

Manuscript version: Author's Accepted Manuscript

The version presented in WRAP is the author's accepted manuscript and may differ from the published version or Version of Record.

Persistent WRAP URL:

<http://wrap.warwick.ac.uk/111285>

How to cite:

Please refer to published version for the most recent bibliographic citation information. If a published version is known of, the repository item page linked to above, will contain details on accessing it.

Copyright and reuse:

The Warwick Research Archive Portal (WRAP) makes this work by researchers of the University of Warwick available open access under the following conditions.

© 2018 Elsevier. Licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International <http://creativecommons.org/licenses/by-nc-nd/4.0/>.



Publisher's statement:

Please refer to the repository item page, publisher's statement section, for further information.

For more information, please contact the WRAP Team at: wrap@warwick.ac.uk.

Resuscitation

Elsevier Editorial System(tm) for

Manuscript Draft

Manuscript Number: RESUS-D-18-00821

Title: European Resuscitation Council Guidelines for Resuscitation: 2018 update - antiarrhythmic drugs for cardiac arrest

Article Type: Guidelines

Keywords: Advanced Life Support, Amiodarone, Antiarrhythmic drugs, Cardiopulmonary Resuscitation, Guidelines, Heart arrest, Lidocaine, Paediatric Life Support, Neonatal Life Support, Pulseless ventricular tachycardia, Ventricular fibrillation

Corresponding Author: Dr. Jasmeet Soar,

Corresponding Author's Institution:

First Author: Jasmeet Soar

Order of Authors: Jasmeet Soar; Gavin D Perkins; Ian Maconochie; Bernd W Böttiger; Charles D Deakin; Claudio Sandroni; Teresa M Olasveengen; Jonathan Wyllie; Robert Greif; Andrew Lockey; Federico Semeraro; Patrick Van de Voorde; Carsten Lott; Leo Bossaert; Koen Monsieus; Jerry P Nolan

Abstract: This European Resuscitation Council (ERC) Guidelines for Resuscitation 2018 update is focused on the role of antiarrhythmic drugs during advanced life support for cardiac arrest with shock refractory ventricular fibrillation/pulseless ventricular tachycardia in adults, children and infants. This update follows the publication of the International Liaison Committee on Resuscitation (ILCOR) 2018 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations (CoSTR). The ILCOR CoSTR suggests that any beneficial effects of amiodarone or lidocaine are similar. This ERC update does not make any major changes to the recommendations for the use of antiarrhythmic drugs during advanced life support for shock refractory cardiac arrest.

European Resuscitation Council Guidelines for Resuscitation: 2018 update – antiarrhythmic drugs for cardiac arrest

Jasmeet Soar*

Gavin D. Perkins

Ian Maconochie

Bernd W. Böttiger

Charles D. Deakin

Claudio Sandroni

Theresa M. Olasveengen

Jonathan Wyllie

Robert Greif

Andrew Lockey

Federico Semeraro

Patrick Van de Voorde

Carsten Lott

Leo Bossaert

Koenraad G. Monsieurs

Jerry P. Nolan,

on behalf of the European Resuscitation Council

European Resuscitation Council

Emile Vanderveldelaan 35,

BE-2845,

Niel, Belgium

*Corresponding author

jasmeet.soar@nbt.nhs.uk

Abstract

This European Resuscitation Council (ERC) Guidelines for Resuscitation 2018 update is focused on the role of antiarrhythmic drugs during advanced life support for cardiac arrest with shock refractory ventricular fibrillation/pulseless ventricular tachycardia in adults, children and infants. This update follows the publication of the International Liaison Committee on Resuscitation (ILCOR) 2018 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations (CoSTR). The ILCOR CoSTR suggests that any beneficial effects of amiodarone or lidocaine are similar. This ERC update does not make any major changes to the recommendations for the use of antiarrhythmic drugs during advanced life support for shock refractory cardiac arrest.

Key words

Advanced Life Support, Amiodarone, Antiarrhythmic drugs, Cardiopulmonary Resuscitation, Guidelines, Heart arrest, Lidocaine, Paediatric Life Support, Neonatal Life Support, Pulseless ventricular tachycardia, Ventricular fibrillation

