Clinical question.

"In adult cardiac arrest (asystole, pulseless electrical activity, pulseless VT and VF) (prehospital [OHCA], in-hospital [IHCA]) (P), does the use of antiarrhythmic drugs (lidocaine, procaainamide, amiodarone, bretylium, magnesium) or combination with other drugs (I) compared with not using drugs (or a standard drug regimen) (C), improve outcomes (eg. ROSC, survival) (O)."

Is this question addressing an intervention/therapy, prognosis or diagnosis? intervention/therapy

State if this is a proposed new topic or revision of existing worksheet: revision

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).

Dr Ong’s search strategy
PubMed “heart arrest” or “cardiopulmonary resuscitation” or “cardiac arrest” as MESH (headings) AND “Anti-Arrhythmia Agents” or “Lidocaine” or “Lignocaine” or “procaainamide” or “amiodarone” or “bretylium” or “magnesium” as textword in headings or abstract
EMBASE search using text words (all fields) “Anti-Arrhythmia Agents” or “Lidocaine” or “Lignocaine” or “procaainamide” or “amiodarone” or “bretylium” or “magnesium” AND (cardiac arrest OR resuscitation) AHA EndNote Master library, Cochrane database for systematic reviews, Central Register of Controlled Trials, “Anti-Arrhythmia Agents”, “Lidocaine”, “Lignocaine”, “procaainamide”, “amiodarone”, “bretylium”, “magnesium”
Review of references from articles. Forward search using SCOPUS and Google scholar.
Repeat review of references on 22 Aug 2009

Dr Link’s search strategy
Two different search strategies have been pursued, both targeting the same population: cardiac arrest, heart arrest, cardiopulmonary, resuscitation, post-cardiac arrest, and postresuscitation (textword and MeSH headings when applicable).
As for the intervention, search strategy #1 focused on the keywords arrhythmia, anti-arrhythmic, and unstable (MeSH headings when applicable), while search strategy #2 looked at prophylactic use of single antiarrhythmic agents.
Database searched: PubMed, Cochrane Library (including Cochrane database for systematic reviews and Cochrane Central Register of Controlled Trials), Embase, and AHA EndNote Master Library.
Moreover, cross-references from articles and reviews, and forward search using SCOPUS and Google scholar are ongoing.
Details of search are reported below.
PubMed
Search strategy #1: ("Heart Arrest"[Mesh]) OR (cardiac arrest) OR (cardiopulmonary resuscitation) OR ("Resuscitation"[Mesh]) AND ((Arrhythmia) OR (Anti-Arrhythmic) OR (Unstable)) AND ((Post-Cardiac Arrest) OR (postresuscitation))
Search strategy #2: ("Amiodarone"[Mesh]) OR ("Lidocaine"[Mesh]) OR ("Procaainamide"[Mesh]) OR ("Magnesium Sulfate"[Mesh]) OR ("Diltiazem"[Mesh]) OR ("Verapamil"[Mesh]) OR ("Digoxin"[Mesh]) OR ("Flecainide"[Mesh]) OR ("Propafenone"[Mesh]) OR ("Sotalol"[Mesh]) OR ("esmolol"[Substance Name]) OR
("Atenolol"[Mesh]) OR ("Metoprolol"[Mesh])) AND (((prophylactic) OR (Post-Cardiac Arrest) OR (postresuscitation))) AND ((("Resuscitation"[Mesh]) OR ("Cardiopulmonary Resuscitation"[Mesh]) OR (cardiopulmonary resuscitation) OR ("Heart Arrest"[Mesh]) OR (cardiac arrest)))

Cochrane
Search strategy #1: ((prophylac*:ti,ab,kw) AND ((Arrhythmia):ti,ab,kw) OR ("Anti-Arrhythmia Agents"[Mesh])) AND ("Heart Arrest"[Mesh]) OR ("Cardiopulmonary Resuscitation"[Mesh])
Search strategy #2: single antiarrhythmic agents[Mesh] AND prophylac* AND ("Heart Arrest"[Mesh]) OR ("Cardiopulmonary Resuscitation"[Mesh])

Embase
Search strategy #1: ("Heart Arrest"[Mesh]) OR ("Resuscitation"[Mesh]) AND (Arrhythmia[Mesh]) OR (Anti-Arrhythmic[Mesh]) OR (Unstable[Mesh]) AND (Post-Cardiac Arrest) OR (postresuscitation)
Search strategy #2: (single antiarrhythmic agents[Mesh]) AND (((prophylactic) OR "Prophylaxis"[Mesh]) OR (Post-Cardiac Arrest) OR (postresuscitation))) AND ("Heart Arrest"[Mesh]) NOT (resuscitation)

