Resuscitation 107 (2016) 31–37

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Review article

Amiodarone or lidocaine for cardiac arrest: A systematic review and meta-analysis☆

F. Sanfilippo[a,*], C. Corredor[b], C. Santonocito[a], G. Panarello[a], A. Arcadipane[a], G. Ristagno[c,d], T. Pellis[d,e]

[a] Department of Anesthesia and Intensive Care, IRCCS-ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione), Via Tricomi 5, 90127 Palermo, Italy
[b] Cardiovascular Anaesthesiology and Critical Care, Toronto General Hospital, 200 Elizabeth Street, Toronto, ON M5G 2C4, Canada
[c] IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy
[d] Italian Resuscitation Council—Scientific Committee, Bologna, Italy
[e] Anesthesia Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, UAE

ARTICLE INFO

Article history:
Received 25 May 2016
Received in revised form 14 July 2016
Accepted 18 July 2016

Keywords:
Out-of-hospital cardiac arrest
Placebo
Hospital admission
Hospital discharge
Return of spontaneous circulation

ABSTRACT

Background: Guidelines for treatment of out-of-hospital cardiac arrest (OOH-CA) with shockable rhythm recommend amiodarone, while lidocaine may be used if amiodarone is not available. Recent underpowered evidence suggests that amiodarone, lidocaine or placebo are equivalent with respect to survival at hospital discharge, but amiodarone and lidocaine showed higher hospital admission rates. We undertook a systematic review and meta-analysis to assess efficacy of amiodarone vs lidocaine vs placebo.
Methods: We included studies published in PubMed and EMBASE databases from inception until May 15th, 2016. The primary outcomes were survival at hospital admission and discharge in OOH-CA patients enrolled in randomized clinical trials (RCT) according to resuscitation with amiodarone vs lidocaine vs placebo. If feasible, secondary analysis was performed including in the analysis also patients with in-hospital CA and data from non-RCT.
Results: A total of seven findings were included in the metanalysis (three RCTs, 4 non-RCTs). Amiodarone was as beneficial as lidocaine for survival at hospital admission (primary analysis odds ratio—OR 0.86–1.23, $p = 0.40$) and discharge (primary analysis OR 0.87–1.30, $p = 0.56$; secondary analysis OR 0.86–1.27, $p = 0.67$). As compared with placebo, survival at hospital admission was higher both for amiodarone (primary analysis OR 1.12–1.54, $p < 0.0001$; secondary analysis OR 1.07–1.45, $p < 0.005$) and lidocaine (secondary analysis only OR 1.14–1.58, $p = 0.0005$). With regards to hospital discharge there were no differences between placebo and amiodarone (primary outcome OR 0.98–1.44, $p = 0.08$; secondary outcome OR 0.92–1.33, $p = 0.28$) or lidocaine (secondary outcome only OR 0.97–1.45, $p = 0.10$).
Conclusions: Amiodarone and lidocaine equally improve survival at hospital admission as compared with placebo. However, neither amiodarone nor lidocaine improve long-term outcome.

Introduction

Sudden cardiac arrest (CA) is an emergency with high incidence ranging between 320,000 and 700,000 events per year in the United States and Europe.[1,2] Among out-of-hospital (OOH) CA, survival at hospital admission is approximately 35–40%,[3,4] while at hospital discharge is much lower (8–24%).[3–8] Importantly, favorable neurological outcome is reported only in less than half of patients admitted to ICU after return of spontaneous circulation (ROSC).[9,10]

The recent guidelines for the treatment of OOH-CA with a shockable rhythm (ventricular fibrillation – VF – or pulseless ventricular tachycardia – VT –) suggest only amiodarone as antiarrhythmic drug after three defibrillation attempts, while lidocaine may be used as alternative, if amiodarone is not available.[11,12] However, in a recent randomized controlled trial (RCT) amiodarone, lidocaine or placebo had similar results, although the RCT was possibly underpowered. Interestingly, amiodarone and lidocaine showed a significantly higher number of patients admitted alive to the hospital, and a higher survival at hospital discharge in the subgroup of

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2016.07.235.

* Corresponding author.
E-mail addresses: fgsanfilippo@ismett.edu, filipposanfi@yahoo.it (F. Sanfilippo), carloscorredor@doctors.org.uk (C. Corredor), cristina.santonocito@gmail.com (C. Santonocito), gpanarello@ismett.edu (G. Panarello), aarcadipane@ismett.edu (A. Arcadipane), gristag@gmail.com (G. Ristagno), thomas.pellis@gmail.com (T. Pellis).

http://dx.doi.org/10.1016/j.resuscitation.2016.07.235
0300-9572/

Table 1
"PICOS" approach for selecting clinical studies in the systematic search and meta-analysis. CA: cardiac arrest; VF: ventricular fibrillation; VT: ventricular tachycardia (pulseless).

