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Resuscitation Outcomes Consortium - Amiodarone, Lidocaine or Placebo Study (ROC-ALPS): Rationale and Methodology Behind an Out-of-Hospital Cardiac Arrest Antiarrhythmic Drug Trial

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Abstract

Background—Despite their wide use, whether antiarrhythmic drugs improve survival after out-of-hospital cardiac arrest (OHCA) is not known. The Resuscitation Outcomes Consortium Amiodarone, Lidocaine, or Placebo Study (ROC-ALPS) is evaluating the effectiveness of these drugs for OHCA due to shock-refractory ventricular fibrillation or pulseless ventricular tachycardia (VF/VT).

Methods—ALPS will randomize 3000 adults across North America with non-traumatic OHCA, persistent or recurring VF/VT after ≥1 shock and established vascular access to receive up to 450 mg amiodarone, 180 mg lidocaine, or placebo in the field using a double-blind protocol, along with standard resuscitation measures. The designated target population is all eligible randomized recipients of any dose of ALPS drug whose initial OHCA rhythm was VF/VT. A safety analysis includes all randomized patients regardless of their eligibility, initial arrhythmia or actual receipt of ALPS drug. ALPS' primary outcome is survival to hospital discharge; a secondary outcome is functional survival at discharge assessed as a Modified Rankin Score ≤3.

Results—ALPS' principal aim is to determine if survival is improved by amiodarone compared to placebo; secondary aims are to determine if survival is improved by lidocaine versus placebo, and/or by amiodarone versus lidocaine. Prioritizing comparisons in this manner acknowledges where differences in outcome are most expected based on existing knowledge. Each aim also represents a clinically relevant comparison between treatments that is worth investigating.

Conclusions—Results from ALPS will provide important information about the choice and value of antiarrhythmic therapies for VF/VT arrest with direct implications for resuscitation guidelines and clinical practice.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a common and the most lethal presentation of cardiovascular disease. It accounts for over 350,000 unexpected deaths each year in the United States and Canada, nearly 100,000 of which are specifically attributable to shockable arrhythmias (ventricular fibrillation or pulseless ventricular tachycardia (VF/VT)). [1, 2] Of all presentations of cardiac arrest, VF/VT is considered the most treatment-responsive and boasts the highest rate of survival. Nonetheless, outcome remains poor with approximately only 1 in 5 persons with VF/VT discharged alive from the hospital.[1]

Resuscitation of VF/VT involves a sequence of interventions known as the "chain of survival,"[3] the centerpiece of which is defibrillation. While highly effective for its termination, defibrillation cannot prevent recurrences of VF/VT, which are common during resuscitation and can become progressively resistant to repeated shocks.[4, 5, 6, 7, 8] Antiarrhythmic medications are frequently deployed in this setting in hope of promoting the return of an organized rhythm and preventing relapses of VF/VT.[9] Antiarrhythmics exert their effects by altering ion flow across cellular channels, thereby changing the excitatory, conduction and/or refractory properties of cardiac tissue.[10] This can result in direct

pharmacologic termination of some arrhythmias, increase the threshold required to provoke VF/VT, and/or suppress triggers responsible for the re-emergence of VF/VT.[11, 12, 13, 14] Paradoxically, the same drugs can have precisely the opposite effect, rendering arrhythmias more resistant to shock by raising the energy required for defibrillation, altering tissue electrical characteristics in a manner that promotes new arrhythmias or makes existing arrhythmias more recalcitrant, along with adverse hemodynamic consequences (hypotension, bradycardia and impaired contractility) that could compromise circulatory stability in the aftermath of a seemingly successful shock.[15, 16, 17, 18, 19, 20, 21, 22, 23, 24]

Lidocaine has been the traditional drug of choice for VF/VT, based on decades of experience, its low cost and relative ease of administration. In observational OHCA studies, lidocaine was sometimes found to improve return of circulation and hospital admission rates, but not survival to discharge. [9, 25] By comparison, amiodarone achieved higher hospital admission rates after OHCA than either placebo or lidocaine, but with an increased risk of hypotension, and without an established effect on survival.[6, 26] Many Emergency Medical Services (EMS) agencies routinely carry lidocaine and/or amiodarone.[27, 28] Yet the observed variability in antiarrhythmic drug use by EMS to treat VF/VT arrest exemplifies the degree of uncertainty about their efficacy.[27] Most concerning is that despite our extensive knowledge about the effects of these drugs and their inclusion in international treatment guidelines, their actual impact on survival after OHCA still remains unproven.[29]

