

Question

Should AMIODARONE vs LIDOCAINE be used for adults with shock refractory VF/pVT

PROBLEM:	Shock refractory VF/pVT	BACKGROUND: Both in 2015 CoSTR. Amiodarone favoured. Lidocaine has been recommended as an alternative to amiodarone (the current antiarrhythmic of choice in refractory VF/pVT), largely based on two studies - Kudenchuk 1999 (amiodarone vs placebo) and Dorian 2002 (amiodarone vs lidocaine) – they reporting improved survival to hospital with amiodarone (but without an improvement in hospital discharge rates).
OPTION:	AMIODARONE plus standard care	
COMPARISON:	LIDOCAINE 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	<p>Is the problem a priority?</p> <ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>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.</p> <table border="1"> <tr> <td>Lidocaine — no./total no. (%)</td> <td>246/12,629 (1.9)</td> <td>229/11,034 (2.1)</td> <td>0.46</td> </tr> <tr> <td>Amiodarone — no./total no. (%)</td> <td>561/12,629 (4.4)</td> <td>541/11,034 (4.9)</td> <td>0.37</td> </tr> </table> <p>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).</p> <p>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).</p>	Lidocaine — no./total no. (%)	246/12,629 (1.9)	229/11,034 (2.1)	0.46	Amiodarone — no./total no. (%)	561/12,629 (4.4)	541/11,034 (4.9)	0.37	<p>(K 2016) published after ALS CoSTR 2015 provides new data on Lidocaine v placebo v amiodarone. This was the highest ranked priority topic by the ILCOR ALS TF.</p>
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DESIRABLE EFFECTS	<p>How substantial are the desirable anticipated effects?</p> <ul style="list-style-type: none"> <input type="radio"/> Trivial <input checked="" type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 		<p>See ETDs for Amiodarone versus placebo, and Lidocaine versus placebo</p>								

UNDESIRABLE EFFECTS	<p>How substantial are the undesirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small ○ Trivial <ul style="list-style-type: none"> ○ Varies ○ Don't know 	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">Outcomes [importance]</th> <th style="text-align: center;">No of participants (studies)</th> <th style="text-align: center;">Certainty of the evidence (GRADE)</th> <th style="text-align: center;">Relative effect (95% CI)</th> <th style="text-align: center;">Anticipated absolute effects</th> <th style="text-align: center;">Risk with standard care</th> <th style="text-align: center;">Risk difference with Intervention + standard care</th> </tr> </thead> <tbody> <tr> <td colspan="7">Amiodarone versus lidocaine</td> </tr> <tr> <td>Survival to hospital discharge with good neurological outcome [Critical]</td> <td style="text-align: center;">1951 (1 RCT)</td> <td style="text-align: center;">Moderate</td> <td style="text-align: center;">RR 1.08 (0.89 to 1.30)</td> <td style="text-align: center;">175 per 1,000</td> <td style="text-align: center;">14 more per 1,000</td> <td style="text-align: center;">(from 19 fewer to 52 more)</td> </tr> <tr> <td>Survival to hospital discharge (combined)[Critical]</td> <td style="text-align: center;">2302 (2 RCTs)</td> <td style="text-align: center;">Very Low</td> <td style="text-align: center;">RR 1.04 (0.89 to 1.22)</td> <td style="text-align: center;">207 per 1,000</td> <td style="text-align: center;">8 more per 1,000</td> <td style="text-align: center;">(from 23 fewer to 45 more)</td> </tr> <tr> <td>Survival to hospital discharge (lidocaine with polysorbate 80)[Critical]</td> <td style="text-align: center;">347 (1 RCT)</td> <td style="text-align: center;">Very Low</td> <td style="text-align: center;">RR 1.67 (0.57 to 4.88)</td> <td style="text-align: center;">30 per 1,000</td> <td style="text-align: center;">20 more per 1,000</td> <td style="text-align: center;">(from 13 fewer to 116 more)</td> </tr> <tr> <td>Survival to hospital discharge [Critical]</td> <td style="text-align: center;">1955 (1 RCT)</td> <td style="text-align: center;">Moderate</td> <td style="text-align: center;">RR 1.03 (0.88 to 1.21)</td> <td style="text-align: center;">237 per 1,000</td> <td style="text-align: center;">7 more per 1,000</td> <td style="text-align: center;">(from 28 fewer to 50 more)</td> </tr> <tr> <td>Return of spontaneous circulation [Important]</td> <td style="text-align: center;">1966 (1 RCT)</td> <td style="text-align: center;">High</td> <td style="text-align: center;">RR 0.90 (0.80 to 1.01)</td> <td style="text-align: center;">399 per 1,000</td> <td style="text-align: center;">40 fewer per 1,000</td> <td style="text-align: center;">(from 80 fewer to 4 more)</td> </tr> </tbody> </table> <p>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</p>	Outcomes [importance]	No 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 lidocaine							Survival to hospital discharge with good neurological outcome [Critical]	1951 (1 RCT)	Moderate	RR 1.08 (0.89 to 1.30)	175 per 1,000	14 more per 1,000	(from 19 fewer to 52 more)	Survival to hospital discharge (combined)[Critical]	2302 (2 RCTs)	Very Low	RR 1.04 (0.89 to 1.22)	207 per 1,000	8 more per 1,000	(from 23 fewer to 45 more)	Survival to hospital discharge (lidocaine with polysorbate 80)[Critical]	347 (1 RCT)	Very Low	RR 1.67 (0.57 to 4.88)	30 per 1,000	20 more per 1,000	(from 13 fewer to 116 more)	Survival to hospital discharge [Critical]	1955 (1 RCT)	Moderate	RR 1.03 (0.88 to 1.21)	237 per 1,000	7 more per 1,000	(from 28 fewer to 50 more)	Return of spontaneous circulation [Important]	1966 (1 RCT)	High	RR 0.90 (0.80 to 1.01)	399 per 1,000	40 fewer per 1,000	(from 80 fewer to 4 more)	<p>No statistically significant differences reported for critical and important outcomes although all point estimates point towards amiodarone.</p> <p>No differences in secondary outcomes</p>
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CERTAINTY OF EVIDENCE	<p>What is the overall certainty of the evidence of effects?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High <ul style="list-style-type: none"> ○ No included studies 	<p>STD AND STD with good neurology: V LOW TO MOD ROSC: HIGH</p>	<p>See ETDs for Amiodarone versus placebo, and Lidocaine versus placebo levels of certainty</p> <p>In opinion of TF the combined level of certainty would be LOW</p>																																																	
VALUES	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability 	<p>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.</p>	<p>Longer term outcomes, and HRQoL not addressed in available studies.</p>																																																	

