WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)

Tommaso Pellis, MD
Mark S. Link, MD

Date Submitted for review September 30th 2009. Data reviewed, search strategy re-run: no further revisions are needed.

Clinical question.

"In adult patients with ROSC after cardiac arrest (prehospital or in-hospital) (P), does the use of prophylactic antiarrhythmic drugs (I) as opposed to standard care (C), improve outcome (O) (eg. survival)?"

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).

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 ("Procainamide"[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)

- State inclusion and exclusion criteria

Exclusion criteria: reviews, case reports, letters, and studies not relevant to the clinical question such as studies focusing on post myocardial infarction patients or on anti-arrhythmic agents only in the context of cardiac arrest and not in post-resuscitation settings..
Inclusion criteria: peer-review only, some reviews have been retained for bibliographic search. Five reviews have been retained for orientation and cross-referencing.

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

24 studies met inclusion criteria for further review, of these only 2 were classified as LOE 4 and 17 as LOE 5. Five are reviews.

Summary of evidence

Evidence Supporting Clinical Question

Good					
Fair				**[Skrifvars et al. 2003] E**	[Nademanee et al. 2000] C* [Somberg et al. 2002] B*
Poor					
	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
* different patient population from worksheet question

Evidence Neutral to Clinical question

Good					[Dorian et al. 2002] B* [Kudenchuk et al. 1999] B*
Fair					[Connolly et al. 2006] E*
Poor					
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint
B = Survival of event D = Intact neurological survival *Italics = Animal studies*
* different patient population from worksheet question

Review

[Anderson 1995]
[Bourque et al. 2007]
[Huikuri et al. 2001]
[John 2004]
[Reiter et al. 1998]

Evidence Opposing Clinical Question

Good					[1997] E* [Anderson 1995] E* [Connolly et al. 2000] E* [Connolly et al. 2000] E* [Kuck et al. 2000] E*
Fair				**[Engdahl et al. 2000] C**	[Buxton et al. 1999] E* [Salukhe et al. 2004]. E* [Wever et al. 1995] E* [Hennersdorf et al. 2003] E* [1991] E* [Greene et al. 2000] E* [Credner et al. 1998] E*
Poor					
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint
B = Survival of event D = Intact neurological survival *Italics = Animal studies*
* different patient population from worksheet question

REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

"In adult patients with ROSC after cardiac arrest (prehospital or in-hospital) (P), does the use of prophylactic antiarrhythmic drugs (I) as opposed to standard care (C), improve outcome (O) (eg. survival)?"

There are no controlled studies (LOE 1-3) that specifically and directly address the use of prophylactic antiarrhythmic drugs (AAD) after hospitalization following resuscitation from cardiac arrest (CA). There are only two retrospective (LOE 4) studies evaluating post-resuscitation care but that do not circumstantiate the precise number of patients treated with AAD. Because of the lack of data strictly pertinent to the original worksheet question, available evidence from other populations (i.e. CA victims with ongoing resuscitation and refractory ventricular fibrillation [VF] / ventricular tachycardia [VT], survivors of CA undergoing late secondary AAD prophylaxis or ICD implantation) has been also reviewed, with the intent of possibly inferring relevant information. However, although the patient population is the same, the time frame is different and thus all these studies are considered LOE 5 (reported not in bold and marked with an asterisk in the summary tables).

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

We have interpreted our assigned question as falling into time period 2. However, there are no trials that address antiarrhythmic agents during this time period, and even the data on recurrent VT and VF is scant. Thus, we have also evaluated trials from time periods 1 and 3. However, because the time frame of treatment is different we have considered all these studies as LOE 5.