EndNote
Search strategy #1: (Cardiac Arrest OR Resuscitation) AND (Arrhythmia OR Anti-Arrhythmic OR Unstable) AND (Post-Cardiac Arrest OR postresuscitation)
Search strategy #2: (single antiarrhythmic agents) AND (prophylactic OR Prophylaxis OR Post-Cardiac Arrest OR postresuscitation) AND (Cardiac Arrest OR Resuscitation)


Task force comments included. Combined submission with Dr Mark Link

**State inclusion and exclusion criteria**
Inclusion criteria included: human studies of adult cardiac arrest and anti-arrhythmic agents, peer-review
Exclusion criteria included: review articles and case reports, case series, not pertinent studies.

**Number of articles/sources meeting criteria for further review:**

PubMed “heart arrest” or “cardiopulmonary resuscitation”” or “cardiac arrest” as MESH (headings) AND “Anti-Arrhythmia Agents” or “Lidocaine” or “Lignocaine” or “procainamide” or “amiodarone” or “bretylium” or “magnesium” as textword in abstract 185 articles

On further evaluation of relevant articles:

25 studies met inclusion criteria for further review. Of these 9 were LOE 1, 2 LOE 2, 2 LOE 3, 5 LOE 4, 7 LOE 5.
## Summary of evidence
### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
</table>
| Good              | {Dorian, 2002, 884} B (amiodarone vs lidocaine)  
{Kudenchuk, 1999, 871} B (amio vs lido) | Herlitz, 2003, 25 (lido vs no lido)  
{Herlitz, 1997, 199} A (lidocaine vs no lidocaine) | {Gorgels, 1996, 43} E (procainamide vs lido)  
{Somberg, 2002, 853} B (amio vs lido) |
| Fair              | {Nowak, 1981, 404} B (bretlyium vs placebo) | {Ohshige, 2005, 53} C (lidocaine vs no lidocaine) | |
| Poor              | | | {Ohshige, 2005, 53} C (lidocaine vs no lidocaine) |

### Level of evidence
- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint

**Italics** = Animal studies

## Evidence Neutral to Clinical question

<table>
<thead>
<tr>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
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| Good | {Allegra, 2001, 245} A (Mg vs placebo)  
{Hassan, 2002, 57} A (Mg vs placebo)  
{Olson, 1984, 807} B (Bretylium vs Lido)  
{Haynes, 1981, 353} C (bretylium vs lido) | {Pollak, 2006, 199} C (amio vs lido)  
{Rea, 2006, 1617} E (amio vs lido)  
{Stiell, 1995, 264} B | {Kovoor, 2005, 518} C (sotalol vs lignocaine)  
{Thel, 1997, 1272} A (Mg vs placebo)  
{Tahara, 2006, 442} B (nifekalan t vs lido)  
{Skrifvars M 2004, 582} E (amio)  
{Kowey, 1995, 3255} E (amio vs lido)  
{Levine JH 1996, 67} E (amio) |
<table>
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<tr>
<th>Poor</th>
<th>{Fatovich, 1997, 237} A (Mg vs placebo)</th>
<th>(bretylium, lido, procainamide)</th>
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**Level of evidence**

- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint

**Evidence Opposing Clinical Question**

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<th>Poor</th>
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| 1    | 2 | 3 | 4 | 5 |

**Level of evidence**

- **A** = Return of spontaneous circulation
- **B** = Survival of event
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint

*Italics = Animal studies*
Reviewers' Final Comments and Assessment of Benefit / Risk:

"In adult cardiac arrest (asystole, pulseless electrical activity, pulseless VT and VF) (prehospital [OHCA], in-hospital [IHCA]) (P), does the use of antiarrhythmic drugs (lidocaine, procainamide, amiodarone, bretylium, magnesium) or combination with other drugs (I) compared with not using drugs (or a standard drug regimen) (C), improve outcomes (eg. ROSC, survival) (O)."

This is a revision of worksheet 21 from ILCOR 2005.

We have divided the three time frames of resuscitation and treatment into:
1) During resuscitation
2) After admission to the hospital/ED (implying ROSC has returned)
3) Prior to hospital discharge and continuing long-term (implying patient recovery)

Our question and the focus of this worksheet, ALS-D-025, addresses the first time frame. Another worksheet questions addresses time frame 2. There is no specific worksheet question which address time frame

There are actually several parts to this question, and we have divided the evidence according to the type of antiarrhythmic drugs being studied in various publications. However we should note that nearly all of the studies report interventions for Ventricular Fibrillation (VF) and pulseless Ventricular Tachycardia (VT) rather than for asystole or PEA. Only one study (Nowak, 1981) included patients in asystole or PEA. Evidence from Randomised Controlled Trials (RCT) is scant, and most of the studies use another antiarrhythmic drug as a control, rather than a placebo or no treatment. Thus, conclusions are limited to the relative effectiveness of antiarrhythmic drugs.

