ORIGINAL ARTICLE

Effect of amiodarone and lidocaine on shock-refractory cardiac arrest: a systematic review and meta-analysis

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KEY WORDS
antiarrhythmic drug, cardiac arrest, cardiopulmonary resuscitation, meta-analysis, systematic review

ABSTRACT

BACKGROUND Appropriate pharmacotherapy during advanced resuscitation procedures may affect the return of spontaneous circulation. Current guidelines on cardiopulmonary resuscitation recommend amiodarone for shock-refractory cardiac arrest or when lidocaine is not available.

AIMS The aim of this study was to systematically analyze the available literature and to conduct a meta-analysis to determine the effect of amiodarone and lidocaine on survival and neurological outcome after shock-refractory cardiac arrest.

METHODS PubMed, Scopus, Embase, Web of Science, and Cochrane Library databases were searched. Two independent reviewers screened randomized and quasi-randomized controlled trials as well as cohort and cross-sectional trials evaluating amiodarone or lidocaine for the treatment of adults with cardiac arrest.

RESULTS After screening 682 unique references, 8 were selected for this meta-analysis. A higher number of cases with return of spontaneous circulation was observed in the amiodarone group compared with the lidocaine group (OR, 1.03; 95% CI, 0.87–1.21; $P = 0.75$). A similar relationship was observed for survival to hospital discharge (OR, 1.12; 95% CI, 0.92–1.38; $P = 0.26$), as well as survival with favorable neurological outcome (OR, 1.11; 95% CI, 0.89–1.39; $P = 0.35$).

CONCLUSIONS We found no statistically significant survival benefit of resuscitation with amiodarone compared with lidocaine. Future randomized controlled trials are needed to identify which antiarrhythmic drug should be use in shock-refractory cardiac arrest.

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INTRODUCTION The European Resuscitation Council (ERC) and the American Heart Association (AHA) guidelines for resuscitation recommend amiodarone or lidocaine in patients with shock-resistant ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT).[1,2] The 2018 update of the International Liaison Committee on Resuscitation on lidocaine was an important document on the basis of which AHA modified the recommendations on the use of antiarrhythmic drugs during and immediately after shock-refractory VF or pVT cardiac arrest, enabling the use of either amiodarone or lidocaine in these cases.[3]

Amiodarone prolongs phase 3 of the action potential of the cardiac conduction cells, reducing

WHAT'S NEW?

This meta-analysis analyzes the latest research into the use of amiodarone and lidocaine in cardiac arrest. We found no statistically significant survival benefit of resuscitation with amiodarone compared with lidocaine. A direct comparison of amiodarone and lidocaine showed that survival to hospital discharge as well as survival with a favorable neurological outcome were slightly higher with amiodarone.

the outflow of potassium ions from the cells.[4,5] Lidocaine causes reversible inhibition of impulse conduction in the nerve fibers by blocking the potassium sodium pump and inhibiting the permeability of the neuron membrane to sodium ions.[6,7] Until the publication of the 2000 Guidelines for Cardiopulmonary Resuscitation, lidocaine was the antiarrhythmic drug of choice in patients with shock-resistant ventricular fibrillation.[8] Comparative studies with amiodarone changed that, and lidocaine is currently recommended only when amiodarone is not available.[9] Despite the above, there is an ongoing debate on the choice of antiarrhythmic drug in defibrillation-resistant VF and pVT.

The aim of this study was to systematically assess the available literature and conduct a meta-analysis to determine the effect of amiodarone and lidocaine on survival and neurological outcome after shock-refractory cardiac arrest. We hypothesized that amiodarone compared with lidocaine would improve survival and neurological outcome after shock-refractory cardiac arrest.

METHODS

We systematically reviewed randomized controlled trials as well as cohort and cross-sectional trials, following the guidance from the Cochrane Collaboration. The systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] The PRISMA checklist is provided in the Supplementary material. Before commencing the study, all authors agreed on the analysis methods as well as inclusion and exclusion criteria. The protocol of this meta-analysis study was not registered. For this meta-analysis, neither ethics committee approval nor patient consent were required.