1) Evidence from two (LOE 5 – due to different time frame of treatment – good quality) large controlled trials on treatment of OOH-CA victims with refractory VT/VF (different patient population), although only powered for a difference in survival to hospital admission, demonstrate the superiority of amiodarone over placebo and lidocaine [Kudenchuk et al. 1999] [Dorian et al. 2002]. Both of these trials randomized patients with on-going cardiac arrests, and specifically targeted those individuals who had failed defibrillation or had recurrent VT/VF. Continuation of antiarrhythmic agents in the hospital was not part of the study design and it is not clear how many if any had continuation of study drugs. A small industry-sponsored randomized controlled trial (LOE 5 – due to different time frame – fair quality) on in-hospital patients also supports the use of amiodarone over lidocaine for incessant VT [Somberg et al. 2002]. Survival at 24 hours, the primary endpoint, was of 1 (9%) and 7 (39%) patients respectively in the amiodarone and lidocaine group ($p<0.01$).

2) A retrospective study with no controls (LOE 4, fair quality), focusing on early post-resuscitation care of patients initially in VF/VT, demonstrated that in-hospital administration of AAD such as amiodarone or lidocaine were seldom necessary and, by multiple logistic regression analysis, that were not independently associated with improved 6 months survival [Skrifvars et al. 2003]. To the contrary, the use of β-blockers was positively associated with survival: mortality was 44% in patients receiving early treatment with metoprolol or bisprolol as compared to 79% among those who did not. Beta-blockers did not impact negatively on hemodynamic variables.

Although flawed by several important limitations, a prospective study suggests that in patients with electrical storm, sympathetic blockade rapidly reduced the episodes of VF, improved short term survival and hospital discharge when compared to conventional ACLS-guided therapy [Nademanee et al. 2000]. The main criticisms to this study are: the absence of randomization (assignment to treatment protocol was based only on physician preference), ACLS-guided therapy relied on old antiarrhythmic knowledge according to the 1994 guidelines and, the sympathetic blockade group received when possible concomitant therapy with oral amiodarone. In addition, the patient population was not one of cardiac arrest, but ongoing arrhythmias in hospital. The only other supportive study [Somberg et al. 2002], suffers from the same limitation; the patients are those with ongoing arrhythmias while in hospital. Patients in these two studies were not give prophylactic antiarrhythmic agents, but were give antiarrhythmic agents for treatment of ongoing arrhythmias.

Data from trials which evaluate the hospital course of resuscitated patients do not demonstrate a high frequency of recurrent arrhythmias. In Engdahl's et al [Engdahl et al. 2000] study only 53 of 1038 cardiac arrest survivors had VF/VT after hospital admission.

3) When examining the high risk population of CA survivors from VF/VT, the available evidence on late secondary prophylaxis, although not always univocal, can be summarized as follows:

1. ICD are superior to AAD therapy, specifically amiodarone, metoprolol or class 1 antiarrhythmics, in improving all cause mortality [1991, 1997, Connolly et al. 2000, Hennersdorf et al. 2003, Wever et al. 1995] and sudden death [Connolly et al. 2000, Hennersdorf et al. 2003, Kuck et al. 2000, Salukhe et al. 2004, Wever et al. 1995].
2. Amiodarone plus β-blockers reduce the number of painful shocks [Connolly et al. 2006] and amiodarone is successful in treating and preventing electrical storms [Credner et al. 1998, Greene et al. 2000], hence contributing to an improved quality of life in ICD recipients.

In summary, the are no studies specifically addressing the use of AAD after admission to the hospital in patients resuscitated from CA. The only retrospective study focusing more in general on post-resuscitation care indirectly provides information relevant to the worksheet question. This investigation suggests that β-blockers are positively associated with survival. To the contrary, amiodarone and lidocaine are rarely used (as confirmed by other evaluations of the hospital course of resuscitated patients) and are not associated with with improved survival at multiple logistic regression analysis. Studies on AAD early after ROSC and on post-resuscitation care should be encouraged.

Acknowledgements:

Citation List

(1991). "Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation (the CASCADE study)". Am J Cardiol 67: 578-84.

LOE 5, fair quality, opposing, E
This randomized controlled clinical trial compared empiric amiodarone to "other" or conventional antiarrhythmic treatment (when possible guided by EPS) in patients that survived VF/VT arrest. Mortality much higher in patients treated with antiarrhythmics than those with implantable defibrillators.
No comment about industry funding

(1997). "A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators". N Engl J Med 337: 1576-83.