PICOS	
1. Participants	Patients in CA with a shockable rhythm (VF/VT), including both in- and out-of-hospital setting
2. Intervention	Administration of amiodarone
3. Comparison	Placebo, lidocaine (primary analysis); no drug administered (secondary analysis)
4. Outcomes	Survival at hospital admission; survival at hospital discharge; favorable neurological outcome (modified Rankin scale score ≤3 or return to independent living activities)
5. Study design	RCT (primary analysis); prospective and retrospective studies (secondary analysis)

patients with bystander-witnessed CA. Before this RCT, a recent meta-analysis analyzed the efficacy of anti-arrhythmic drugs in the treatment of CA,[13] but it included drugs not currently recommended and suffered from large biases in the studies included. For instance, many of these studies were retrospective chart reviews, with unbalanced baseline characteristics,[14] or different timing of drug administration and severely under-dosed treatments.[15]

To overcome such limitations and in view of the recently published large RCT, we conducted a meta-analysis aiming at assessing the efficacy of amiodarone as compared with lidocaine or placebo.

Methods

Search strategy and criteria

We undertook a systematic web-based advanced literature search through the *NHS Library Evidence* tool on the effects of amiodarone in patients with CA. We followed the approach suggested by the PRISMA statement for reporting systematic reviews and meta-analyses[16] and a PRISMA checklist is provided separately (Supplemental digital content 1).

An initial computerized search of MEDLINE (PubMed) was conducted from inception until April 10th, 2016 to identify the relevant articles. With these findings, we wrote a draft of the prospective study protocol. A final search was re-performed at the end of the analysis (May 15th, 2016) to identify further findings. Our core search was structured by combining a group of findings containing the term "cardiac arrest" or "hear arrest" with a second group including the word "amiodarone" and/or "lidocaine". Two further searches were performed manually combining the words "amiodarone" and "cardiac arrest" or "lidocaine" and "cardiac arrest". Inclusion criteria were pre-specified according to the PICOS approach (Table 1).

We a priori decided to consider a secondary analysis including non-randomized prospective and retrospective clinical studies. We excluded experimental animal studies, book chapters, reviews, editorials and letters to editor. Case series were not included in the secondary analysis unless reporting at least 10 patients per group. Study selection for determining the eligibility for inclusion in the systematic review and data extraction were performed independently by four reviewers (FS, CC, CS, AA). Discordances were resolved by involving the other three authors and/or by consensus. Language restrictions were applied: we read the full manuscript only for articles published in English, French, Spanish, German or Italian. For prospective and retrospective studies published in other languages, we read the abstract and, if necessary, contacted the authors for further information. A manual search was conducted independently by three authors (FS, CS, AA), exploring also the list of references of the findings of the systematic search.

Groups and endpoints

We primarily compared the efficacy of amiodarone vs lidocaine vs placebo with regards of survival at hospital admission and hospital discharge in patients with OOH-CA enrolled in RCTs. If available, the incidence of favorable neurological outcome (as defined by a modified Rankin scale score ≤3 or return to independent living activities) was assessed. A secondary analysis was performed including also results from non-RCTs and studies including patients suffering from in-hospital CA.

Quality assessment

Methodological quality of included RCTs was performed using the Cochrane Collaboration tool which incorporated the following domains: selection, performance, detection, attrition, performance and other potential sources of bias.[17] Risk of bias assessment for observational studies was performed using the Newcastle–Ottawa scale (NOS) which gives up to nine points if all criteria of quality assessment are fulfilled. The scale has three main domains and according to their score studies are classified at high risk (1–3 points), intermediate risk (4–5 points) and low risk of bias (6–9 points).[18–20]

Statistical analysis

The Mantel–Haenszel method was used to analyze dichotomous outcomes of survival at hospital admission and at hospital discharge and survival with good neurological outcome. Results are reported as odd ratios (OR) with 95% confidence intervals (CI) and two tailed p values. p values were considered significant if <0.05. The presence of statistical heterogeneity was assessed using the X2 (Cochran Q) test. Heterogeneity was likely if $Q > df$ (degrees of freedom) suggested and confirmed if $p \leq 0.10$. Quantification of heterogeneity was performed and values of I^2 ranging 0–24.9%, 25–49.9%, 50–74.9% and >75% were considered as none, low, moderate and high heterogeneity, respectively. If heterogeneity was quantified as low or above, a random-model was also used for sensitive analyses.[21]

Results

Our systematic search identified 528 findings via *NHS Library Evidence* search. No other findings were retrieved manually. As shown in the PRISMA flow diagram (Supplemental digital content 2), after the evaluation of all findings, only seven studies were judged of interest for our analyses: three RCTs, one prospective observational study and three retrospective chart review studies.