Search strategy for identification of relevant studies

Studies were included if they met the following criteria: 1) randomized and quasi-randomized controlled trials, cohort and cross-sectional studies; 2) intravascular access; 3) comparison of amiodarone and placebo, lidocaine and placebo, or amiodarone and lidocaine; 4) reporting at least return of spontaneous circulation (ROSC) outcome; 5) adult patients with cardiac arrest. Review articles, experimental animal trials, simulation trials, conference papers, letters to the editor, and case studies were excluded.

Two authors (LS and KJF) searched for relevant studies published until May 16, 2020 and included in PubMed, Scopus, Embase, Web of Science, Cochrane Library without any language restrictions.

The following terms were used: *amiodarone* or *lidocaine* and *heart arrest* or *cardiac arrest* or *resuscitation*. Additionally, the electronic database search was supplemented by searching Google Scholar.

Review methods and selection criteria

The references independently retrieved by electronic search were imported to and managed by the EndNote X7 software. Two independent investigators (JS and KL) screened both the titles and abstracts to exclude nonpermanent studies. Discrepancies were resolved by a third author (LS). Relevant full-text articles were retrieved and analyzed for eligibility with the application of predefined inclusion criteria. Reference lists of these studies were also searched to ensure that other relevant articles were not omitted.

Data extraction Two authors (KL and JRŁ) extracted the following data independently using an electronic data abstraction form: investigators or study name; recruitment period; year of publication of the primary findings; randomized treatment comparison; type of treatment (amiodarone vs placebo, lignocaine vs placebo, or amiodarone vs lidocaine); information about the study population (mean age, number of participants, number of men); the primary and secondary measures; inclusion and exclusion criteria; and study quality.

Study outcome definition The primary outcome of this systematic review was ROSC. The secondary outcome was survival to hospital discharge and survival to hospital discharge with favorable neurological outcome. Favorable neurological outcome was defined as the patient discharged home or for rehabilitation, Cerebral Performance Categories Scale score of 1 or 2, or a modified Rankin Scale score of 0.1 or 2.[11,12]

Assessment of the risk of bias Two authors (LS and JS) estimated the risk of bias. The quality of each study was assessed with the "risk of bias" tool of the Review Manager software, version 5.3 (RevMan; Cochrane Collaboration, Oxford, United Kingdom) developed for randomized trials. The following domains were evaluated for randomized controlled trials: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective

TABLE 1 Characteristics of randomized controlled trials included in the study

Study	Country / region	Study type	Intervention	Population characteristics				Primary endpoint
				Patients, n	Age, y, mean (SD)	Male sex, n (%)	Inclusion criteria	
Daya et al[18]	North America (United States and Canada)	Randomized double-blind trial	Amiodarone vs lidocaine vs placebo	3019	62.6 (14.4)	2416 (80)	Adults with nontraumatic out-of--hospital cardiac arrest presenting as shock--refractory VF/pVT	Survival to hospital discharge
Dorian et al[19]	United States	Randomized controlled trial	Amiodarone vs lidocaine	347	67 (14)	272 (78.4)	Out-of-hospital ventricular fibrillation resistant to 3 shocks, intravenous epinephrine, and further shock; or if they had recurrent ventricular fibrillation after initially successful defibrillation	Survival to admission to the hospital intensive care unit
Kudenchuk et al[20]	United States	Randomized double-blind placebo--controlled trial	Amiodarone vs placebo	504	65.4 (14)	290 (57.5)	Adults with nontraumatic out-of--hospital cardiac arrest, if ventricular fibrillation or pulseless ventricular tachycardia (on initial presentation or any time in the course of the resuscitation attempt) was present after 3 or more precordial shocks, if intravenous access had been established, and if paramedics were on the scene with the study drug or placebo.	Admission to the hospital with a spontaneously perfusing rhythm (a sufficiently stable, organized rhythm and blood pressure [with or without the use of pressor drugs])

Abbreviations: pVT, pulseless ventricular tachycardia; VF, ventricular fibrillation

reporting (reporting bias), and other biases.[13] Each was graded "yes", "no", or "unclear", which reflected a high risk of bias, low risk of bias, and uncertain bias, respectively (Supplementary material, *Figure S1*). The reviewing authors' judgment on each risk of bias item are provided in Supplementary material, *Figure S2*. The overall risk of bias of a study was rated low if 7 or more domains were rated low, moderate, if 4 to 6 were rated low, and high, if 1 to 3 were rated low. The Newcastle-Ottawa quality assessment scale was used to appraise the outcome of interest in cohort studies. The modified Newcastle-Ottawa scale was used in cross-sectional studies.[14]