[h1]Introduction

This is the second European Resuscitation Council (ERC) guidelines update following the decision by the International Liaison Committee on Resuscitation (ILCOR) to move to a continuous evidence evaluation process.¹⁻³ This update follows the publication of the ILCOR 2018 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations (CoSTR) Summary.⁴ The 2018 ILCOR CoSTR focused on the use of antiarrhythmic drugs to treat cardiac arrest with a shockable rhythm in adults, children and infants and provides an update to the ILCOR 2015 Advanced Life Support (ALS) and Paediatric CoSTRs.^{5,6} This topic was prioritised by ILCOR following the publication of a large randomised controlled trial (RCT) that compared amiodarone, lidocaine and placebo (ALPS) in out-of-hospital cardiac arrest (OHCA) patients with shock refractory ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT).⁷ Here the ERC updates the 2015 ALS and Paediatric guidelines on the use of antiarrhythmic drugs during cardiopulmonary resuscitation (CPR) and immediately after return of spontaneous circulation (ROSC).^{8,9}

[h1]Background

The primary treatment for cardiac arrest with a shockable rhythm (VF/pVT) is early defibrillation and, if required, high-quality chest compressions with minimum interruption.^{3,10} Approximately 20% of adult cardiac arrests (in and out-of-hospital) have a shockable rhythm when first monitored.¹¹⁻¹³ Current guidelines recommend that those patients not responding to defibrillation attempts for a primary shockable rhythm, or a non-shockable rhythm that turns shockable require an antiarrhythmic drug, with the aim of increasing defibrillation success with subsequent defibrillation attempts. In a large OHCA RCT of continuous versus interrupted chest compressions, 22.5% of patients had an initial monitored rhythm of VF/pVT and about 6.7% received an antiarrhythmic drug.¹¹ For in-hospital cardiac arrest (IHCA), the Get With The Guidelines–Resuscitation registry data show that about 18% of adult patients had an initial monitored rhythm of VF/pVT, and about 25% received an antiarrhythmic drug.¹² Shockable rhythms are less common in paediatric cardiac arrest and the incidence varies with age (OHCA 1% to 6% in under 5 years-old and 15-20% in adolescence, IHCA 9% to 14% overall). Only limited data are available on the use of antiarrhythmic drugs after paediatric IHCA; about a quarter of cases receive an antiarrhythmic drug.⁴ Shockable rhythms at birth are thought to be extremely rare. However, the lack of heart rhythm monitoring during most resuscitation at birth means that data is sparse. Arrests due to shockable rhythms do occur after birth in the neonatal period.

This update focuses only on the use of antiarrhythmic drugs, but it is likely that other interventions have a role in some patients with a refractory shockable cardiac arrest. Observational data suggest that successful resuscitation in some patients may require mechanical CPR or extracorporeal CPR (eCPR) to buy time for treatment of the underlying cause of cardiac arrest (e.g. percutaneous coronary intervention (PCI) for coronary artery occlusion).^{5,14} The role of eCPR will be considered in the 2019 ILCOR CoSTR and ERC Guidelines update.¹⁵

[h1] ILCOR CoSTR 2018

The ILCOR CoSTR 2018 addressed the use of antiarrhythmic drugs in adults and children in any setting (in-hospital or out-of-hospital) with cardiac arrest and a shockable rhythm (VF/pVT) at any time during CPR or immediately after ROSC (defined by consensus as within 1 hour of ROSC). The systematic review informing the CoSTR identified 14 adult RCTs (16 articles) and 19 non-RCTs (18 adult studies, 1 paediatric study, 22 articles).¹⁶ Given the availability of comparative data from large RCTs, the ILCOR ALS Task Force did not include non-RCTs in establishing the confidence in the estimated effect size of amiodarone and lidocaine. No RCTs of IHCA were identified. The ERC considered the 2018 CoSTR in the context of contemporary resuscitation practice in Europe. **Table 1** presents a summary of the ILCOR 2018 CoSTR and relevant 2015 ERC guidelines. More detailed information is presented below. This update will focus on the use of amiodarone, lidocaine and magnesium during cardiac arrest and the use of prophylactic antiarrhythmic drugs immediately after ROSC in adults, children and infants.

[h1] Amiodarone and lidocaine use in adult cardiac arrest

As part of this guideline update the ERC surveyed its member National Resuscitation Councils (NRCs) regarding the use of antiarrhythmic drugs during CPR. All of the 24 NRCs that responded reported that amiodarone was the antiarrhythmic drug used most commonly for IHCA. For OHCA, amiodarone was reported as the main antiarrhythmic drug used in 22 countries, lidocaine was the main antiarrhythmic drug used in one country, and the main antiarrhythmic drug used was uncertain in one country.

