed an absolute survival benefit of almost 10 percentage points, eclipsing any effect of drug intervention.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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This article was published on April 4, 2016, at NEJM.org.


DOI: 10.1056/NEJMe1602790
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