Statistical analysis The statistical analysis was performed in Review Manager, version 5.3 (Cochrane Collaboration). All analyses were performed according to the intention-to-treat principle. The Mantel-Haenszel method was used to pool dichotomous data and to compute pooled risk ratios (RRs) with 95% CIs. The inverse variance method was used to pool continuous data and to calculate weight mean differences with 95% CIs. When the continuous outcome was reported in a study as a median, range, and interquartile range, we estimated means (SD) using the formula described by Hozo et al.[15] The random effect or fixed effects model was used for the meta-analysis according to study characteristics. The I^2 test was used to assess statistical heterogeneity. I^2 values higher than 50% and higher than 75% were considered to indicate moderate and significant heterogeneity among studies, respectively.[16] All statistical tests were 2-tailed and were considered when a P value was less than 0.05.

RESULTS FIGURE 1 illustrates the process used for trial screening and selection. The initial search strategy yielded 682 relevant articles, of which 133 were duplicates. Of the 549 titles and abstracts receded, 23 full-text articles were retained for further screening. A single article[17] was removed from the study even though it met the inclusion criteria because an updated version was published in 2020[18] and was included in our analysis. Finally, we included 8 articles.[18-25]

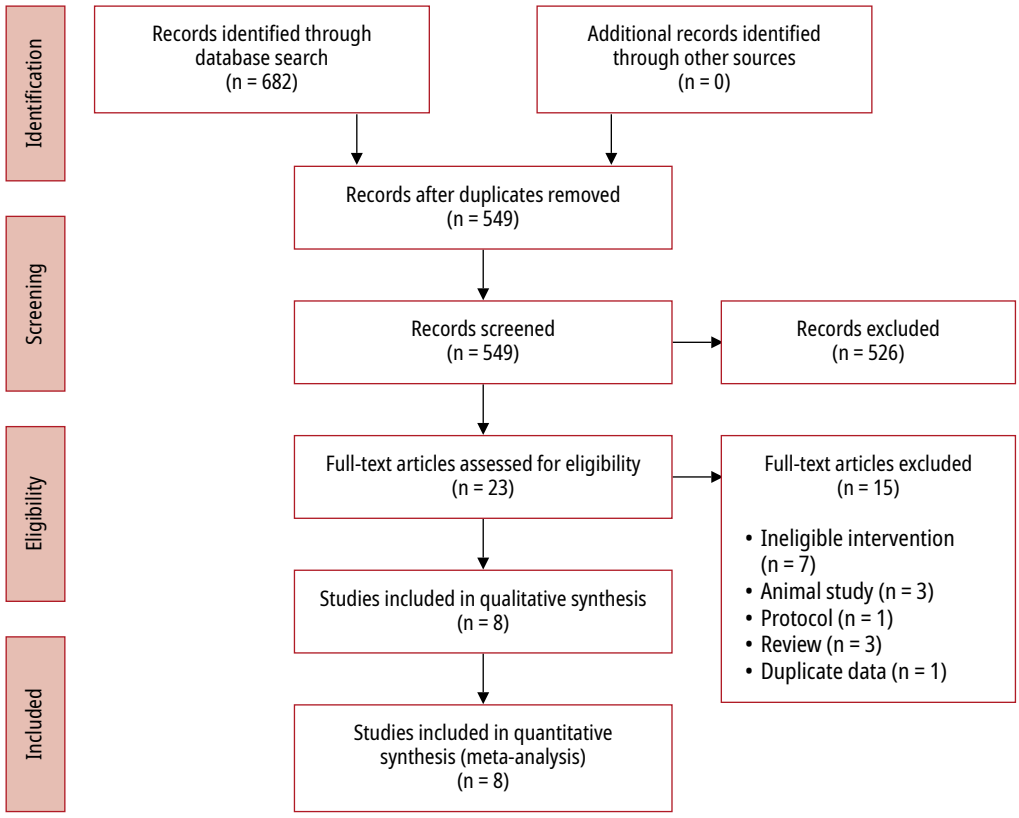

FIGURE 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram

Study characteristics and patient demographics The studies included in this meta-analysis were published between 1981 and 2020 (see TABLES 1 and 2).[18-25] Four studies were carried out in the United States,[19-21,23] and others in Taiwan,[25] Finland,[24] Sweden,[22] and in North America (United States and Canada).[18] Three were randomized [18-20] and 5 were retrospective cohort studies.[21-25]