Accordingly, the Resuscitation Outcomes Consortium (ROC), a North American multicenter network with an emphasis on prehospital trials, is conducting the Amiodarone, Lidocaine or Placebo Study (ALPS) which will compare the effectiveness of these pharmacological interventions for OHCA due to shock-resistant VF/VT. With its focus on survival, including functional survival, ALPS' findings will have important implications for defining the role of these agents in resuscitation and the care of patients with cardiac arrest.

Methods

Funding Support

The ROC is supported by a series of cooperative agreements to nine regional clinical centers and one Data Coordinating Center (Appendix 1, 3) from the National Heart, Lung and Blood Institute in partnership with the U.S. Army Medical Research & Material Command, The Canadian Institutes of Health Research - Institute of Circulatory and Respiratory Health, Defense Research and Development Canada, the Heart, Stroke Foundation of Canada and the American Heart Association. Study drugs are being provided at no cost by Baxter Pharmaceuticals, Deerfield, IL, who otherwise have no role in the trial. The authors declare no conflicts of interest with respect to this research activity and are solely responsible for the drafting and editing of this paper and its final contents. Debra Egan is an employee of National Heart, Lung, and Blood Institute at National Institutes of Health. Her participation in this manuscript was performed as an official duty activity; the views expressed do not necessarily represent those of the Institutes.

Setting and oversight

ALPS is being performed by EMS in 9 ROC regions across North America[30] under exception from informed consent in emergency research in accordance with United States Food and Drug administration (FDA) regulation 21CFR50.24 and Article 2.8 of the Canadian Tri-Council Agreement for research in emergency health situations. All drugs are licensed products approved by FDA, but whose use in clinical research mandates the trial's conduct under an Investigational Drug application. Accordingly, the trial receives oversight from FDA and Health Canada, along with institutional review boards in all communities where it is being performed, and by an independent Data Safety Monitoring Board (DSMB) appointed by the National Heart, Lung and Blood Institute. The trial meets all regulatory requirements for exception from informed consent including community consultation and public disclosure. All participants and/or their legally authorized representatives receive notification of their enrollment as soon as feasible which includes detailed information about the trial, and offers them an opportunity to withdraw, thereby preventing further access to their medical records by study personnel.

Study population

Patients aged ≥18 years with non-traumatic OHCA, documented persistent or recurring VF/VT after ≥1 shock and established vascular access are eligible for randomization. ALPS will only enroll patients with active (or presumed active) VF/VT at the time of drug administration, and is not addressing the use of antiarrhythmics for secondary prophylaxis after a stable perfusing rhythm is restored. Also excluded are patients who have a written advance directive, blunt, penetrating or burn-related trauma, exsanguination, prior recipients of open label lidocaine or parenteral amiodarone during the EMS encounter or a known hypersensitivity to these drugs, protected populations (children, prisoners, or obvious pregnancy), and patients who in response to advance public disclosure activities have requested and wear a bracelet denoting their wish to be excluded from the study.

Study drugs

ALPS uses licensed parenteral preparations of lidocaine, normal saline, and a newly FDA-approved formulation of amiodarone (Nexterone, Baxter Pharmaceuticals, Deerfield, IL) in which the drug is solubilized in Captisol, an inert diluent, that can be given as a parenteral bolus without any acute hemodynamic effects,[23,31, 32, 33, 34] but is otherwise bioequivalent to other formulations of amiodarone. Use of the new formulation permits rapid parenteral administration of amiodarone from pre-filled syringes without delay or concern for hypotension, which may have compromised the observed survival outcomes in previous studies that used the conventional (older) formulation. Prior to the trial's start, study drugs were determined to maintain their stability after multiple 24 hour-cycled exposures to extremes of temperature (−20°C to 70°C) which far exceed those typically encountered in the EMS environment of ROC communities.[35]

ALPS drugs are packaged in a sealed study kit that holds 3 syringes. Each syringe is pre-filled with an identical volume of colorless fluid containing 150 mg amiodarone (450 mg total in the amiodarone kit), or 60 mg lidocaine (180 mg total in the lidocaine kit) or normal saline. Designated kits and their respective syringes are indistinguishable except by a coded

study number and are assigned in a ratio of 1:1:1 based on permuted blocks of concealed size within strata defined by the participating site and agency. A single kit is assigned to an eligible patient and upon opening, its contained treatment (amiodarone, lidocaine or placebo) determines their randomized ALPS assignment. Drug kits are distributed to sites and tracked centrally by an electronic bar-coding system.