Of the RCTs, the most recent was a "three-arm" trial enrolling 3026 patients (per-protocol population) divided in amiodarone ($n = 974$), lidocaine ($n = 993$) or placebo ($n = 1059$).[6] Such trial was by far the largest trial since the other two comparing amiodarone with lidocaine[22] or with placebo[23] included only a total of 347 and 304 patients, respectively.

The only prospective observational study that compared lidocaine vs no lidocaine in OOH-CA patients and included 116 patients and was over 25 years old[24]; the three retrospective studies included 290 (lidocaine vs no lidocaine),[25] 180 (amiodarone vs no amiodarone)[14] and 118 patients (amiodarone vs lidocaine).[15] Only the latter study was performed in patients suffering from in-hospital CA.

Table 2
Summary of the results of meta-analyses comparing amiodarone vs lidocaine vs placebo. The outcome analysed, the number of studies included in the analysis, the odds ratio (OR), the *p* value, the heterogeneity (I^2) and the figure of the forest plot are reported in separate columns. In bold are highlighted the p values reaching a statistically significant difference.

Comparison	Outcome	OR	*p*	I^2	Fig.
Amiodarone vs placebo	Survival at hospital discharge	1.19 [0.98–1.44]	0.08	0%	1a
	Survival at hospital admission	1.32 [1.12–1.54]	**0.0006**	0%	1b
	Survival & good neurological outcome	1.16 [0.93–1.44]	0.18	0%	1c
	Survival at hospital discharge[a]	1.11 [0.92–1.33]	0.28	65%	2a
	Survival at hospital admission[a]	1.25 [1.07–1.45]	**0.004**	72%	2b
Lidocaine vs placebo	Survival at hospital discharge[a]	1.19 [0.97–1.45]	0.10	27%	3a
	Survival at hospital admission[a]	1.34 [1.14–1.58]	**0.0005**	0%	3b
Amiodarone vs lidocaine	Survival at hospital discharge	1.06 [0.87–1.30]	0.56	0%	4a
	Survival at hospital admission	1.02 [0.86–1.21]	0.81	86%	4b
	Survival at hospital discharge[a]	1.04 [0.86–1.27]	0.67	0%	4c

[a] Analysis conducted including also non-randomized studies.