LOE 5, good quality, opposing, E
The AVID trial examined the effect on overall survival of initial therapy with an ICD (507 pts) as compared with empiric therapy with amiodarone or EP guided-therapy with sotalol (509 pts) in patients resuscitated from VF or with symptomatic sustained VT. A very small number of patients received sotalol in this trial and thus it was almost totally a trial comparing ICD to amiodarone therapy. At a mean follow-up of 18.2 +/- 12.2 months patients treated with the defibrillator had a better survival throughout the study (death rate were 15.8 +/- 3.2 % in ICD group vs 24.0 +/- 3.7 in AAD group). In the ICD group after 1 year the reduction in mortality was 38% compared to the group on antiarrhythmic drugs. The average unadjusted length of additional life associated with cardioverter–defibrillator therapy was 2.7 months at 3 years. However, more patients were taking β-blockers (P<0.001) and slightly more patients were taking digitalis (P<0.04) in the defibrillator group than in the antiarrhythmic-drug group.
Supported by a contract (N01-HC-25117) with the National Heart, Lung, and Blood Institute, Bethesda, Md.

Anderson JL. (1995). "Contemporary clinical trials in ventricular tachycardia and fibrillation: Implications of ESVEM, CASCADE, and CASH for clinical management". J Cardiovasc Electrophysiol 6: 880-6.

LOE 5, good quality, opposing, E. Review
Review discussing antiarrhythmic trails published shortly before 1995.
CAST (antiarrhythmic prophylaxis post-AMI): compared to placebo, increased mortality was observed with lidocaine (Class IB), 6%, quinidine (Class IA), 19%, flecainide/propaphenone (Class IC), 31%; beta-blockers and amiodarone led to a reduction in the risk of death.
ESVEM evaluated VT/VF (486) patients relatively to appropriateness of: drug prophylaxis and monitoring tool (electrophysiologic study or Holter) to predict drug efficacy. Sotalol (Class II/III agent) was more effective than other drugs (Class I), there was no difference between methods for determining an efficacy prediction.
CASCADE evaluated antiarrhythmic therapy for survivors of OOH-CA not AMI related (n=228): amiodarone reduced mortality form 23% of conventional Class I therapy to 9% at 1 year and from 44% to 24% at 3 years (no true control).
CASH (antiarrhythmic drug therapy vs. ICD in survivors of CA) (n=400): propaphenone group had a higher mortality (20%) when compared to amiodarone, metoprolol and ICD (all 14% mortality).
No comment about industry funding

Bourque D, Daoust R, Huard V, et al. (2007). "beta-Blockers for the treatment of cardiac arrest from ventricular fibrillation?". Resuscitation 75: 434-44.

Review
Setting: treatment of CA
An intriguing review of beta-blockers for the treatment of cardiac arrest from VF or pulseless VT. The authors searched PubMed and Embase from 1996 to 2006. The available evidence, ranging from animal studies to human prospective and randomized trials, is presented.
No comment about industry funding

Buxton AE, Lee KL, Fisher JD, et al. (1999). "A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators". N Engl J Med 341: 1882-90.

Connolly SJ, Dorian P, Roberts RS, et al. (2006). "Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial". JAMA 295: 165-71.