All studies included adult patients in whom resuscitation was performed. Three studies compared amiodarone and placebo or no amiodarone treatment.[18,20,24] In 3 studies, lidocaine and placebo or no-lidocaine treatment was analyzed.[18,20,21] In 4 studies, amiodarone and lidocaine was compared.[18,19,23,25]

Return of spontaneous circulation / survival to hospital admission Forest plots on the effects of management on the incidence of ROSC are presented in FIGURE 2. Three studies considered the effects of amiodarone and placebo on ROSC. Return of spontaneous circulation in patients receiving amiodarone was observed in 45.7% of cases and for placebo in 37.8% of cases (OR, 1.25; 95% CI, 1.08–1.46; P = 0.004; FIGURE 2A).

When comparing lidocaine and placebo, ROSC was different and was 41.9% and 36.3% respectively (OR, 1.36; 95% CI, 1.15–1.6; P <0.001; FIGURE 2B).

Three studies reported amiodarone and lidocaine comparison in terms of ROSC prevalence.[18,19,25] In the group treated with amiodarone, the incidence of ROSC was 44.2%, and in the group treated with lidocaine, 42.3% (OR, 1.03; 95% CI, 0.87–1.21; P = 0.75; FIGURE 2C).

Survival to hospital discharge Three studies[18,20,24] reported survival to hospital discharge, which was higher in the amiodarone group (22.5%) compared with the placebo group (21.1%; OR, 1.11; 95% CI, 0.92–1.33; P = 0.28; FIGURE 3A).

Three studies also reported lidocaine and placebo.[18,21,22] Lidocaine treatment was associated with higher survival to hospital discharge compared with placebo (19.8% vs 19.%, respectively; OR, 1.13; 95% CI, 0.92–1.38; P = 0.25; FIGURE 3B).

Comparison of amiodarone and lidocaine on survival to hospital discharge was observed in 3 studies.[18,19,25] Survival to hospital discharge was higher in the amiodarone group (21.5%) compared with the lidocaine group (19.8%; OR, 1.12; 95% CI, 0.92–1.38; P = 0.26; FIGURE 3C).

Survival with favorable neurological outcome Two studies reported the impact of amiodarone and placebo on survival with favorable neurological outcome,[18,20] 1 compared lidocaine and placebo,[18] and 4 compared amiodarone and lidocaine (FIGURE 4).[18,19,23,25]

TABLE 2 Characteristics of nonrandomized controlled trials included in the study

Study	Country / region	Study type	Intervention	Population characteristics			The Newcastle-Ottawa scale			
				Patients, n	Age, y, mean (SD)	Male sex, n (%)	Selection	Comparability	Outcome	Overall quality score
Harrison[21]	United States	Retrospective cohort study	Lidocaine	116	61.5 (8.7)	79 (68.1)	3	1	2	6
Herlitz et al[22]	Sweden	Multicenter retrospective cohort study	Lidocaine	290	68 (11.9)	167 (57.6)	4	1	2	7
Rea et al[23]	United States	Multicenter retrospective cohort study	Amiodarone vs lidocaine	153	57.4 (16.2)	110 (71.9)	4	2	2	8
Skrifvars et al[24]	Finland	Retrospective cohort study	Amiodarone	180	63.9 (3.6)	137 (76.1)	4	2	2	8
Wang et al[25]	Taiwan	Retrospective cohort study	Amiodarone vs lidocaine	130	67 (15)	91 (70)	4	2	2	8