[h2] ERC Guidelines 2018

We recommend that amiodarone is given after three defibrillation attempts irrespective of whether they are consecutive shocks or interrupted by CPR, or for recurrent VF/pVT during cardiac arrest. An antiarrhythmic drug can be used in cases of a primary shockable rhythm,

or when a shockable rhythm follows a primary shockable cardiac arrest. Give amiodarone 300 mg intravenously; a further dose of 150 mg may be given after five defibrillation attempts. Lidocaine (100 mg) may be used if amiodarone is not available or a local decision has been made to use lidocaine instead of amiodarone. An additional bolus of lidocaine 50 mg may also be given after five defibrillation attempts.

[h2] ILCOR CoSTR in context of ERC Guidelines

The main change in the 2018 ILCOR CoSTR is that the weak recommendation based on low certainty evidence now applies to both amiodarone or lidocaine.⁴ In the previous 2015 CoSTR, amiodarone was given a weak recommendation based on moderate certainty evidence and lidocaine was given a weak recommendation based on very-low certainty evidence.⁵

The most commonly used formulation of amiodarone includes polysorbate 80 as a diluent. Polysorbate 80 can cause hypotension but its effects during CPR are uncertain⁴. A newer formulation of amiodarone (Nexterone[®]) includes a different diluent, Captisol[®] (a sulfobutyl ether β -cyclodextrin) instead of polysorbate 80, that is not thought to have any haemodynamic effects. The Nexterone[®] formulation of amiodarone is not currently readily available in Europe.

The recent OHCA RCT comparing the Nexterone[®] formulation of amiodarone, lidocaine or placebo in patients with VF/pVT refractory after at least one defibrillation attempt reported no difference in survival to discharge or good neurological survival at discharge between the three groups.⁷ Patients receiving lidocaine had a higher incidence of ROSC than placebo (amiodarone was similar to placebo). Both amiodarone and lidocaine increased survival to hospital admission compared with placebo. In addition, a predefined sub-group analysis showed an increase in survival to hospital discharge with amiodarone or lidocaine compared with placebo in patients who had a bystander witnessed cardiac arrest. Finally, survival rate was also higher with amiodarone than with placebo after EMS-witnessed arrest. The previous RCT of amiodarone versus placebo for OHCA refractory to three shocks (ARREST, 1999) compared amiodarone in polysorbate 80 formulation with polysorbate 80 as the placebo and showed an increase in survival to hospital admission with amiodarone.¹⁷ The previous RCT that showed amiodarone (polysorbate 80 formulation) increased survival to hospital admission compared with lidocaine (ALIVE, 2002) also used the amiodarone in polysorbate 80 formulation and to help with blinding polysorbate 80 was added to the lidocaine.¹⁸ The impact of the polysorbate 80 in the comparator groups in the ARREST and ALIVE studies is uncertain.

The ILCOR ALS Task Force opinion was that any beneficial effects on ROSC for amiodarone and lidocaine are similar, and that these drugs are most effective when given early after the onset of cardiac arrest. Even when pooled, the available studies lack sufficient power to be certain of longer-term benefits, but the risk of harm appears small. The ILCOR ALS Task Force considered an increase in ROSC to be an important outcome. The task force did consider that an increase in ROSC could burden healthcare systems without an increase in the number of patients surviving to discharge. The task force also considered that patients who die after a sustained period of ROSC, and their families, may value ROSC as it provides family members with some preparation time before a final declaration of death. Patients, families, and society may also value ROSC because among those who subsequently die there is the potential to enable organ donation.

A major consideration for leaving the ERC recommendation largely unchanged is that in our survey of NRCs, 21 out of 24 respondents stated that amiodarone would remain the main antiarrhythmic drug used during CPR despite the evidence suggesting that any beneficial effects of amiodarone and lidocaine are similar. The main reasons given for continuing to use amiodarone are that amiodarone is readily available, its use is established and widely implemented, and any change to lidocaine would have implementation and training issues and could cause confusion. This ERC accepts that given the ILCOR CoSTR some NRCs may wish to change to lidocaine.

[h1] Magnesium use in adult cardiac arrest in adults

Magnesium therapy has a role in correcting hypomagnesaemia, hypokalaemia, and during the treatment of polymorphic VT (torsade de pointes).^{8,19}

[h2] ERC Guidelines 2018

The recommendations of the ERC are unchanged in that we recommend magnesium is not used routinely for the treatment of cardiac arrest.

[h2] ILCOR CoSTR in context of ERC Guidelines

The ILCOR CoSTR did not identify any new RCTs published since the 2015 CoSTR. The CoSTR does state that there is a role for magnesium in specific circumstances during refractory VF/pVT (e.g. hypomagnesemia, torsade de pointes). The existing ERC guidelines therefore remain unchanged.^{8,19}

[h1] Prophylactic antiarrhythmic drugs immediately after ROSC in adults

[h2] ERC Guidelines 2018

The ERC has not made any previous recommendation on the prophylactic use of antiarrhythmic drugs after a cardiac arrest with a shockable rhythm, and this remains the case after the ILCOR 2018 CoSTR.