LOE 5, fair quality, neutral, E
This randomized double-blind controlled trial compared both amiodarone (administered with a b-blocker) and sotalol with standard b-blocker therapy for prevention of ICD shocks in patients with spontaneous or inducible VT or VF, receiving an ICD. Population investigated: patients with sustained VT, VF, or cardiac arrest (not within 72 hours of acute myocardial infarction) and a left ventricular ejection fraction of 40% or lower, inducible VT or VF by programmed ventricular stimulation. Patients randomized to receive a b-blocker could receive metoprolol, carvedilol, or bisoprolol. Due to slower than expected enrolment the revised single hypothesis was that treatment with either amiodarone plus b-blocker or with sotalol would reduce the risk of shocks compared with treatment with a b-blocker alone. There were no differences in baseline patients characteristics. Amiodarone plus b-blocker significantly reduced the risk of shock compared with b-blocker alone (HR, 0.27; P<0.001) and sotalol (HR, 0.43; P=0.02). A significant reduction was observed in the risk of a shock when the 274 patients randomized to either of the 2 active treatment groups, sotalol or amiodarone plus b-blocker, were compared with the 138 patients randomized to b-blocker alone (HR, 0.44; P<0.001). Although there was a trend, sotalol did not significantly reduce the risk of shock compared with b-blocker alone (HR, 0.61; P=0.055). Compared with b-blocker treatment alone, approximately 35 patients would need to be treated for 1 year with amiodarone plus b-blocker therapy to prevent a shock occurring in 10 patients. Limitations of the study: decreased quality of life is a major consequence of ICD shocks, however, quality of life was not formally assessed; one cannot extrapolate from our study that patients with primary prevention ICD would benefit similarly from amiodarone or sotalol.
Drs Connolly, Dorian, and Hohnloser have received research grants from St Jude Medical. As a St Jude Medical employee, Dr Fain is a stockholder in the company. This study was funded by St Jude Medical, Sylmar, Calif.

Connolly SJ, Gent M, Roberts RS, et al. (2000). "Canadian implantable defibrillator study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone". Circulation 101: 1297-302.

LOE 5, good quality, opposing, E
Randomized trial of ICD vs. amiodarone for late secondary prophylaxis in patients resuscitated from previous sustained ventricular arrhythmia (659 pts, respectively 328 and 331).
The primary outcome event was death from any cause. The secondary outcome event was arrhythmic death. Mean follow-up was 3 years. Concomitant medications: at 3 years, the rate of concomitant use of amiodarone in ICD patients was 21.7%, and the use of the ICD in amiodarone patients was 18.6%; significantly more drugs were used in patients randomized to ICD treatment, and particularly in the use of either sotalol or another β-blocker: 22.9% for the amiodarone group and 53.3% for the ICD group. A nonsignificant reduction in all-cause mortality occurred with the ICD compared with amiodarone, from 10.2% per year to 8.3% per year (19.7% relative risk reduction [RRR]; P =0.142), and in arrhythmic death with the ICD, from 4.5% per year to 3.0% per year (32.8% RRR;P =0.094). The authors conclude that in light of the results of the AVID study, this trial provides further support for the superiority of the ICD over amiodarone in the treatment of patients with symptomatic sustained VT or resuscitated cardiac arrest. Supported by the Medical Research Council of Canada. The amiodarone was supplied by Wyeth-Ayerst Pharmaceuticals, Ltd.

Connolly SJ, Hallstrom AP, Cappato R, et al. (2000). "Metal-analysis of the implantable cardioverter defibrillator secondary prevention trials". Eur Heart J 21: 2071-8.

LOE 5, good quality, opposing, E
A meta-analysis of the 3 randomized trials (AVID, CASH, and CIDS) on ICD vs amiodarone for late prophylaxis in patients that suffered malignant ventricular arrhythmia. The analysis demonstrated a significant reduction in both all-cause mortality and in arrhythmic death with the ICD. For total mortality, the hazard ratio (ICD:amiodarone) was 0.73 (P<0·001), and for arrhythmic death the hazard ratio was 0.49 (P<0·001). For arrhythmic death there appears to be steady incremental separation throughout the 6 years between the two treatment arms. The prolongation of life by the ICD over amiodarone was 2.1 months at 3 years of follow-up and 4.4 months at 6 years. An ICD would have to be implanted in 29 patients to save one life per year of follow-up. Analysis of subgroup interactions in the pooled database showed that patients with left ventricular ejection fraction >35% had significantly less benefit from the ICD than those with ejection fraction of =<35% (P=0·011). Second, There was no significant interaction between beta-blocker use at discharge and ICD benefit (P=0·095).
In conclusion, the meta-analysis demonstrates a 28% relative reduction in death with the ICD.
No comment about industry funding

Connolly SJ, Hallstrom AP, Cappato R, et al. (2000). "Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg . Canadian Implantable Defibrillator Study". Eur Heart J 21: 2071-8.

