Question

Should LIDOCAINE vs no lidocaine be used for adults with shock refractory VF/pVT

PROBLEM:	Shock refractory VF/pVT
OPTION:	LIDOCAINE 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

BACKGROUND: Lidocaine has been recommended as an alternative to amiodarone (the current anti-arrhythmic drug of choice in refractory 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

Assessment

<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?

○ No
○ Probably no
○ Probably yes
○ <u>Yes</u>

○ Varies
○ Don't know</td><td>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.
<table><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>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).</td><td>In many settings lidocaine is less expensive than amiodarone, or already used.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?

○ Trivial
○ <u>Small</u>
○ Moderate
○ Large

○ Varies
○ Don't know</td><td><table><tr><th>Outcomes [importance]</th><th>№ of participants (studies)</th><th>Certainty of the evidence (GRADE)</th><th>Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects</th></tr><tr><th></th><th></th><th></th><th></th><th>Risk with standard care</th><th>Risk difference with Intervention + standard care</th></tr><tr><td colspan="6">Lidocaine versus placebo</td></tr><tr><td>Survival to hospital discharge with good neurological outcome [Critical]</td><td>2039 (1 RCT)</td><td>Moderate</td><td>RR 1.05 (0.87 to 1.28)</td><td>166 per 1,000</td><td>8 more per 1,000 (from 22 fewer to 46 more)</td></tr><tr><td>Survival to hospital discharge [Critical]</td><td>2041 (1 RCT)</td><td>Moderate</td><td>RR 1.13 (0.96 to 1.32)</td><td>210 per 1,000</td><td>27 more per 1,000 (from 8 fewer to 67 more)</td></tr><tr><td>Return of spontaneous circulation [Important]</td><td>2051 (1 RCT)</td><td>High</td><td>RR 1.16 (1.03 to 1.29)</td><td>346 per 1,000</td><td>55 more per 1,000 (from 10 more to 100 more)</td></tr></table></td><td>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 pooled estimates based on</td></tr>
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			combining studies and also just those from the individual studies. Many of the practices used in the ALIVE study (D2002) (patients enrolled 1995-2001) have been superseded. The ALIVE study included patients with initial VF/pVT who had received 3 shocks, adrenaline and a further shock for recurrent VF/pVT after an initial successful shock, whereas ROC ALPS (K2016) included those with an initial arrest rhythm of VF/pVT who had received at least one shock. In the ALIVE study, the lidocaine was mixed with polysorbate 80 (the diluent for amiodarone) to improve blinding – polysorbate 80 is viscous. It is uncertain if the addition of polysorbate 80 (with its potential adverse hemodynamic effects) to the lidocaine adversely affected outcomes in the lidocaine group.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ **Small** ○ Trivial ○ Varies ○ Don't know	Few undesirable effects of lidocaine use in cardiac arrest reported	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ○ **Moderate** ○ High ○ No included studies	For critical outcomes: Survival to discharge and Survival to hospital discharge with good Neurological function – moderate Important outcome ROSC – High	Lidocaine increased ROSC in K2016. Amiodarone did not. This is a new finding. There was no difference between amiodarone and lidocaine overall in K2016 for critical outcomes
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?**	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	Longer term outcomes, and HRQoL not addressed in available studies.

	○ Important uncertainty or variability ○ **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	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.	
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	More than 50% chance that lidocaine works. Point estimate in favor of Lidocaine in all studies, but only ROSC was statistically significant. Predefined and reported bystander witnessed arrest subgroup (n=1934) analysis of the ROC ALPS study (Kudenchuk 2016) that showed a significant improvement with an antiarrhythmic drug for the critical outcome of survival to hospital discharge. Specifically, survival was higher with lidocaine (27.8%) than with placebo (22.7%). This absolute risk difference was significant for lidocaine (5.2%; 95% CI, 0.5 to 9.9; P = 0.03) versus placebo, but not between amiodarone and lidocaine (−0.1%; 95% CI, −5.1 to 4.9; P = 0.97). Early use likely to be important. Need to ensure that does not distract from early CPR, defibrillation	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 (Lidocaine v N Saline) ARR 5.2% (95% CI: 0.5, 9.9) p=0.04 (52 more per 1000 (5 more to 99 more). No in-hospital RCTs
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 Resource requirement to changing guidelines and current practice – training/implementation. No evidence on whether there is an additional burden from survivors with severe disability.	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 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. amiodarone).	Already used by many services and is currently part of guidelines, albeit it currently with lower ranking than amiodarone 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.	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	Many services already use this intervention or are capable of using this intervention.	Lidocaine widely available and relatively inexpensive compared with amiodarone in most settings.

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 (StD)	High (ROSC)			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; LIDOCAINE vs no 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 lidocaine in adults with shock refractory VF/pVT				
JUSTIFICATION	Already used in many centers. Despite no clear consistent evidence of benefit, no significant evidence of harm. Improved ROSC in K2016, 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 witnessed OHCA (surrogate for earlier administration?).				
IMPLEMENTATION CONSIDERATIONS	Already used in some centers (in and out of hospital). May be less expensive than alternatives				
MONITORING AND EVALUATION	Use of anti-arrhythmic drugs should be included in OHCA and IHCA registry data.				
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? • Is there a difference in effectiveness between intravenous (IV) and intraosseous (IO) antiarrhythmic drug use during VF/pVT cardiac arrest?				