Studies looking at the use of Lidocaine in adult cardiac arrest:
{Herlitz, 1997, 199} LOE2, Fair Quality, Supporting – OHCA retrospective review, looking at the use of Lidocaine for VF. Reported increased ROSC with lidocaine
{Ohshige, 2005, 53} LOE2, Poor Quality, Supporting – OHCA controlled trial, looking at the use of Lidocaine for VF. Found increased survival in the group treated with lidocaine
{Kovoor, 2005, 518} LOE1, Fair Quality, Neutral - OHCA RCT looking at the use of Lidocaine vs Sotalol for VF. Reported no difference in ROSC.
{Weaver, 1990, 2027} LOE 1, Fair Quality, Neutral (lidocaine vs epinephrine) and LOE 3, Fair Quality, Opposing - OHCA, looking at the use of lidocaine vs bicarbonate for VF. Reported decreased survival to admission with lidocaine.
{Tahara, 2006, 442} LOE3, Fair Quality, Neutral - OHCA historical controls, looking at the use of nifekalant and lidocaine for VF. Reported decreased survival to admission with lidocaine.
{van Walraven, 1998, 544} LOE2, Fair Quality, Opposing – In-hospital, retrospective review, looking at the use of Lidocaine for VF. Reported decreased survival to 1h associated with lidocaine.

Studies looking at the use of Amiodarone in adult cardiac arrest:
{Kudenchuk, 1999, 871} LOE1, Good Quality, Supporting – OHCA RCT looking at the use of Amiodarone vs placebo (although 92% of placebo group received antiarrhythmic drugs, predominantly lidocaine, before randomization and 82% received antiarrhythmic drugs after randomization) for VF. Reported improved survival to admission for Amiodarone.
{Levine JH 1996, 67} LOE5, Fair Quality, Neutral - Trial in which in-patients with recurrent sustained hypotensive VT or VF who had failed treatment with procainamide, lidocaine and bretylium were given one of three doses of IV amiodarone. Of 273 patients 40% survived 24 hours without another arrhythmic episode. There was no clear difference between the three different doses of amiodarone.
{Skrifvars M 2004, 582} LOE 4, Fair Quality, neutral- Retrospective case series of IV amiodarone use in Helsinki which shows that undiluted amiodarone can be used safely.
Studies looking at the use of Magnesium in adult cardiac arrest:
{Allegra, 2001, 245} LOE1, Good Quality, Neutral – Prehospital RCT looking at the use of Mg vs placebo for VF Reported no difference in ROSC
{Thel, 1997, 1272} LOE1, Fair Quality, Neutral - ICU, RCT, looking at the use of Mg vs placebo for VF. Reported no difference in ROSC
{Fatovich, 1997, 237} LOE1, Fair Quality, Neutral - ED RCT looking at the use of Mg vs placebo for VF. Reported no difference in ROSC

Studies looking at the use of Bretylium in adult cardiac arrest:
{Nowak, 1981, 404} LOE1, Fair Quality, Supporting – ED RCT, looking at the use of Bretylium vs placebo for all cardiac arrest rhythms. Found improved survival to admission for bretylium

Studies looking at the use of Procainamide & Lidocaine in adult cardiac arrest:
{Gorgels, 1996, 43} LOE5, Fair Quality, Supporting - Inhospital, randomized prospective, looking at the use of Procainamide vs Lidocaine for sustained VT. Reported improved termination of VT with Procainamide. Not all patients were in cardiac arrest.

Studies looking at the use of Procainamide & quinidine in adult cardiac arrest:
{Hallstrom, 1991, 1025} LOE4, Fair Quality, Opposing - OHCA, retrospective review, looking at the use of antiarrhythmics for VF. Reported that use of procainamide & quinidine was associated with decreased survival

Studies looking at the use of Bretylium & Lidocaine in adult cardiac arrest:
{Haynes, 1981, 353} LOE1, Good Quality, Neutral, {Olson, 1984, 807} LOE2, Good Quality, Neutral – OHCA, randomised trials, looking at the use of Bretylium vs Lidocaine for VF. Reported no difference in survival

Studies looking at the use of Bretylium & Amiodarone in adult cardiac arrest:
{Kowey, 1995, 3255} LOE5, Fair Quality, Neutral – Inhospital, prospective trial, looking at the use of Bretylium & Amiodarone for unstable VT or VF. However not all patients were in cardiac arrest. Reported no difference in survival to 48h.