Credner SC, Klingenheben T, Mauss O, et al. (1998). "Electrical storm in patients with transvenous implantable cardioverter-defibrillators: incidence, management and prognostic implications". J Am Coll Cardiol 32: 1909-15.

LOE 5, fair quality, opposing, E
The incidence of electrical storms, defined as VT or VF resulting in device intervention > or = 3 times during a single 24-h period, was investigated in 136 recipients of an ICD. During follow up (403+/-242 days). Electrical storm (median 8 VT/VF; range: 3 to 50) occurred in 10% (14/136 patients) at an average of 133+/-135 days after ICD implantation. The most successful antiarrhythmic strategy was a combined therapy with beta-blockers and intravenous amiodarone whereas class I antiarrhythmic drugs were only occasionally effective in managing the electrical storm. Survival as estimated by the Kaplan-Meier curve was negatively influenced by electrical storm episodes.
No comment about industry funding

Dorian P, Cass D, Schwartz B, et al. (2002). "Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation". N Engl J Med 346: 884-90.

LOE 5, good quality, neutral, B
Randomized double-blind trial comparing amiodarone (n=180) with lidocaine (n=167) for refractory VF/VT suggesting that amiodarone leads to substantially higher rates of survival to hospital admission. 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).
Sponsored by Wyeth-Ayerst Laboratories

Engdahl J, Abrahamsson P, Bang A, et al. (2000). "Is hospital care of major importance for outcome after out-of-hospital cardiac arrest? Experience acquired from patients with out-of-hospital cardiac arrest resuscitated by the same Emergency Medical Service and admitted to one of two hospitals over a 16-year period in the municipality of Goteborg.". Resuscitation 43: 201-11.

LOE 4, fair quality, opposing, E
This retrospective study provides a description of in-hospital post-resuscitation care and its impact on survival to hospital discharge. 1038 victims of OOH-CA rescued by the same EMS were admitted to one of the two city hospitals between October 1980 and December 1996. None of the documented prehospital variables differed significantly between the two cohorts. There was a significant difference in survival to hospital discharge between hospital #1 (44%) and #2 (33%); a larger percentage of hospitalised patients underwent different investigations and interventions at hospital #1. In-hospital complications were also not different, including the relatively low rate of VF, 2.5% (26/1038), and VT, 2.6% (27/1038). Although the study doves not provide data on the use of post-resuscitation antiarrhythmic agents, it demonstrates a surprisingly low frequency of recurrent arrhythmias.
No comment about industry funding.

Greene M, Newman D, Geist M, et al. (2000). "Is electrical storm in ICD patients the sign of a dying heart? Outcome of patients with clusters of ventricular tachyarrhythmias". Europace 2: 263-9.

LOE 5, fair quality, opposing, E
Electrical storms occur frequently (35% first discharge) in patients with ICD and unpredictably, often late post-implant. Electrical storm does not carry an ominous prognosis as demonstrated by this retrospective comparison (40 pts with electrical storm, 57 with appropriate isolated ICD therapy, and 125 with no or inappropriate ICD therapy). There were no differences in survival in the three groups, annual mortality rate at 5 years respectively: 4.5%, 3.0%, and 1.1% (p=ns). Many of these patients do not have further device activity after storm cessation (average 1.5 storms at 5 years). Amiodarone was found to be effective in terminating electrical storm due to VT. Limitations: retrospective, uncontrolled, limited numbers.
No comment about industry funding

Hennersdorf MG, Niebch V, Vester EG, et al. (2003). "Long-term follow-up of sudden cardiac arrest survivors and electrophysiologically guided antiarrhythmic therapy". Cardiology 99: 190-7.

