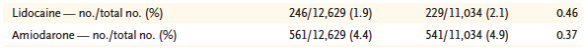
Question

Should AMIODARONE vs. no amiodarone be used for adults with shock refractory VF/pVT

PROBLEM:	Shock refractory VF/pVT	**BACKGROUND:**	Amiodarone has been recommended as the antiarrhythmic drug of choice in VF/pVT, largely based on two studies - the ARREST study (Kudenchuk 1999 871) of amiodarone vs 'placebo', and the ALIVE study (Dorian 2002 884) of amiodarone vs lidocaine – these studies reported improved survival to hospital admission for amiodarone
OPTION:	Amiodarone plus standard care		
COMPARISON:	Placebo plus standard care		
MAIN OUTCOMES:	Survival to discharge with good neuro/ survival to discharge/ROSC		
SETTING:	OHCA/IHCA		
PERSPECTIVE:	Patient perspective		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	Only those cases where VF/pVT persists after defibrillation attempts require an antiarrhythmic drug. In a large RCT (n= 23,711) of continuous or interrupted chest compressions during cardiopulmonary resuscitation (CPR) for OHCA (Nichol 2015 2203), 22.5% of patients had an initial rhythm of VF/pVT and about 6.7% of all patients received an antiarrhythmic drug (amiodarone 4.7%, lidocaine 2.0%) during CPR.  A large observational study (n= 108,079) on airway management using data from the American Heart Association Get With The Guidelines Registry of IHCA reported that about 18% of all patients had an initial rhythm of VF/pVT, and 25% of all patients received an antiarrhythmic drug (amiodarone 17%, lidocaine 8%) during CPR (Andersen 2017 494). This update about the role of antiarrhythmic drugs was prioritized by the ALS Task Force following publication of a large RCT comparing amiodarone, lidocaine and placebo ('ROC ALPS') (Kudenchuk 2016 1711) which was published after the CoSTR in 2015 (Callaway 2015 s84, Soar 2015 e71).	There are potential financial, logistic, and opportunity cost issues with administering amiodarone, which are worth it if it improves survival. Amiodarone is not currently used in all settings.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	Desirable effect is itself substantial but the actual magnitude of effect is small. In US a 1% absolute number of survivors extrapolates to 600 additional survivors/year.	We discussed the benefits of pooling or keeping the studies separate in the systematic review and meta-analyses. The benefits of increasing precision of an estimate of effect were weighed against the detrimental effects of combining distinctly different studies. We have provided

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
○ **Small**
○ Trivial

○ Varies
○ Don't know

Outcomes [importance]	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with Intervention + standard care
Amiodarone versus placebo					
Survival to hospital discharge with good neurological outcome (combined) [Critical]	2526 (2 RCTs)	Very Low	RR 1.13 (0.95 to 1.36)	146 per 1,000	19 more per 1,000 (from 7 fewer to 53 more)
Survival to hospital discharge with good neurological outcome (Cordarone) [Critical]	504 (1 RCT)	Very Low	RR 1.11 (0.59 to 2.10)	66 per 1,000	7 more per 1,000 (from 27 fewer to 72 more)
Survival to hospital discharge with good neurological outcome (Nexterone) [Critical]	2022 (1 RCT)	Moderate	RR 1.13 (0.94 to 1.37)	166 per 1,000	22 more per 1,000 (from 10 fewer to 61 more)
Survival to hospital discharge (combined) [Critical]	2530 (2 RCTs)	Very Low	RR 1.14 (0.98 to 1.33)	195 per 1,000	27 more per 1,000 (from 4 fewer to 64 more)
Survival to hospital discharge (Cordarone) [Critical]	504 (1 RCT)	Very Low	RR 1.02 (0.65 to 1.59)	132 per 1,000	3 more per 1,000 (46 fewer to 78 more)
Survival to hospital discharge (Nexterone) [Critical]	2026 (1 RCT)	Moderate	RR 1.16 (0.99 to 1.37)	210 per 1,000	34 more per 1,000 (2 fewer to 78 more)
Return of spontaneous circulation (combined) [Important]	2537 (2 RCT)	Very Low	RR 1.13 (0.93 to 1.37)	345 per 1,000	45 more per 1,000 (from 24 fewer to 128 more)
Return of spontaneous circulation (Cordarone) [Critical]	504 (1 RCT)	Very Low	RR 1.27 (1.02 to 1.59)	345 per 1,000	93 more per 1,000 (from 7 more to 204 more)
Return of spontaneous circulation (Nexterone) [Critical]	2033 (1 RCT)	Moderate	RR 1.04 (0.92 to 1.17)	346 per 1,000	14 more per 1,000 (from 28 fewer to 59 more)