Studies looking at the use of Lidocaine & Amiodarone in adult cardiac arrest:
{Dorian, 2002, 884} LOE1, Good Quality, Supporting – OHCA RCT looking at the use of Amiodarone vs Lidocaine for VF Reported improved survival to admission with Amiodarone.
{Rea, 2006, 1617} LOE2, Fair Quality, Neutral – Inhospital, retrospective review, looking at the use of Amiodarone vs Lidocaine for VF Reported no difference in survival to 24h
{Pollak, 2006, 199} LOE4, Fair Quality, Neutral – Inhospital, retrospective review, looking at the use of Amiodarone vs Lidocaine for VF. Reported no difference in survival.
{Somberg, 2002, 853} LOE1, Fair Quality, Supporting – Inhospital RCT, looking at the use of Amiodarone vs Lidocaine for VF. Reported improved survival to 1h with Amiodarone

Studies looking at the use of Lidocaine-procainamide-bretylium in adult cardiac arrest:
{Stiell, 1995, 264} LOE2, Fair Quality, Neutral –Inhospital, retrospective review, looking at the use of antiarrhythmics for VF. Reported increased survival to 1h with procainamide, but no difference compared to patients who did not receive anti arrhythmic drugs with bretylium and lidocaine.
{Nademanee, 2000, 742} LOE 5, Fair Quality, Opposing – Inhospital, controlled trial, looking at the use of antiarrhythmics vs sympathetic blockade for prevention of VF. Reported decreased survival with antiarrhythmics compared to sympathetic blockade.

Acknowledgements:

Dr Peter Morley for his inputs

Citation List


LOE1, Good Quality, Neutral, – Prehospital RCT looking at the use of Mg vs placebo for VF Reported no difference in ROSC


Randomized double-blind trial comparing amiodarone (n=180) with lidocaine (n=167) for refractory VF/VT demonstrating that amiodarone leads to substantially higher rates of survival to hospital admission. Refractory VF was defined as VF that did not terminate after a series of 3 shocks, epinephrine and fourth shock or VF that recurred after successful defibrillation or VF that occurred for the first time when their initial cardiac arrest rhythm was asystole or PEA. The mean time interval from arrest to drug administration was 25 minutes. The treatment groups had similar clinical profiles. Following administration of amiodarone 22.8% of patients were admitted alive, as compared to 12.0% in the lidocaine group (p=0.009; odds ratio, 2.17). However, there was no difference in survival to hospital discharge. Among the 41 patients who survived to hospital admission after receiving amiodarone, 9 (5 percent of the entire group) survived to hospital discharge, as compared with 5 of the 20 initial survivors in the lidocaine group (3 percent of the entire group, P= 0.34). In addition, there was no placebo group, thus whether amiodarone was beneficial or lidocaine harmful could not be ascertained.

LOE 1, good quality, neutral for question which includes all antiarrhythmic drugs, but does show superiority of amidarone over lidocaine, B


LOE1, Fair Quality, Neutral - ED RCT looking at the use of Mg vs placebo for VF. Reported no difference in ROSC


LOE 5, Fair Quality, Supporting - Inhospital, randomized prospective, looking at the use of Procainamide vs Lidocaine for sustained VT, not cardiac arrest. Reported improved termination of VT with Procainamide.


LOE4, Fair Quality, Opposing - OHCA, retrospective review, looking at the use of antiarrhythmics for VF. Reported that use of procainamide & quinidine was associated with decreased survival


LOE1, Good Quality, Neutral – Prehospital RCT looking at the use of Mg vs placebo for VF Reported no difference in ROSC


LOE1, Good Quality, Neutral, – OHCA, randomised trial, looking at the use of Bretylium vs Lidocaine for VF. Reported no difference in survival


LOE 2, Fair Quality, Supporting – A retrospective study of the use of lidocaine in cardiac arrest. There was an inherent bias in who received lidocaine in this study because only ambulances with nurses on board could give lidocaine in the field. Yet the patients receiving lidocaine were more likely to survive to hospital admission, but not to hospital discharge.


20 year retrospective review of survival in cardiac arrest. In multivariate analysis those give lidocaine in the ED had an improvement in survival (odds ratio of 1.64; 95% CI of 1.12 to 2.10).

LOE 2, retrospective, fair quality, supportive C


LOE1, Fair Quality, Neutral – Small OHCA RCT looking at the use of Lidocaine vs Sotalol for VF. Reported no difference in ROSC.