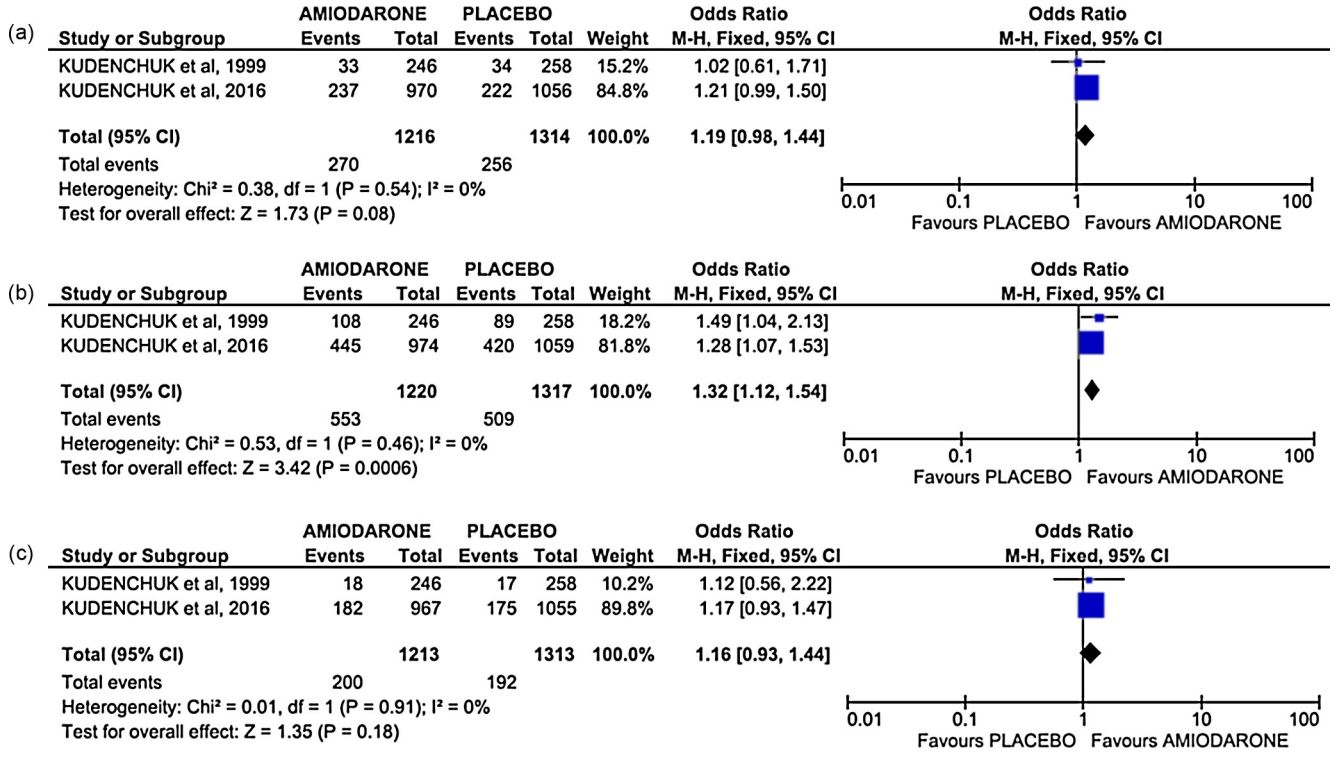

Fig. 1. Forest plots comparing amiodarone vs placebo. (1a) Survival at hospital discharge; (1b) survival at hospital admission; (1c) survival at with good neurological outcome.

The results of the three comparison between amiodarone, lidocaine and placebo are reported separately as subparagraphs and summarized in Table 2.

Amiodarone vs placebo

Two RCTs compared amiodarone vs placebo in the treatment of CA victims[6,23] including up to 2537 patients. Amiodarone showed a trend toward higher survival at hospital discharge ($p = 0.08$, Fig. 1a) and a significantly higher survival at hospital admission ($p = 0.0006$, Fig. 1b). There was no difference in discharge with favorable neurological outcome between amiodarone and placebo ($p = 0.18$, Fig. 1c). There was no heterogeneity in these three results.

In the secondary analysis conducted adding one retrospective study[14] with further 180 patients, amiodarone was not associated with survival at hospital discharge ($p = 0.28$; Fig. 2a) but remained significantly associated with survival at hospital admission ($p = 0.004$; Fig. 2b). In both analyses, there was a moderate degree of heterogeneity ($I^2 = 65\%$ and 72% respectively). However, using a random-effect model, the secondary analysis showed no difference between amiodarone and placebo also with respect to survival at hospital admission (OR 1.13 [0.77–166], $p = 0.53$).

Lidocaine vs placebo

Only one RCT compared lidocaine vs placebo in the treatment of CA patients.[6] One prospective[24] and one retrospective[25] study evaluated the administration of lidocaine vs none in patients with OOH-CA. In the analyses of these three studies with data up to 2458 patients, lidocaine showed a trend toward higher survival at hospital discharge ($p = 0.10$, Fig. 3a). This result showed mild heterogeneity ($I^2 = 27\%$) and the analysis with the random effect made the trend non-significant ($p = 0.41$, result not shown). Lidocaine showed a significantly higher survival at hospital admission ($p = 0.0005$, Fig. 3b). There was no heterogeneity in this result.

Amiodarone vs lidocaine

Two RCT compared amiodarone vs placebo in the treatment of CA victims[6,22] including up to 2302 patients. There were no dif-