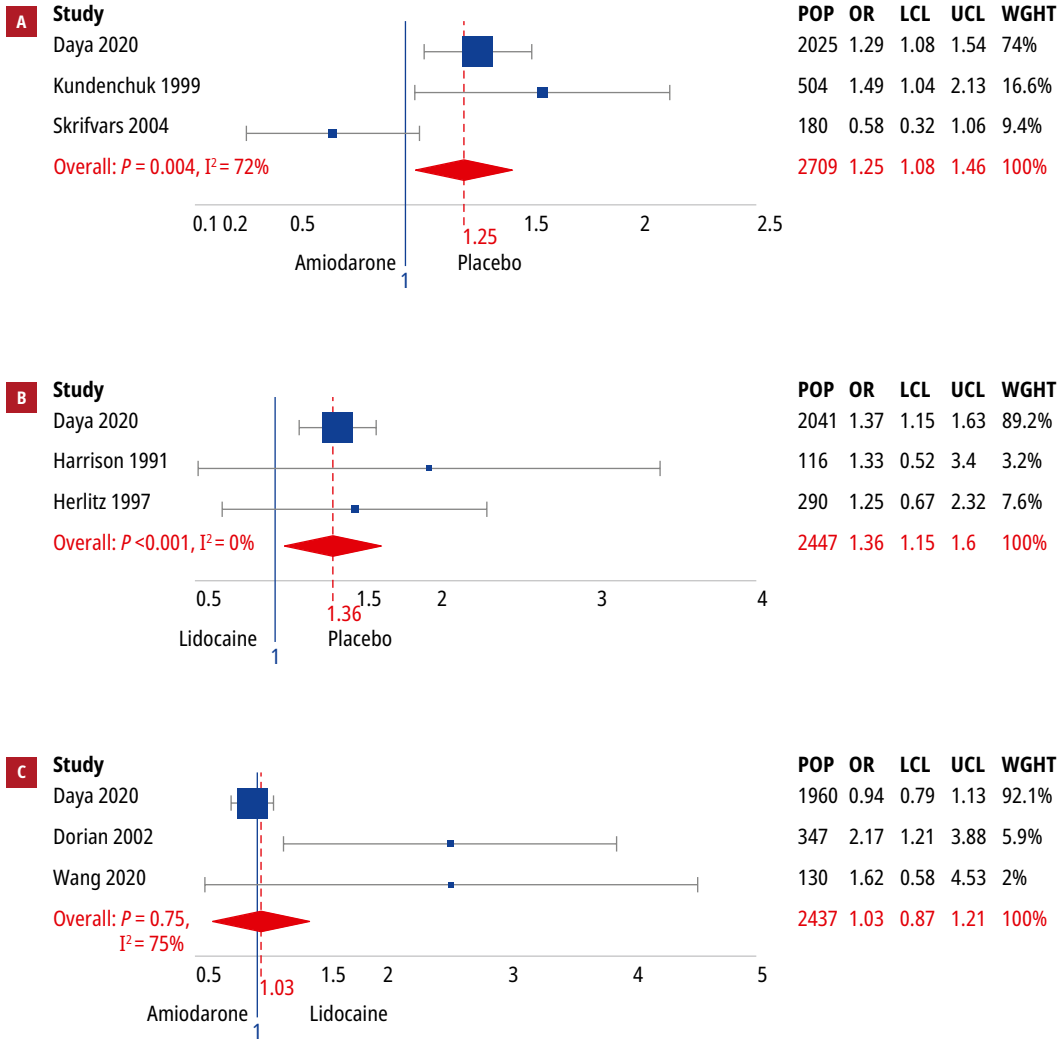

FIGURE 2 Forest plots showing the association between amiodarone versus placebo (**A**), lidocaine versus placebo (**B**), and amiodarone versus lidocaine (**C**), relative to return of spontaneous circulation. The center of each square represents the weighted odds ratio for individual trials; corresponding horizontal line, 95% CI; diamonds, pooled results.
Abbreviations: LCL, lower confidence interval limit; OR, odds ratio; POP, population; UCL, upper confidence interval limit; WGHT, weight; M-H, Mantel-Haenszel