LOE 5, fair quality, opposing, E
Cardiac arrest survivors (204), following initial electrophysiology ventricular stimulation, were assigned to antiarrhythmic drug therapy (AAD; mexiletine, propaphenone or sotalol; amiodarone was not chosen as first drug when possible), if still inducible an

ICD was implanted and AAD discontinued. There were no difference in baseline characteristics between the AAD and ICD groups. The majority of patients in the AAD group (60%) received sotalol. ICD implantation significantly reduced overall mortality (primary endpoint) as well as cardiac and arrhythmogenic mortality.
No comment about industry funding

Huikuri HV, Castellanos A, Myerburg RJ. (2001). "Sudden death due to cardiac arrhythmias". N Engl J Med 345: 1473-82.
No abstract available

An intriguing review on sudden death secondary to cardiac arrhythmias. The section devoted to secondary prevention of cardiac arrest can be summarized as follows: there is no evidence from trials that drug treatment, including the use of beta-blockers and amiodarone, or surgical interventions, prevent the recurrence of life-threatening arrhythmic events. The only evidence-based therapeutic strategy for patients who have survived a life-threatening arrhythmic event is the implantation of a cardioverter-defibrillator (as demonstrated by the AVID Trial). Similar results have been reported in two smaller randomized trials, the Canadian Implantable Defibrillator Study and the Cardiac Arrest Study Hamburg. In a subgroup analysis of the AVID data base, it was observed that among patients with better-preserved left ventricular function - ejection fractions in the range of 35 to 40 percent - cardioverter-defibrillator therapy had no advantage over drug therapy. This was a secondary analysis, however, which suggests but does not prove that cardioverter-defibrillator therapy fails to provide a survival benefit in this subgroup.
Supported by the Finnish Academy of Science, Helsinki, Finland. Dr. Myerburg is supported in part by the Louis Lemberg Chair in Cardiology and the American Heart Association Chair in Cardiovascular Research at the University of Miami, Miami.

John RM. (2004). "Sudden cardiac death". Current Treatment Options in Cardiovascular Medicine 6: 347-55.

Review
When acute ischemia is the documented cause of cardiac arrest, revascularization by PCI or CABG is the best treatment. The risk of recurrence is determined by residua LVEF. In the AVID trial and Canadian trial of Implantable Defibrillators, ICDs did not offer any survival benefit in patients with preserved LV function (> 35%). Thus post-revascularization electrophysiologic evaluation is recommended only in patients with impaired LVEF.
Survivors of malignant arrhythmias other than due to a reversible cause, such as severe metabolic disturbance, toxic drug effect, or acute MI, are best treated with an ICD. In the largest prospective randomized trial of drugs vs. an implantable defibrillator (AVID) the ICD reduced mortality by 39% at 1 year and 31% at 3 years, compared with amiodarone (or sotalol). In the absence of specific contraindications, ICD therapy is currently the standard of care for secondary prevention of life-threatening arrhythmic events.
No comment about industry funding

Kuck KH, Cappato R, Siebels J, et al. (2000). "Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH)". Circulation 102: 748-54.

Kudenchuk PJ, Cobb LA, Copass MK, et al. (1999). "Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation". N Engl J Med 341: 871-8.

LOE 5, good quality, neutral, B
Double-blind randomized controlled trial suggesting that amiodarone improves, compared to placebo, survival to hospital admission in out-of-hospital cardiac arrest victims. Refractory VF/VT (resistant to >3 shocks). Baseline characteristics of the 2 groups were similar (amiodarone n=246, placebo n=258). 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).
Supported by the Medic One Foundation and by a grant from Wyeth–Ayerst Laboratories. Dr. Kudenchuk has been a member of a speakers' bureau sponsored by Wyeth–Ayerst Laboratories

Nademanee K, Taylor R, Bailey WE, et al. (2000). "Treating electrical storm : sympathetic blockade versus advanced cardiac life support-guided therapy". Circulation 102: 742-7.

LOE 5, fair quality, supportive, C.
Prospective evaluation on the efficacy of sympathetic blockade in treating patients with electrical storm (ES) and compared the outcome with that of patients with ES treated according to ACLS guidelines. The study included patients with recent MI and ES, defined as >= 20 VT/VF episodes per day or >= 4 VT/VF episodes per hour. After initial treatment according to the ACLS guidelines, 2 treatment approaches were used: patients in group 1 (n=27) received sympathetic blockade (6 with left stellate ganglion blockade, 7 with esmolol, and 14 with propranolol), patients in group 2 (n=22) continued to received conventional ACLS-guided therapy (lidocaine-procainamide-bretylium). After the initial acute sympathetic blockade treatment, patients who were able to take oral drugs were also given oral amiodarone. The two groups were similar with regard to clinical characteristics. All group 1