Treatment protocol (Figure)

Patients with OHCA are treated in accordance with local EMS protocols based upon American Heart Association (AHA) Basic Life Support (BLS) and Advanced Cardiac Life Support (ACLS) guidelines.[29] ROC is concurrently conducting a BLS-based randomized trial comparing continuous chest compression CPR against conventional (30:2) CPR prior to intubation, in which ALPS patients may be co-enrolled.[36]

Eligible patients with persistent or recurrent VF/VT after ≥1 shock and established intravenous (IV) or intraosseous (IO) vascular access are allocated as quickly as possible in double-blind fashion to one of three treatment arms as determined by the contents of a randomly assigned study drug kit. Patients will initially receive a vasopressor (epinephrine or vasopressin) followed by ALPS drug via rapid bolus injection (two syringes, corresponding to 300 mg amiodarone, or 120 mg lidocaine, or saline placebo, depending upon treatment assignment), followed by defibrillation along with all standard resuscitation measures. If VF/VT persists or recurs, a supplemental dose of the same ALPS drug (a third syringe, corresponding to an additional 150 mg amiodarone or 60 mg lidocaine or placebo) can be given, for a total possible cumulative dose of 450 mg amiodarone or 180 mg lidocaine. For amiodarone, this dosing schedule corresponds to that found to improve hospital admission rates in previous clinical trials;[6,26] and for lidocaine approximates the recommended initial dose of 1–1.5 mg/kg while not exceeding a maximum acute dose of 3 mg/kg.[37] In patients estimated to weigh <100 lbs (45 kg), the total dose of ALPS drug is limited to 300 mg amiodarone, or 120 mg lidocaine, or placebo (2 syringes). Patients with persistent VF/VT after ALPS drug is exhausted are eligible for all standard prehospital interventions (exclusive of open label lidocaine or amiodarone) which may include additional defibrillation, magnesium, beta blockers and/or procainamide, as available, along with the option of rapid transport to hospital for further clinically-directed therapies. Field termination of resuscitation efforts is permitted, in accordance with local practice.

Drug administration practice

When prior defibrillation attempts fail to terminate VF/VT, current ACLS Guidelines recommend that antiarrhythmic medications be administered during the period of CPR that immediately follows a shock under the presumption that VF/VT is still present.[29] Taking time to confirm the post-shock rhythm diagnosis before treatment is considered undesirable under such circumstances because it unnecessarily interrupts chest compressions and compromises circulation. However, an alternative held view is that a brief pause in CPR for rhythm confirmation post-shock is prudent since treating patients in the absence of such knowledge (for example, were defibrillation to result in asystole) could result in inappropriate therapy, and exposure to unnecessary and potentially harmful effects of antiarrhythmic drugs. Both approaches to drug administration during cardiac arrest are

practiced clinically across the Consortium (about one-quarter of participating agencies subscribe to post-shock rhythm confirmation) without compelling evidence as yet for the superiority of one over the other. Consequently ROC agencies are permitted to administer ALPS drug in either manner during the trial in accordance with their pre-specified usual clinical practice, so long as study entry criteria (documented persistent or recurrent VF/VT after ≥1 shocks) are met. Outcomes associated with each approach are being tracked as a pre-specified subgroup analysis, affording the opportunity to explore both the effectiveness of antiarrhythmic drugs and how this may be influenced by the manner in which they are administered.