BALANCE OF EFFECTS	<p>Does the balance between desirable and undesirable effects favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ <u>Does not favor either the intervention or the comparison</u> ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know 	No clear benefit of either drug	No published subgroup benefits. No in-hospital RCTs
RESOURCES REQUIRED	<p>How large are the resource requirements (costs)?</p> <ul style="list-style-type: none"> ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ <u>Don't know</u> 	No formal cost-effectiveness studies performed. Many services already use these interventions.	Will vary across ILCOR Councils – for local determination. Already used in some setting. May be potential saving for those who switch from amiodarone to lidocaine in some settings (but drugs cost change with time/preparation etc.)
CERTAINTY OF EVIDENCE OF RESOURCES REQUIRED	<p>What is the certainty of the evidence of resource requirements (costs)?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ○ <u>No included studies</u> 	No studies identified.	No specific studies, indirect evidence
COST EFFECTIVENESS	<p>Does the cost-effectiveness of the intervention favor the intervention or the comparison?</p> <ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ <u>No included studies</u> 	No studies identified.	<p>Not formally studied</p> <p>Unspecified cost of guideline change and training to change practice</p>
EQUITY	<p>What would be the impact on health equity?</p>	Uncertain, no relevant studies identified. Probably no impact.	Some EMS systems have IV+ drug v No IV responders – our

	<ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ● <u>Probably no impact</u> ○ Probably increased ○ Increased ○ Varies ○ Don't know 	<p>May be potential saving for those who switch from amiodarone to lidocaine in some settings (but drugs cost change with time/preparation etc.)</p>	<p>guidance would not change this.</p>
ACCEPTABILITY	<p>Is the intervention acceptable to key stakeholders?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ○ <u>Probably yes</u> ○ Yes ○ Varies ○ Don't know 	<p>Many services already use this intervention. Not all services have made this intervention available.</p>	<p>May be potential saving for those who switch from amiodarone to lidocaine in some settings (but drugs cost change with time/preparation etc.)</p>
FEASIBILITY	<p>Is the intervention feasible to implement?</p> <ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ <u>Yes</u> ○ Varies ○ Don't know 	<p>Many services already use these interventions or are capable of using this interventions</p>	

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	Low	Moderate	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 LIDOCAINE 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 or lidocaine in adults with shock refractory ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT) (weak recommendation, low quality evidence).				
JUSTIFICATION	Both drugs already used in many centers. No comparative evidence of harm. No consistent benefit with either drug over the other. Amiodarone or lidocaine probably better than placebo for short term outcomes and when give early. [see ETDs for AMIODARONE vs. placebo, and LIDOCAINE VS. placebo for further justification]				
SUBGROUP CONSIDERATIONS	Possible benefits for both drugs (amiodarone v placebo, and lidocaine v placebo) seen in witnessed OHCA (surrogate for earlier administration and therefore can be extrapolated to IHCA where drugs are given much earlier). We identified one further RCT that would have met our inclusion criteria (Kudenchuk 2017 2119). This RCT compared the role of amiodarone, lidocaine and saline placebo for non-shockable turned shockable OHCA and was underpowered for the primary endpoint of survival to hospital discharge.				
IMPLEMENTATION CONSIDERATIONS	Already used in many centers (in and out of hospital).				
MONITORING AND EVALUATION	Use of anti-arrhythmic drugs should be included in OHCA and IHCA registry data.				
RESEARCH PRIORITIES	<p>Current knowledge gaps include but are not limited to:</p> <ul style="list-style-type: none"> • 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 many defibrillation attempts)? • Is multiple antiarrhythmic drug use (e.g. amiodarone followed by lidocaine) more effective than single drug use? • What is the impact of bystander CPR on the effectiveness of antiarrhythmic drugs? • 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? • Does CPR quality impact antiarrhythmic drug effectiveness during CPR? 				