patients continued to have multiple VF episodes before sympathetic blockade (25+/-12). After sympathetic blockade therapy was initiated, the mean number of VF episodes was reduced to 2.6+/-1.7 in group 1 (P<0.01). In contrast, 91% of patients in group 2 continued to have VF episodes. At 1 week, 18 (82%) group 2 patients died, in contrast with only 6 (22%) patients in group 1. Survival to hospital discharge was of 20 patients in group 1 and only 2 in group 2. Important limitations: there was no randomization, assignment to treatment protocol was based only on physician preference; ACLS-guided therapy relied on old antiarrhythmic concepts according to the 1994 guidelines; the sympathetic blockade group received when possible concomitant therapy with oral amiodarone.
No comment about industry funding

Reiter MJ, Reiffel JA. (1998). "Importance of beta blockade in the therapy of serious ventricular arrhythmias". Am J Cardiol 82: 9I-19I.

Review, LOE 5, good quality, supportive.
Detailed review of available evidence for use of b-blockers for primary or secondary prevention of arrhythmic events. In-depth analysis of the potential antiarrhythmic effects is provided. Clinical studies on b-blockers are analyzed, with particular reference to the primary prevention in high-risk populations post-myocardial infarction, congestive heart failure, secondary prevention in patients with history of sustained ventricular arrhythmia or cardiopulmonary arrest, beta-blockers as monotherapy, and beta-blockers in combination with class III agents and ICDs. The authors conclude that beta-blockade as monotherapy in survivors of a cardiopulmonary arrest or in patients with sustained VT is unproved, but possibly effective, therapy. The beneficial effects of beta-blockers on survival are greatest in those with decreased left ventricular function, and treatment regimens that include beta-blockade in some form should be sought rather than avoided.
No comment about industry funding

Salukhe TV, Dimopoulos K, Sutton R, et al. (2004). "Life-years gained from defibrillator implantation: markedly nonlinear increase during 3 years of follow-up and its implications". Circulation 109: 1848-53.

LOE 5, fair quality, opposing, E
Analysis of 8 randomized (except one) clinical trials of ICDs implanted in patients at high risk of ventricular arrhythmias. The authors investigated the average dependency of the benefit on duration of follow-up. It was calculated that the vertical gap between 2 survival curves enlarges with time, whereas the horizontal duration of follow-up also lengthens with time. The number of life-years gained, being the area enclosed by the Kaplan-Meier survival curves, therefore grows approximately with the square of follow-up duration for the 3 years after implantation. Of note, trials of device therapy are often terminated and the results reported long before the full clinical benefit is observed. Typically, this occurs because the trial design commits the investigators to stopping the trial if and when statistical cutoffs are reached. The expected benefit in life span (life-years gained) for a patient who has a defibrillator implanted is dramatically dependent on the time window over which the benefit is assessed. For the first 3 years, this benefit rises with the square of time.
Supported by the British Heart Foundation

Skrifvars MB, Pettila V, Rosenberg PH, et al. (2003). "A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation". Resuscitation 59: 319-28.

LOE 4, fair quality, supportive, E
A retrospective study evaluating specifically immediate post-resuscitation care. A multiple logistic regression model was used to predict survival at 6 months. Investigation included, among treatments initiated within the first 72 h, the use of AAD (amoidarone or lidocaine) and b-blockers (metoprolol or bisprolol). In two years 98 pts initially in VF/VT were admitted to hospital alive. Beta-blocking agents during early post-resuscitation care were independently associated with 6 months survival (p=0.002); of 79 pts who received beta-blocking agents mortality was 44% as compared to 79% among those who did not. The maximal and minimal systolic and diastolic blood pressure levels and the use vasopressor agents were similar among patients who received beta-blocking agents and those who did not. The initiated beta-blocking therapy had to be discontinued in two patients due to hypotension. However, the occurrence of hypotension in the post-resuscitation period was not associated with mortality. AAD therapy with amiodarone or lidocaine was not associated with improved survival (p=0.2). The number of patents treated with AAD is not specified but appears to be low, judging from the median proportion of 4-h periods in which the treatment was given of 0% (IQR 0-11%).
Sponsored by the Laerdal Foundation for Acute Medicine.