Risk of harm with amiodarone small. In K2016 increase in temporary pacing in the first 24 hours after ROSC in the amiodarone group compared with lidocaine and placebo (4.9% v 3.2% v 2.7%) in the per protocol population (P=0.02). No difference between amiodarone, lidocaine, or placebo in the number of patients with a poor neurological outcome (modified Rankin scale 4, 5) on hospital discharge (5.4% v 6.1% v 4.3%) in the per protocol population.

pooled estimates based on combining studies and also just those from the individual studies.

The ARREST study (K1999) included patients with VF/pVT at any stage in the resuscitation attempt who had received 3 shocks, whereas the ROC ALPS (K2016) included only those with an initial arrest rhythm of VF/pVT who had received at least one shock. K1999 used amiodarone in polysorbate 80 preparation versus polysorbate 80 placebo. P80 may have hemodynamic effects and its role in the study is uncertain.
K2016 used the Nexterone formulation of amiodarone and an inactive placebo (0.9% sodium chloride). K1999 (patients enrolled 1994-1997, used the 1992 AHA guidelines) that have now been superseded. We are unable to ascertain the intention to treat population for the ARREST study, and so can only compare the per protocol analysis.

CERTAINTY OF EVIDENCE

What is the overall certainty of the evidence of effects?

○ Very low – K 1999
○ **Low**
○ Moderate – K2016
○ High

○ No included studies

K1999 - Cordarone v Polysorbate 80: very low
K2016 Nexterone v N Saline: moderate

VALUES

Is there important uncertainty about or variability in how much people value the main outcomes?

○ Important uncertainty or variability
○ **Possibly important uncertainty or variability**
○ Probably no important uncertainty or variability
○ No important uncertainty or

Most people would agree on the value of survival to hospital discharge, and survival with good neurology at hospital discharge. There is however substantial debate about the value of ROSC: discussed the possibility that patients and families of patients who will not survive to hospital discharge may value ROSC as it provides them with time to grieve before a final declaration of death and this is a knowledge gap. Patients, families and society may also put a value on ROSC based on the possibility of organ donation and ongoing care to enable organ donation. In addition, we considered that ROSC may lead to an increased burden on health care systems if patients are not surviving to hospital discharge.

Longer term outcomes, and HRQoL not addressed in available studies.

	variability		
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	Point estimate in favor of Amiodarone in all studies (i.e. it is probably useful), but only ROSC in Cordarone (v Polysorbate 80) was statistically significant. Predefined and reported bystander witnessed arrest subgroup (n=1934) analysis of K2016 showed a significant improvement for survival to hospital discharge. Survival was higher with amiodarone (27.7%) or lidocaine (27.8%) than with placebo (22.7%). This absolute risk difference was significant for amiodarone (5.0%; 95% CI, 0.3 to 9.7; P = 0.04) versus placebo K2016 survival to hospital discharge was also higher among amiodarone recipients than placebo recipients with EMS-witnessed arrest subgroup (n=154) - amiodarone (38.6%) than with placebo (16.7%) – this was associated with earlier drug use: the time from cardiac arrest to the first dose of trial drug was 11.7±5.8 min for EMS-witnessed arrest versus a time from 911-call to the first study drug of 19.3±7.1 for non-EMS-witnessed cardiac arrest.	Depends on weight placed on ROSC and subgroup analysis (reasonable to consider). Subgroup analysis: bystander witnessed (possibly surrogate for earlier administration) higher survival to hospital discharge (Nexterone v N Saline) ARR 5.0% (95% CI: 0.3, 9.7) p=0.04 (50 more per 1000 (3 more to 97 more). Also consistent with unpublished Post Hoc Observational Analyses from the ARREST Trial. No in-hospital studies identified.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ **Don't know**	No formal cost-effectiveness studies performed. Many services already use this intervention. ROSC costs money – ICU costs etc Potential resource requirement to changing guidelines and current practice – training/implementation	Will vary across ILCOR Councils and for local determination.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ○ **No included studies**	No studies identified. Uncertain impact on resources.	Uncertainty surrounding Hospital Length of Stay, and burden of poor neurologic outcomes No specific studies identified so can only rely on indirect evidence.