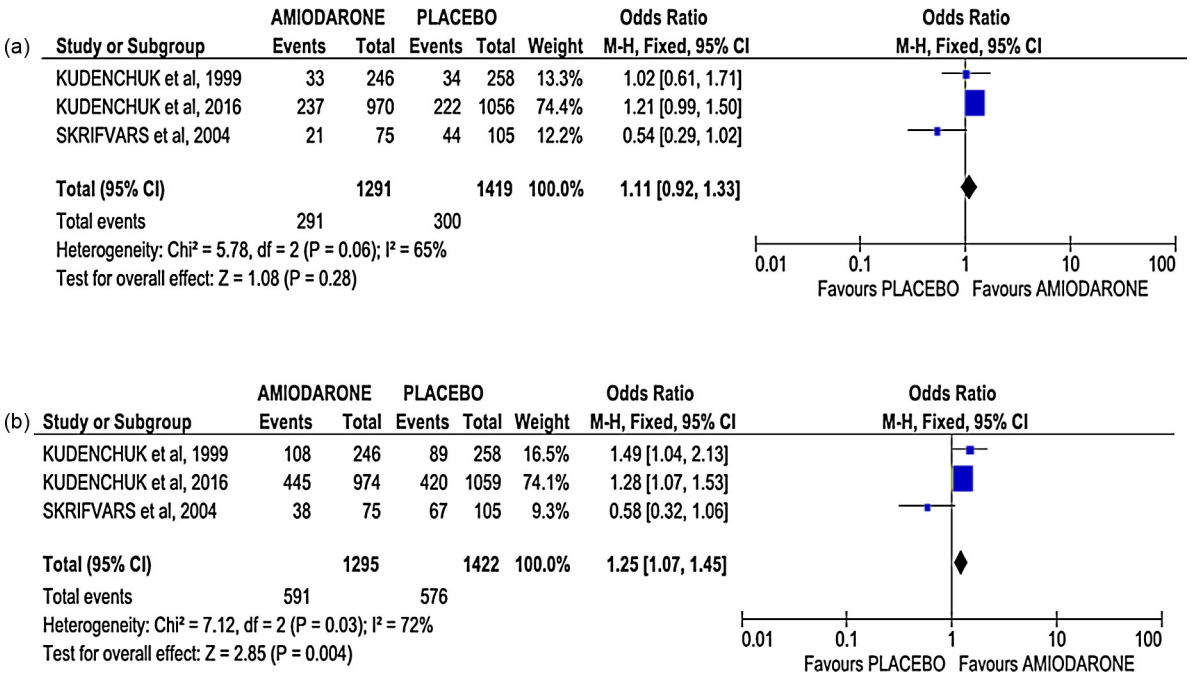

Fig. 2. Forest plots comparing amiodarone vs placebo including in the analysis also one non-randomized controlled study. (2a) Survival at hospital discharge; (2b) survival at hospital admission.

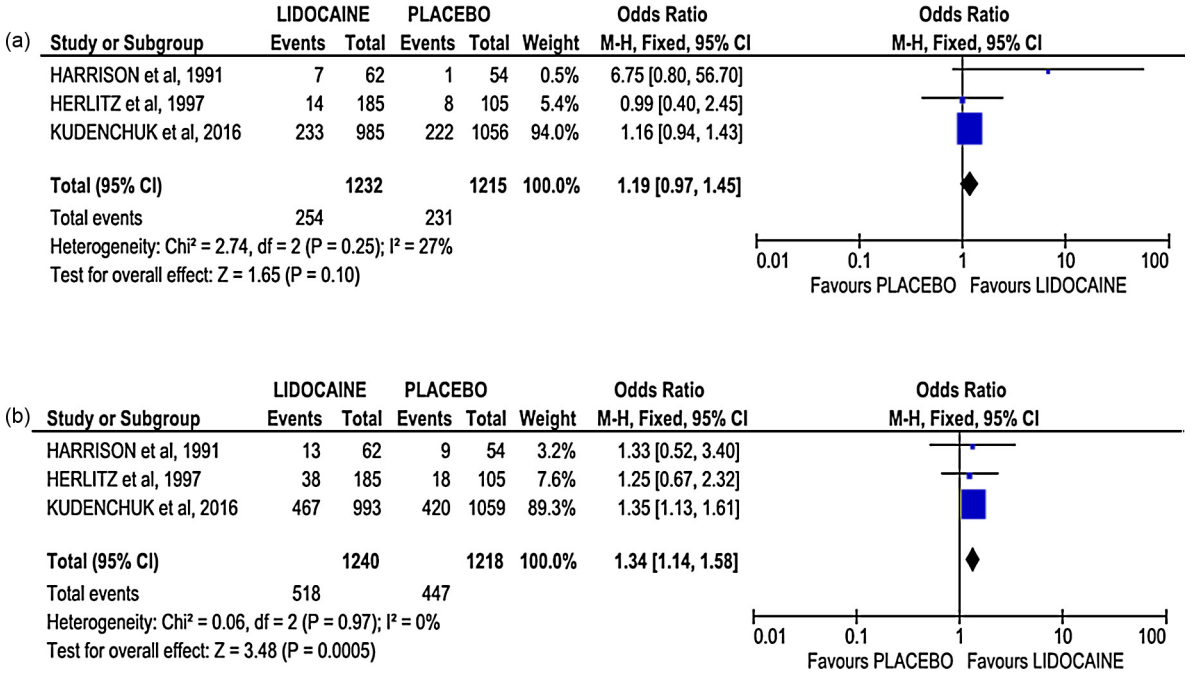

Fig. 3. Forest plots comparing lidocaine vs placebo including in the analysis also two non-randomized controlled studies. (3a) Survival at hospital discharge; (3b) survival at hospital admission.