LOE5, Fair Quality, Neutral – Inhospital, prospective trial, looking at the use of Bretylium & Amiodarone for unstable VT or VF. However not all patients were in cardiac arrest. Reported no difference in survival to 48h.


LOE1, Good Quality, Supporting Double-blind randomized controlled trial of amiodarone vs placebo in OOH VT or VF arrest resistant to 3 defibrillatory shocks. This study demonstrated an improved survival to hospital admission in patients administered amiodarone compared to placebo. Baseline characteristics of the 2 groups were similar (amiodarone n=246, placebo n=258). Elapsed time from arrest to amiodarone administration averaged 21.4 minutes. Post-ROSC hypotension or bradycardia were more frequent in the amiodarone group. Odds ratio favoring amiodarone for hospital admission was 1.6 (p=0.02). There was no difference in survival to hospital discharge (13.4 to 13.2%).


LOE5, Fair Quality, Neutral - Trial in which in-patients with recurrent sustained hypotensive VT or VF who had failed treatment with procainamide, lidocaine and bretylium were given one of three doses of IV amiodarone. Of 273 patients 40% survived 24 hours without another arrhythmic episode. There was no clear difference between the three different doses of amiodarone.


LOE 5, Fair Quality, Opposing – Inhospital, controlled trial, looking at the use of antiarrhythmics vs sympathetic blockade for prevention of VF. Reported decreased survival with antiarrhythmics compared to sympathetic blockade.


LOE1, Fair Quality, Supporting – ED RCT, looking at the use of Bretylium vs placebo for all cardiac arrest rhythms. Found improved survival to admission for bretylium.


LOE2, Poor Quality, Supporting – OHCA controlled trial, looking at the use of Lidocaine for VF. Ambulances manned with physicians who were allowed to use epinephrine, lidocaine and atropine were compared to ambulances manned without physicians. Survival was improved in those patients lucky enough to be cared for
by a more advanced EMS system in which lidocaine was allowed. However, this study suffers from so many confounders that it offers little support for lidocaine.


LOE1, Good Quality, Neutral – OHCA, randomised trials, looking at the use of Bretylium vs Lidocaine for VF. Reported no difference in survival


LOE2, Fair Quality, Neutral A retrospective study of in-hospital arrest. Inclusion criteria was VT or VF arrest. Of 95 patients, roughly a third received amiodarone and the remainder chiefly lidocaine. In this small study there was no difference in survival between the groups given amiodarone vs lidocaine


LOE2, Fair Quality, Neutral – Inhospital, retrospective review, looking at the use of Amiodarone vs Lidocaine for VF Reported no difference in survival to 24h


LOE 4, Fair Quality, neutral, Retrospective case series of IV amiodarone use in Helsinki which shows that undiluted amiodarone can be used safely.


LOE 5, Fair Quality, A very small multicenter double-blinded, parallel-designed, randomized trial evaluating the effectiveness of amiodarone (Amio-Aqueous) and lidocaine on shock resistant VT (lidocaine as control) Amiodarone was superior to lidocaine in: (1) termination of the VT, (2) survival at 1 hour, (3) survival at 24 hours (primary end point). However, there was no placebo group thus it is not clear whether amiodarone was beneficial or lidocaine harmful

LOE 2, Fair Quality, Neutral – Inhospital, retrospective review, looking at the use of antiarrhythmics for VF. Reported increased survival to 1h with procainamide, but no difference compared to patients who did not receive antiarrhythmic drugs with bretylium and lidocaine.


LOE3, Fair Quality, Neutral - Retrospective study evaluating 120 OOH cardiac arrest patients refractory to 3 shocks from a defibrillator, epinephrine and a 4th shock who then received nifekalant (a class III AAD) or lidocaine. Nifekalant administration was associated with better ROSC and 24 hour survival. However there was no control group, thus whether nifekalant was beneficial or lidocaine detrimental could not be ascertained.


LOE1, Fair Quality, Neutral - ICU, RCT, looking at the use of Mg vs placebo for VF. Reported no difference in ROSC


LOE 4, Fair Quality, Opposing - Small retrospective case series of patients with hemodynamically tolerated VT in which IV amiodarone terminated VT in 6/41 patients within 20 minutes, and 12/41 within 1 hour


LOE2, Fair Quality, Opposing – Inhospital, retrospective review, looking at the use of Lidocaine for VF. Reported decreased survival to 1h associated with lidocaine


LOE 1, Fair Quality, Neutral (lidocaine vs epinephrine); LOE 3, Fair, Opposing (Lidocaine versus bicarbonate infusion) - OHCA, looking at the use of lidocaine vs retrospective group using bicarbonate for VF. Reported decreased survival to admission with lidocaine.