Hospitalization

All study interventions are completed before hospitalization. Upon hospital arrival, a study notification document is given to care providers which briefly describes the study, the possible treatments received before hospital arrival, and indicates that all acute hospital-initiated therapies, including open label lidocaine and amiodarone, may be administered as clinically required. Providers are advised that additional amiodarone at standard doses (totaling up to 2.1 gms/24 hours[38]) and/or lidocaine (an additional 120 mg, up to a cumulative dose of 3 mg/kg[37]) may be administered acutely in the Emergency Department at their discretion regardless of ALPS treatment assignment. Thereafter, supplemental dosing is to be guided by clinical criteria. There is also a provision for immediate unblinding via a dedicated telephone line available to all hospital care providers in instances where the identity of study drug is deemed essential to ongoing patient care. Because usual hospital care of patients is not changed by their enrollment in ALPS, unblinding is envisioned to be rarely necessary, except in exceptional circumstances of suspected anaphylaxis/toxicity to study drug, or the immediate need for high doses of lidocaine. All providers will otherwise remain blinded to study treatment.

Post-cardiac arrest clinical care of hospitalized patients in accordance with AHA Guidelines is encouraged.[39] The components of this care include therapeutic hypothermia, hemodynamic monitoring and support, ventilation/oxygenation, cardiac catheterization, monitoring for seizures, antiarrhythmic drugs, insulin therapy, and withdrawal of support. These components are monitored but not standardized by protocol. Periodic reports summarizing this information are distributed to hospitals during the course of the trial along with post-resuscitation care recommendations from published guidelines.[39]

Data collection

Data from all prehospital patient care records, including paramedic and dispatch documentation and electronic recordings are subsequently analyzed by trained study staff to document the course of resuscitation, including the timing of drug administration and other interventions. Rhythms are classified using standard definitions.[5, 6] Impedance and/or accelerometer signals are used to record EMS CPR process measures, including rates and depth of chest compression and hands-on intervals. These and other parameters describing CPR performance are regularly assessed by a Study Monitoring Committee for all agencies against uniform performance benchmarks, with provisions for remediation if not met (Appendix 2).

These data, along with possible adverse effects from ALPS treatment and clinical outcomes obtained from hospital records will be systematically abstracted and entered into a web-based data system by study personnel who are blinded to treatment assignment. The data entry system uses internal checks for consistency of data and comparisons to reference ranges. Additionally, audits and site visits are regularly performed to verify data accuracy.

Outcomes and comparisons

ALPS' primary outcome is survival to hospital discharge; a secondary outcome is functional survival at hospital discharge, assessed as a Modified Rankin Score (MRS) ≤3.[40] Drug safety focuses on the incidence of severe allergy, seizures, thrombophlebitis requiring medical or surgical intervention, bradyarrhythmias requiring temporary pacing within the first 24 hours of study drug administration and any unexpected severe adverse effects.

Rates of survival to discharge will be assessed in context of primary and secondary aims. Based on prior studies,[6,26] IV amiodarone is hypothesized to be an effective antiarrhythmic agent for cardiac arrest, whereas the effectiveness of lidocaine is less certain. Accordingly, ALPS' principal aim is to determine if survival is improved by amiodarone as compared with placebo. The secondary aims of the trial are to determine if survival is improved by lidocaine versus placebo, and/or by amiodarone versus lidocaine. Prioritizing comparisons in this manner acknowledges where differences in outcome are most expected, based on existing knowledge. Each aim also represents a clinically relevant comparison and possible differential effects between treatments in OHCA that are worthy of investigation.

Analysis populations

Resuscitation research poses unique operational and analytical challenges. For example, arrhythmias can evolve rapidly over the course of resuscitation,[41] making it inevitable that study kits will be opened in anticipation of use, but never administered because of a subsequent change in clinical eligibility for treatment (e.g. conversion of VF/VT to sustained PEA/asystole). It is also known that patients who develop VF/VT after initially presenting with asystolic/PEA arrest have a very low likelihood of survival regardless of antiarrhythmic treatment[6, 42, 43] and ideally should be excluded from an effectiveness trial. However, their exclusion would provide potentially confusing directives to prehospital providers for when to treat or not treat VF/VT with ALPS drug, which could compromise overall patient care. To accommodate such challenges in a manner that maintains ALPS' applicability to usual clinical practice, yet ensures scientific integrity, study outcomes will be evaluated in two populations: a modified intention to treat (MITT) or "efficacy population" and an intention to treat (ITT) or "safety population".