Somberg JC, Bailin SJ, Haffajee CI, et al. (2002). "Intravenous lidocaine versus intravenous amiodarone (in a new aqueous formulation) for incessant ventricular tachycardia". Am J Cardiol 90: 853-9.

LOE 5, fair quality, supportive, B.
A multicenter double-blinded, parallel-designed, randomized trial evaluating the effectiveness of amiodarone (Amio-Aqueous) and lidocaine on shock resistant VT (lidocaine as control). Initially, the patient received a bolus of either 150 mg amiodarone or 100 mg

lidocaine administered over 2 minutes. If VT persisted, the patient received a second bolus. If VT terminated, the patient continued with a 24-hour infusion. If the patient failed to respond to the first assigned sequence, a crossover was allowed so the patient could receive the alternative sequence. The following end points were measured to evaluate efficacy: (1) termination of the VT, (2) survival at 1 hour, (3) survival at 24 hours (primary end point). Both groups had similar baseline characteristics. Amiodarone resulted in VT termination in 78% of the patients, whereas the success rate for lidocaine was 27% ($p<0.05$). At 1 hour after the initial bolus, 1 lidocaine patient was alive (9%) vs 12 (67%) randomized to amiodarone ($p<0.01$). At 24 hours 1 (9%) and 7 (39%) patients respectively were alive ($p<0.01$). In conclusion, Amio-Aqueous, a water soluble intravenous amiodarone preparation, is more effective than lidocaine for the termination of shock-resistant VT and in terms of survival. Limitations: low number of patients enrolled (11 vs 18). The study was prematurely discontinued due to amiodarone superiority after interim analysis.
Sponsored by Academic Pharmaceuticals, Lake Bluff, Illinois.

Wever EF, Hauer RN, van Capelle FL, et al. (1995). "Randomized study of implantable defibrillator as first-choice therapy versus conventional strategy in postinfarct sudden death survivors". Circulation 91: 2195-203.

LOE 5, fair quality, opposing, E
Randomized trial comparing ICD implantation as first-choice therapy (n=29) with conventional strategy of starting antiarrhythmic drugs (n=31) in patients resuscitated from sudden out-of-hospital cardiac arrest from ventricular fibrillation or rapid ventricular tachycardia. The arrhythmic event had to be related to an old myocardial infarction (at least 1 month). The first step in the conventional strategy was always the pharmacological treatment: drugs with short half-lives were prescribed (class IA, IC, and III); amiodarone was preferably not chosen for early prescription. In case of drug failure, further strategy included catheter ablation, ablation surgery, antiarrhythmic drugs after ablation, and if even that failed ICD implantation (late ICD group - third, forth choice). Median follow-up was 24 months. Primary endpoint was total mortality, prolonged syncope with signs of circulatory arrest, and pump failure of such a degree that cardiac transplantation was deemed necessary. In the early ICD group, four patients died, two during initial hospitalization and two during further follow-up, all of cardiac causes. In the conventional strategy group, total mortality during initial hospitalization and further follow-up was 11 patients: 4 died suddenly, 5 died of pump failure, and 2 died of noncardiac causes. Antiarrhythmic drugs failed in a high proportion (65%) of patients, as reflected by persistent inducibility. The total number of main outcome events was significantly lower in the early ICD group. Better exercise tolerance, shorter hospitalization duration, a lower number of invasive procedures, and fewer antiarrhythmic therapy changes were all significantly more favorable for early ICD implantation. Conventionally treated patients were likely to end up with an ICD, and those who remained on antiarrhythmic drugs as sole therapy had a high risk of death regardless of efficacy assessment, including programmed electrical stimulation. Limitations: relatively small number of enrolled patients, the use of class IA, IC, and III drugs while amiodarone only as last resort.
No comment about industry funding