[h2] ILCOR CoSTR in context of ERC Guidelines

No new studies of the use of prophylactic antiarrhythmic drugs in patients immediately (within 1 hour) after ROSC following a VF/pVT cardiac arrest were identified in the 2018 ILCOR CoSTR. Observational studies of beta-blocker or lidocaine use after ROSC were reviewed in the 2015 ILCOR ALS CoSTR⁵. These data are of insufficient quality to enable any recommendation. This has been identified as a knowledge gap.

[h1] Antiarrhythmic drugs for cardiac arrest in infants and children

Amiodarone and lidocaine are also the two most commonly used antiarrhythmic drugs used during CPR in infants and children.

[h2] ERC Guidelines 2018

The recommendations of the ERC are unchanged for the use of antiarrhythmic drugs in infants and children.⁹ For VF/pVT give amiodarone 5 mg kg⁻¹ after the third shock once CPR has been resumed. Give a second dose of amiodarone 5 mg kg⁻¹ if still in VF/pVT after the fifth shock. Lidocaine can be used as an alternative to amiodarone. It can be used with a loading dose of 1 mg kg⁻¹ (maximum dose 100 mg/dose) followed by continuous infusion at 20–50 micrograms kg⁻¹ min⁻¹. In the event a VF/pVT cardiac arrest in the neonatal period, these guidelines for infants and children should be followed.

[h2] ILCOR CoSTR in context of ERC Guidelines

The ERC guidelines are consistent with the 2018 ILCOR CoSTR. The ILCOR Paediatric Task Force made a decision not to extrapolate data from adult studies given that most cases of adult refractory VF/pVT are associated with coronary artery disease. The basis of the paediatric recommendations is a single observational study of IHCA from the Get With The Guidelines Registry that was already considered in the 2015 ILCOR CoSTR.^{6,20}

[h1]Conclusion

The ERC acknowledges the quality and rigour of the evidence appraisal conducted by ILCOR. The ERC review of the newly gathered evidence on antiarrhythmic drugs does not

lead to any immediate changes in the ERC teaching materials, course content or programs. The review should enable laypeople and healthcare professionals to be confident that guidelines are based on the most up to date evidence.

Implementation of the key messages from Guidelines 2015 with a 2017 and 2018 update supports the ERC's mission to preserve human life by making high-quality resuscitation available to all.

[h1] Conflict of interest statement

All authors and contributors have formal roles within the ERC and their respective National Resuscitation Councils. JPN is Editor-in-Chief of Resuscitation. JS and GDP are Editors of Resuscitation.

[h1] References

1. Olasveengen TM, de Caen AR, Mancini ME, et al. 2017 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations Summary. *Resuscitation* 2017; **121**: 201-14.
2. Perkins GD, Neumar R, Monsieurs KG, et al. The International Liaison Committee on Resuscitation-Review of the last 25 years and vision for the future. *Resuscitation* 2017; **121**: 104-16.
3. Perkins GD, Olasveengen TM, Maconochie I, et al. European Resuscitation Council Guidelines for Resuscitation: 2017 update. *Resuscitation* 2018; **123**: 43-50.
4. Soar J, Donnino MW, Maconochie I, et al. 2018 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations Summary. *Resuscitation* 2018.
5. Soar J, Callaway CW, Aibiki M, et al. Part 4: Advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation* 2015; **95**: e71-120.
6. Maconochie IK, de Caen AR, Aickin R, et al. Part 6: Pediatric basic life support and pediatric advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation* 2015; **95**: e147-68.
7. Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest. *N Engl J Med* 2016; **374**(18): 1711-22.