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ **No included studies**	No studies identified.	Not formally studied
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	Uncertain, no relevant studies identified. Probably no impact. Uncertainty surrounding opportunity cost of treating individuals who reach hospital. Consideration given to burden of administering IV drugs, and alternatives (eg. lidocaine).	Already used by many services and is currently part of guidelines. Some EMS systems have IV+ drug v No IV responders – guidance would not change this.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	Many services already use this intervention. Not all services have made this intervention available.	Variable according to ILCOR Council/setting. Additional drug cost may be a consideration. Switching drugs/protocols may be an issue. Potential savings if cheaper drug, though costs vary over time.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Many services already use Cordarone preparation, but Nexterone less widely available.	Nexterone only available in North America according to manufacturer [April 2018]

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low (K1999)	Low	Moderate (K2016)	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions: Should AMIODARONE vs no amiodarone be used for adults with shock refractory VF/pVT

TYPE OF RECOMMENDATION	Strong recommendation against the option ○	Conditional recommendation against the option ○	Conditional recommendation for either the option or the comparison ○	**Conditional recommendation for the option** ○	Strong recommendation for the option ○
RECOMMENDATION	We suggest the use of amiodarone in adults with shock refractory VF/pVT				
JUSTIFICATION	Improved ROSC in K1999, with no/small evidence of harm, already part of guidelines, and subgroup analyses – beneficial when given early. Early use likely to apply to IHCA.				
SUBGROUP CONSIDERATIONS	Possible benefits seen in bystander and EMS witnessed OHCA (possibly a surrogate for earlier administration). Current guidelines delay use until shock refractory (after at least 2 shocks and 1 mg dose epinephrine).				
IMPLEMENTATION CONSIDERATIONS	Already used in many centres (in and out of hospital). Newer formulation (Nexterone) not widely available.				
MONITORING AND EVALUATION	Use of anti-arrhythmic drugs should be included in OHCA and IHCA registry data collection				
RESEARCH PRIORITIES	Discussions included: • What is the role of antiarrhythmic drugs for in-hospital cardiac arrest? • What is the optimal bundle of care for shock refractory VF/pVT (defibrillation attempts versus drugs versus mechanical CPR/extracorporeal CPR/percutaneous coronary intervention(PCI))? • Does the etiology of cardiac arrest (e.g. coronary artery disease, cardiomyopathy, inherited heart rhythm disorder, congenital heart disease, drug-induced arrhythmia, long-QT syndromes and pulmonary embolism) have an impact on the effectiveness of antiarrhythmic drugs during CPR? • Do patients and families value short term outcomes (e.g. ROSC, intensive care unit admission) after cardiac arrest for those patients who subsequently die prior to hospital discharge? • What is the cost effectiveness of antiarrhythmic drug treatment during CPR? • What is the effect of antiarrhythmic drugs during CPR on long term outcomes and health related quality of life? • Does adrenaline (epinephrine) alter effectiveness of antiarrhythmic drugs? We have no data on the effectiveness of antiarrhythmic drugs used prior to or without adrenaline. • What is the optimal timing of antiarrhythmic drugs during CPR (how early, after how may defibrillation attempts? • Are there differences in the effectiveness of different amiodarone preparations during CPR? • What are the effects of polysorbate 80 during CPR for VF/pVT cardiac arrest? • Is there a difference in effectiveness between intravenous (IV) and intraosseous (IO) antiarrhythmic drug use during VF/pVT cardiac arrest?				