ferences in survival at hospital discharge ($p = 0.56$, Fig. 4a) and at hospital admission ($p = 0.81$, Fig. 4b). Only one study reported neurological outcome,[6] and therefore such analysis was not feasible. There was no heterogeneity in the first result, while a high heterogeneity was seen in the survival at hospital admission ($I^2 = 86\%$) but the analysis with random-effect did not change the results ($p = 0.45$). Survival at hospital discharge was also evaluated by one retrospective study in 118 patients with in-hospital CA.[15] The inclusion of this study in the secondary analysis did not change the result ($p = 0.67$, $I^2 = 0\%$, Fig. 4c).

Risk of bias assessment

The assessment of risk of bias for RCTs, showed that only the recent RCT was at low risk of bias,[6] while the other studies[22,23] had one or more domain with unclear or high risk of bias (Supplemental digital content 3).

The assessment of risk of bias for non-RCTs performed with the NOS method showed that all the studies had low-risk, scoring 6/9 or above. In particular, scores were higher in the two most recent ones (8/9)[14,15] and slightly lower for Herlitz et al. (7/9)[25];

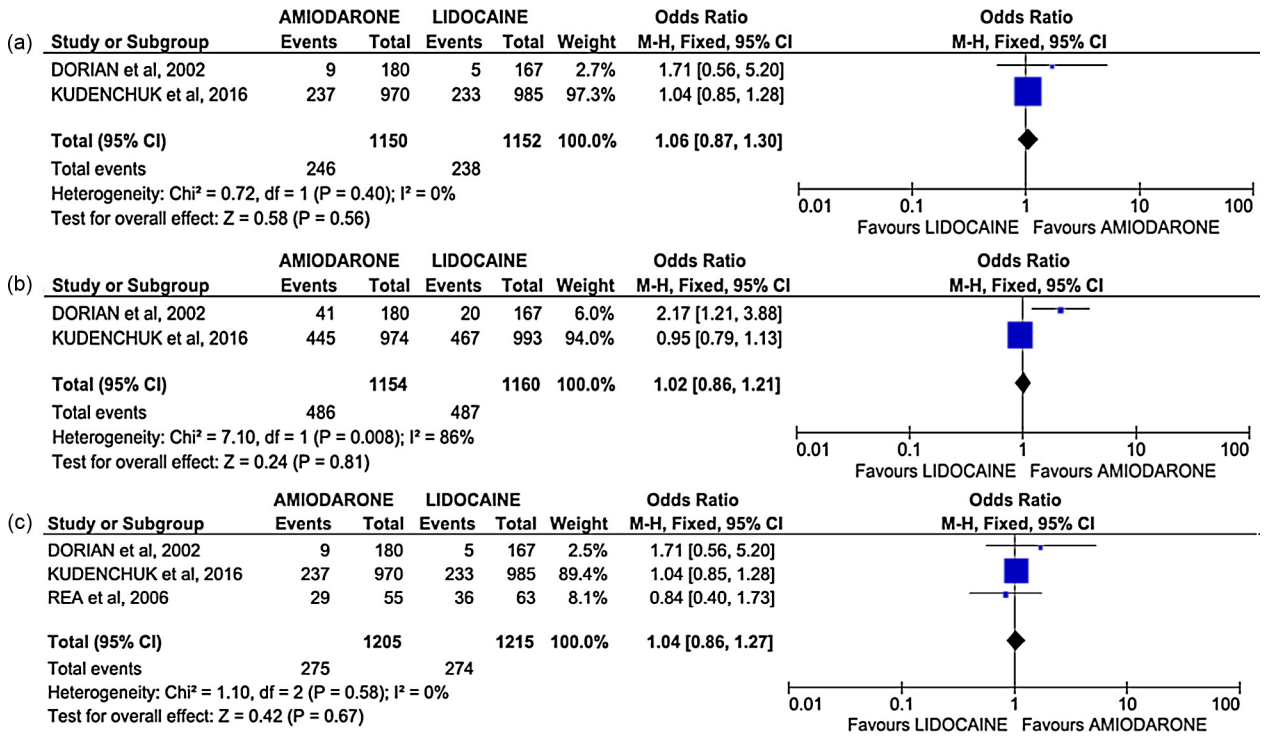

Fig. 4. Forest plots comparing amiodarone vs lidocaine. (4a) Survival at hospital discharge; (4b) survival at hospital admission; (4c) survival at hospital discharge including in the analysis also one non-randomized controlled study.

the lowest score was found for the prospective study (6/9).[24] All these studies had no independent blind assessment/record linkage (Supplemental digital content 4).