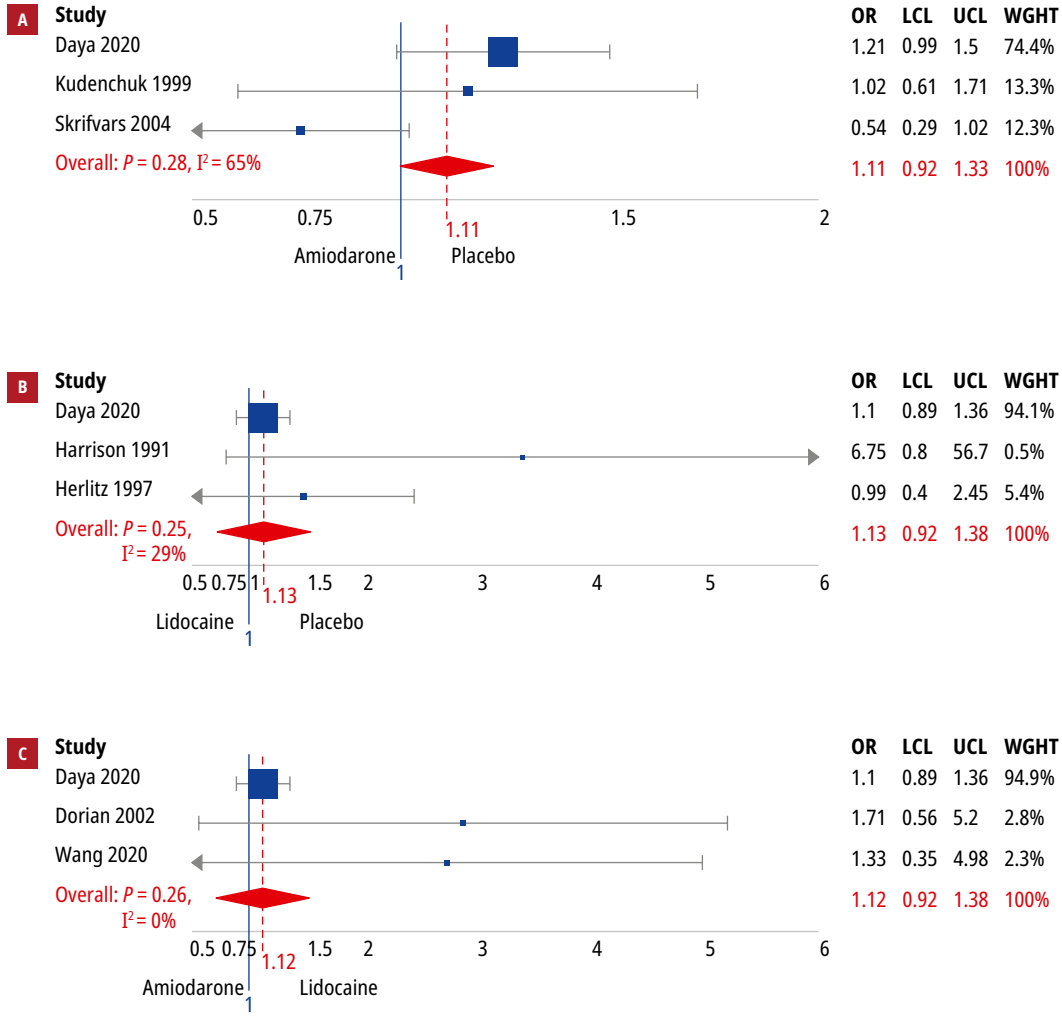

FIGURE 3 Forest plots showing the association between amiodarone versus placebo (**A**), lidocaine versus placebo (**B**), amiodarone versus lidocaine (**C**), relative to survival to hospital discharge. The center of each square represents the weighted odds ratio for individual trials; corresponding horizontal line, 95% CI; diamonds, pooled results.
Abbreviations: see FIGURE 2

Survival with a favorable neurological outcome was higher in the amiodarone group when compared with placebo (16.5% vs 14.6%; OR, 1.16; 95% CI, 0.94–1.44; $P = 0.17$), in the lidocaine group when compared with placebo (17.5% vs 16.6%; $P = 0.57$), as well as in the amiodarone group when compared to the lidocaine group (17.7% vs 17.4%; OR, 1.11; 95% CI, 0.89, 1.39; $P = 0.35$).

DISCUSSION

This meta-analysis included different types of studies relating to the use of amiodarone and lidocaine in shockable rhythms in patients with sudden cardiac arrest. We assessed studies comparing amiodarone and placebo, amiodarone versus lidocaine, and amiodarone versus lidocaine in terms of the effect on various parameters related to ROSC, survival to the hospital admission, and discharge from the hospital with a favorable neurological outcome.