The MITT or efficacy population will consist of all eligible randomized patients receiving any dose of study drug whose initial presenting cardiac arrest rhythm was VF/VT. This is the trial's designated target population, serves as the basis for statistical power calculations and sample size estimates, and represents patients in whom it is hypothesized that a survival effect from antiarrhythmic drugs, if any, will be discerned. Conversely, the ITT or safety population includes all patients randomized to treatment with study drug (defined as those for whom a drug kit was opened) regardless of their eligibility, presenting arrhythmia or its

actual receipt. The safety population will be further stratified by those in whom study drug was administered and those in whom the drug kit was opened but its contents confirmed not to have been given.

Modification of treatment effects on primary and secondary outcomes by predetermined variables (including witnessed arrest status, bystander CPR, arrest location, time-to-ALPS-drug, number of syringes administered, IV versus IO administration, ROC site, CPR parameters, treatment arm of the BLS-CPR trial, and whether the post-shock rhythm was confirmed before drug administration) will also be performed in subgroups of the efficacy and safety populations.

Statistics

Statistical significance of the primary outcome in the MITT/efficacy population treated with amiodarone or placebo (the principal comparison), lidocaine or placebo, and the specified secondary comparisons will be determined using the Z-test for comparison of binomial proportions with pooled variance at a one-sided significance level of 0.025, and a two-sided significance of 0.05 when comparing amiodarone to lidocaine. The comparisons of each active treatment with placebo use 1-sided tests (along with an interim analysis plan that allows stopping early for benefit or for futility) because of the ethical imperative to stop enrolling in an active drug arm once it becomes futile – not permitting evidence to accrue to the point of establishing superiority of placebo over either active drug. This is not the case when comparing amiodarone against lidocaine, which uses symmetric 2-sided testing, allowing either drug to prove superior to the other. Based on projections from prior trials,[6, 26, 44] a target sample size of 3000 in the MITT/efficacy population will provide 90% power to detect an absolute increase in survival of 6.3%, from 23.4% to 29.7%, or a relative improvement of 27%. These projections represent a pragmatic balance between powering a trial to detect differences in survival that are statistically significant and would be clinically meaningful, yet achievable within a trial design facing the usual constraints of time, subjects and available resources.

Analysis of the secondary endpoint (MRS ≤3) will be compared between all treatment groups in the efficacy and safety populations using the Z-test for comparison of binomial proportions with pooled variance, and the Wilcoxon rank-sum test and proportional odds regression during exploratory analyses.[45] Patients who die before hospital admission or discharge will be assigned an MRS of 6.

Interim analyses

The DSMB will use a sequential design to guide decisions regarding stopping or altering the trial. The stopping boundaries for the comparisons of active drug to placebo are asymmetric, one-sided designs with stopping rules for superiority or futility of the active drug; whereas those for monitoring the difference between the two active drugs are symmetric with stopping rules for the superiority of either drug, using p=0.8 for the superiority boundaries and p=0.5 for the futility boundaries.[46, 47] Based on potential outcome scenarios on interim analyses, there are provisions to continue the trial with alternate treatment arms (Appendix 3).

Discussion

Amiodarone and lidocaine represent the standard of care in the treatment of shock-refractory VF/VT. The relevant question regarding these agents being addressed by ALPS is not just which therapy is superior, but whether drug treatment itself is beneficial?[10, 48, 49, 50] A placebo-controlled clinical trial is both scientifically necessary and ethically justifiable to resolve this issue. In the absence of placebo, scientific proof of one antiarrhythmic agent's equivalence or even apparent superiority over another is inconsequential, since this might only mean that one drug is less harmful than the other, or that both are comparably ineffective. By its comparisons, ALPS will provide important information about the choice and value of the most commonly administered antiarrhythmic drugs for OHCA in both absolute and relative terms. Indeed, although amiodarone is hypothesized to improve survival in ALPS, the actual outcome of this trial could challenge the very paradigm of antiarrhythmic drug use in cardiac arrest. ALPS will also provide greater insights into the optimal manner in which antiarrhythmic drugs should be administered during resuscitation that might have clinical implications for resuscitation care in their own right.