Discussion

The primary endpoint of our meta-analysis was to evaluate the effectiveness of antiarrhythmics when administered to adult non-traumatic CA patients with persistent or recurrent shockable rhythms. We found three RCTs comprising 3877 patients, almost 1400 patients receiving amiodarone, over 1150 in the lidocaine group and more than 1300 randomized to placebo.[6,22,23] One prospective observational study[24] and three retrospective studies[14,15,25] were included in the secondary analysis providing data on approximately 700 patients.

All but one study,[15] were conducted in the pre-hospital setting in the US and in Europe. The CPR treatments during ALS were according to current AHA or ERC guidelines at the time of the enrollment, ranging over a period greater than 20 years (1989–2016). The low number of published RCTs and the fact that all of them are underpowered for the critical outcome of survival to hospital discharge prompted this meta-analysis. Indeed, even the most recent RCT had a smaller-than-predicted treatment effect, since sample size was calculated on a predicted 6.3% absolute difference between amiodarone and placebo, which was almost twice than the observed one.[6]

One of the main finding of this meta-analysis is that administration of amiodarone during ALS as compared with placebo did not improve survival at discharge nor survival with favorable neurological outcome. However, administration of amiodarone compared to placebo showed significantly higher survival at hospital admission in both the RCTs. This finding stems from pooling data from one high-quality evidence recent RCT (over 2400 patients)[6] and a smaller low-quality evidence RCT (just over 500 patients) from the same research group conducted over 15 years before[23]; additional data (180 patients) for the secondary analysis were obtained from a retrospective study.[14]

With only one high-quality RCT comparing the effects of lidocaine vs placebo (2041 patients)[6] we could not undertake a metanalysis for the primary outcomes; however two further studies (one prospective[24] and one retrospective[25]) enrolling a total of 406 patients allowed a secondary analysis. Similarly to amiodarone, but with lower degree of evidence, administration of lidocaine compared to no administration significantly improved survival to hospital admission, but there were no differences at hospital discharge.

Finally, when amiodarone was compared to lidocaine, high-quality evidence from 1995 enrolled in a recent RCT[6] together with low-quality evidence from 347 patients included in an earlier RCT[22], showed no difference in survival to hospital admission and discharge between the two drugs. The addition of data retrospectively acquired from 118 patients who suffered an in-hospital CA[15] did not modify the results.

Although amiodarone and lidocaine are considered the standard of care and are included in current guidelines to promote successful defibrillation of shock-refractory VF or pulseless VT, and to prevent recurrences,[11,12] no anti-arrhythmic drug given during CA has been shown to increase survival to hospital discharge. Until the publication of the recent RCT[6] there was limited evidence in favor of the use anti-arrhythmic drugs for the management of arrhythmias in CA and, more specifically, it was limited to survival to hospital admission.[23–25] In response to such need for sufficiently powered RCTs, a large RCT, in which patients have been randomized to amiodarone, lidocaine or saline placebo, was conducted. This study confirmed in over 3000 patients significant benefits from the use of amiodarone or lidocaine with respect to short-term outcome but not on long-term survival or neurological recovery.[6]

According to current AHA end ERC guidelines amiodarone or lidocaine may be considered (class IIb recommendation): in particular, a bolus of 300 mg of amiodarone may be given after three defibrillation attempts, while a bolus of 1–1.5 mg/kg of lidocaine