The effectiveness of defibrillation is affected by many elements, including the quality of chest compression, electrical current flow through the chest, and exclusion of potentially reversible causes of sudden cardiac arres,[26-29] and the use of antiarrhythmic drugs including amiodarone and lidocaine in shockable rhythms.[30] However, the choice of the drug used for shockable rhythms in sudden cardiac arrest may affect the survival of patients, the duration of the resuscitation, and thus, the neurological prognosis and quality of life.[31] Both lidocaine and amiodarone have been used for many years in ventricular arrhythmias, including shockable rhythms (ventricular fibrillation and ventricular tachycardia).[20,23,32] If shockable rhythms occur, both of these medications may be used if defibrillation is ineffective.[2] Current guidelines recommend administering these drugs after the third defibrillation, both in adults and children. In this meta-analysis, we have assessed the effect of the type of pharmacological

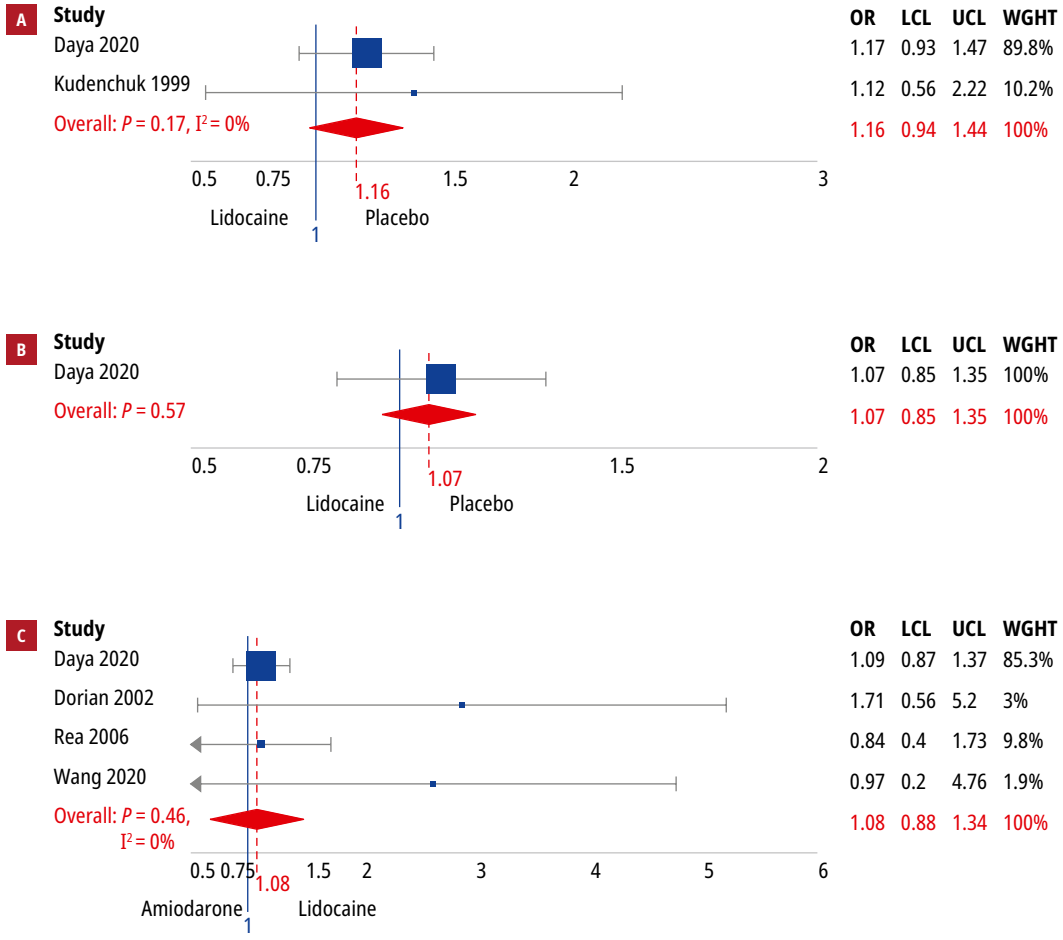

FIGURE 4 Forest plots showing the association between amiodarone versus placebo (**A**), lidocaine versus placebo (**B**), amiodarone versus lidocaine (**C**), relative to survival with favorable neurological outcome. The center of each square represents the weighted odds ratio for individual trials; corresponding horizontal line, 95% CI; diamonds, pooled results.
Abbreviations: see FIGURE 2