Conclusions

ALPS will determine the survival benefit of the best available antiarrhythmic drug therapies against placebo for shock-resistant VF/VT. It addresses timely, scientifically necessary and ethically justifiable questions about the choice and value of drug treatment for OHCA with direct implications for resuscitation guidelines, community-based care and clinical practice.

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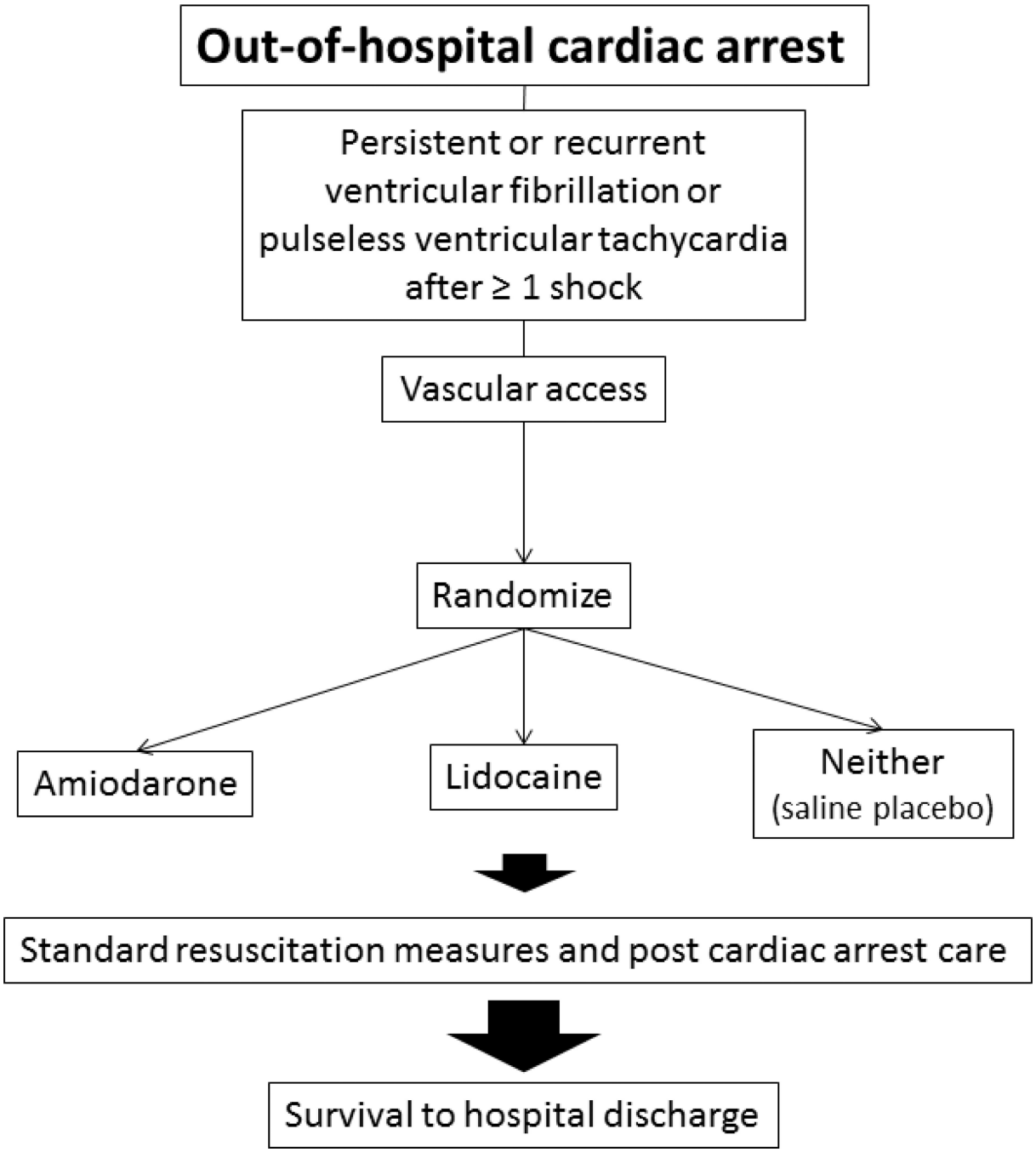

Figure.
ALPS design and treatment algorithm