may be used as alternative, if amiodarone is not available.[11,12] Amiodarone is a membrane-stabilizing anti-arrhythmic drug and improves the response to defibrillation in VF or hemodynamically unstable VT.[14,26–29] The onset of its antifibrillatory action is slower than lidocaine, but its effect is longer-lasting.[30] Events of bradycardia and hypotension post-ROSC have been reported in patients receiving amiodarone during resuscitation.[6,14,23] Lidocaine has been one of the antiarrhythmic drugs for shock-resistant or recurrent VF in the past.[31,32] Interestingly, lidocaine has detrimental effects on counter-shock efficacy due to an increase in lidocaine's affinity for sodium-channel receptors in acidotic environment[33] and has been associated with an increased rate of post-shock asystole.[34] Earlier evidence on the use of lidocaine vs amiodarone was uncertain; while some authors showed higher rates of survival to hospital admission in patients with shock-resistant VF when amiodarone was used as compared to lidocaine,[22] other reports were contradictory.[15] The recent RCT from Kudenchuck et al.[6] demonstrated substantial equivalence in short-term outcomes with either amiodarone or lidocaine, with a potential disadvantage of more numerous episodes of hypotension and bradycardia in the amiodarone group. These adverse events were observed despite the use of a new amiodarone aqueous formulation in which polysorbate 80 has been replaced by captisol and therefore supposedly devoid of hypotensive effects. Thus, although current guidelines advocate amiodarone as the first choice drug in refractory and recurrent VF/pulseless VT, recent evidence may lead to potential discussion and revision on the consensus on science.[35] Indeed, similarly to vasopressors during CPR, there is evidence of benefit only on short-term outcome but not in the long-term survival, meaning that a greater number of patients potentially resuscitated with aid of an anti-arrhythmic drug, subsequently die during hospital stay. Several reasons may provide potential explanation for this evidence.

Among these, the timing of administration of the drug may play a pivotal role. The optimal time at which these drugs should be given when using a single-shock strategy remains unknown but it is likely that their efficacy is gradually lost with delayed administration, in particular during the so-called "metabolic phase", when the ischemic injury results in release of metabolic factors causing additional injury.[36] The beneficial effects from an early intervention is well recognized in the instance of a defibrillation attempt, as well as vasopressors administration during cardiac arrest.[37–39] For instance, epinephrine has been shown effective in improving survival to hospital discharge and survival with good neurological outcome when given within 10 min from collapse, while evidence of possible harm has been reported when it was administered later.[38] In the clinical studies, amiodarone or lidocaine were usually given if VF/VT persisted after at least three shocks,[14,15,22–25] with the exception of the most recent RCT[6] in which at least one shock was delivered prior to drug injection. In the older studies, the time from collapse to drug administration ranged from 15 to 24 min. It is noteworthy that in the recent RCT the first administration of the study drug was performed after a median of three shocks, resulting in mean administration time of 19 min.[6]

Thus, the treatment was administered fairly late in all the studies, when significant end-organ damage had probably already resulted from prolonged hypoperfusion, especially in the central nervous system. For these reasons, the potential benefit of treatment could have been underestimated. This hypothesis is strengthened by the observation in the recent RCT[6] that patients with witnessed CA receiving earlier initiation of resuscitation and a shorter interval to antiarrhythmic drug administration (12 min) had significantly higher survival at hospital discharge (by about 5%). However, only this recent RCT provided data on witnessed CA and therefore we could not perform a sub-analysis of this patient's population. Importantly, post-ROSC treatment of patients was not standardized, nor the quality was evaluated by the studies included in this metanalysis, and this may have played a role on survival.[39] Although the results of our metanalysis are similar to those of the most recent RCT[6], our meta-analysis has some advantages. One is providing the reader with a systematic and up-to-date evidence on the effects of amiodarone and lidocaine on outcomes of CA patients. Another advantage is the reinforcement of Kudenchuck et al. findings[6] highlighted not only by the similar results but also by the absence of heterogeneity in the primary analyses ($I^2 = 0\%$). Moreover, our results suggests a reconsideration of the role of lidocaine that still appears only as a substitute of amiodarone in case of unavailability.[11,12]

We acknowledge several limitations in our meta-analysis. First of all, the studies included are largely different in several aspects. These studies, in fact, reported pooled data from patients who presented differences in the setting of collapse, rate of witnessed events and bystander-initiated CPR, resuscitative protocols employed, that varied based on concurrent guidelines, with different shock protocols and time to drug administration. In this regards, the time lag between the first and the last RCT is over 15 years, and between all the studies included is over 25 years. Finally, different amiodarone formulations (with polysorbate solvent – potentially accounting for hypotension[40] – or aqueous solution), and different dosages of amiodarone or lidocaine were employed.

In conclusion, the above limitation withstanding, both amiodarone and lidocaine seem equally beneficial as compared with placebo with respect to survival to hospital admission. However, neither amiodarone nor lidocaine improves long-term outcome, in term of survival to hospital discharge or neurological recovery.

Conflict of interest statement

None.

Funding

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2016.07.235.

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