treatment (amiodarone vs lidocaine) on shockable rhythms in sudden cardiac arrest. Return of spontaneous circulation is one of the basic elements used to assess the effectiveness of resuscitation.[33] Pooled analysis of the results showed no significant statistical differences between the groups in which amiodarone or lidocaine were used in ROSC. This parameter is of fundamental importance for resuscitation undertaken in both out-of-hospital and in-hospital conditions.[18,20]

A more important parameter for the outcome of treatment is survival to hospital discharge. A direct comparison of amiodarone and lidocaine showed that survival to hospital discharge was slightly higher with amiodarone. Very alarmingly, a comparison of the efficacy of amiodarone and placebo showed a slightly higher efficacy of amiodarone in 3 studies, but the OR was 1.11, which indicates similar efficacy of both treatments.

Studies and guidelines on cardiopulmonary resuscitation state that survival of sudden cardiac arrest with favorable neurological outcome is the basic parameter in assessing the effectiveness of cardiopulmonary resuscitation.[17,19] Within this parameter, minor advantage of amiodarone over placebo, lidocaine over placebo and amiodarone over lidocaine was shown, but differences were not significant. Survival with favorable neurological outcome in the pooled data for amiodarone was 17.7% and for lidocaine 17.4%; however, these differences were not significant.

In 2016, the ROC-ALPS (Resuscitation Outcomes Consortium-Amiodarone, Lidocaine or Placebo Study) was published in the *New England Journal of Medicine*.[17] In this large randomized controlled study, captisol-based amiodarone with lidocaine or placebo in patients with VF or pVT refractory after at least 1 shock was compared. The amiodarone and lidocaine were superior to placebo comparing survival to hospital admission with no difference between amiodarone and lidocaine. In this study, no overall difference in survival with good neurological outcome or survival to hospital discharge was noted and ROSC was higher in the group treated with lidocaine compared with placebo but not for the group treated with

amiodarone compared with placebo. When analyzing the role of antiarrhythmic drugs in sudden cardiac arrest, consideration should be given to the subgroup analysis in the ROC-ALPS study suggesting that early administration of either lidocaine or amiodarone may improve survival by improving efficacy of defibrillation.

The results of this meta-analysis support the 2018 AHA modified recommendations on the use of lidocaine and amiodarone in sudden cardiac arrest[33] and are contradictory to the studies on which the 2015 ERC and AHA guidelines were based, which suggested a significant advantage of amiodarone over lidocaine for shockable rhythms during sudden cardiac arrest in hospital and out-of-hospital settings. The 2015 ERC and AHA guidelines were based on data from studies published at that time. The guidelines mention ongoing randomized clinical trials comparing the use of amiodarone, lidocaine, and placebo. The pooled data obtained in this meta-analysis indicate that the use of lidocaine should not be limited to cases where amiodarone is not available because the drugs have similar efficacy.

The issues related to the use of lidocaine and amiodarone have been analyzed in a previous systematic review and meta-analysis[34]; however, the current study includes important studies, with an important negative trial published in 2020.

Our study has some limitations. First, only 3 studies were randomized clinical trials. Second, not all studies included a comparison of treatment with amiodarone, lidocaine, and placebo. Third, only 2 studies included blinding.

In conclusion, we found no survival benefit of resuscitation with amiodarone compared with lidocaine. Further randomized controlled trials are warranted to identify which antiarrhythmic drug should be used in patients with shock-refractory cardiac arrest.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

ACKNOWLEDGMENTS The study was supported by the European Resuscitation Council Research NET and Polish Society of Disaster Medicine.

CONTRIBUTION STATEMENT KL, LS, and KJF conceived the concept and design of the study. KL developed the search strategy. LS and KJF performed literature search. KL and JS screened the literature. KL and AS performed the data analysis. JRŁ, LS, and KL interpreted the results of the systematic review. LS and KN drafted the manuscript. MJ made important revisions to the draft report. All authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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