8. Soar J, Nolan JP, Bottiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. *Resuscitation* 2015; **95**: 100-47.
9. Maconochie IK, Bingham R, Eich C, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 6. Paediatric life support. *Resuscitation* 2015; **95**: 223-48.
10. Monsieurs KG, Nolan JP, Bossaert LL, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 1. Executive summary. *Resuscitation* 2015; **95**: 1-80.
11. Nichol G, Leroux B, Wang H, et al. Trial of Continuous or Interrupted Chest Compressions during CPR. *N Engl J Med* 2015; **373**(23): 2203-14.
12. Andersen LW, Granfeldt A, Callaway CW, et al. Association Between Tracheal Intubation During Adult In-Hospital Cardiac Arrest and Survival. *JAMA* 2017; **317**(5): 494-506.
13. Grasner JT, Lefering R, Koster RW, et al. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: A prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. *Resuscitation* 2016; **105**: 188-95.
14. Soar J. Antiarrhythmic drug therapy during cardiopulmonary resuscitation: should we use it? *Curr Opin Crit Care* 2018; **24**(3): 138-42.
15. Holmberg MJ, Geri G, Wiberg S, et al. Extracorporeal cardiopulmonary resuscitation for cardiac arrest: A systematic review. *Resuscitation* 2018; **131**: 91-100.
16. Ali MU, Fitzpatrick-Lewis D, Kenny M, et al. Effectiveness of antiarrhythmic drugs for shockable cardiac arrest: A systematic review. *Resuscitation* 2018; **132**: 63-72.
17. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999; **341**(12): 871-8.
18. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med* 2002; **346**(12): 884-90.
19. Truhlar A, Deakin CD, Soar J, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 4. Cardiac arrest in special circumstances. *Resuscitation* 2015; **95**: 148-201.
20. Valdes SO, Donoghue AJ, Hoyme DB, et al. Outcomes associated with amiodarone and lidocaine in the treatment of in-hospital pediatric cardiac arrest with pulseless ventricular tachycardia or ventricular fibrillation. *Resuscitation* 2014; **85**(3): 381-6.

Table 1 Summary of ILCOR CoSTR and ERC Guidelines 2018 – the role of antiarrhythmic drugs during advanced life support. The Table indicates changes to ERC Guidelines and Timescale for implementation.

Topic	ILCOR CoSTR 2018	ERC Guideline 2015	ERC 2018 Guideline change
Antiarrhythmic drugs for cardiac arrest in adults	<p>We suggest the use of amiodarone or lidocaine in adults with shock-refractory VF/pVT (weak recommendation, low-certainty evidence).</p> <p>We suggest against the routine use of magnesium in adults with shock-refractory VF/pVT (weak recommendation, very low-certainty evidence).</p> <p>The confidence in effect estimates is currently too low to support an ALS Task Force recommendation about the use of bretylium, nifekalant, or sotalol in the treatment of adults in cardiac arrest with shock-refractory VF/pVT.</p>	<p>We recommend that amiodarone should be given after three defibrillation attempts irrespective of whether they are consecutive shocks, or interrupted by CPR, or for recurrent VF/pVT during cardiac arrest. Give amiodarone 300 mg intravenously; a further dose of 150 mg may be given after five defibrillation attempts.</p> <p>Lidocaine (100 mg) may be used as an alternative if amiodarone is not available or a local decision has been made to use lidocaine instead of amiodarone. An additional bolus of lidocaine 50 mg can also be given after five defibrillation attempts.</p> <p>We recommend that magnesium is not used routinely for the treatment of cardiac arrest.</p>	Minor changes that show that any beneficial effects of amiodarone and lidocaine are similar.
Post-resuscitation antiarrhythmic drugs in adults	The confidence in effect estimates is currently too low to support an ALS Task Force recommendation about the use of prophylactic antiarrhythmic drugs immediately after ROSC in adults with VF/pVT cardiac arrest.	No specific guidance given	No change

<p>Antiarrhythmic drugs for cardiac arrest in infants and children</p>	<p>We suggest that amiodarone or lidocaine be used in the treatment of paediatric shock-refractory VF/pVT (weak recommendation, very low-certainty evidence).</p>	<p>[For VF/pVT give] amiodarone 5 mg kg⁻¹ after the third shock once CPR has been resumed. Give a second dose of amiodarone 5 mg kg⁻¹ if still in VF/pVT after the fifth shock.</p> <p>Lidocaine may be used as an alternative to amiodarone. It can be used with a loading dose of 1 mg kg⁻¹ (maximum dose 100 mg/dose) followed by continuous infusion at 20–50 micrograms kg⁻¹ min⁻¹.</p> <p>There is no evidence for giving magnesium routinely during cardiopulmonary arrest.</p>	<p>No change</p>
--	---	---	------------------

Abbreviations: ALS Advanced Life Support, CoSTR Consensus on Science and Treatment Recommendation, ERC European Resuscitation Council, ILCOR International Liaison Committee on Resuscitation, ROSC return of spontaneous circulation, VF/pVT ventricular fibrillation/pulseless ventricular tachycardia.

Conflict of interest statement

All authors and contributors have formal roles within the ERC and their respective National Resuscitation Councils. JPN is Editor-in-Chief of Resuscitation. JS and GDP are Editors of Resuscitation.