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Amiodarone, lidocaine, magnesium or placebo in shock refractory ventricular arrhythmia: A Bayesian network meta-analysis

Safi U. Khan, MD [a,*], Lydia Winnicka, MD [a], Muhammad A. Saleem, MD [b], Hammad Rahman, MD [a], Najeeb Rehman, MD [a]

[a] Guthrie Clinic/Robert Packer Hospital, Sayre, PA, USA
[b] Mercy Health, Janesville, WI, USA

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ABSTRACT

Recent evidence challenges, the superiority of amiodarone, compared to other anti-arrhythmic medications, as the agent of choice in pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF). We conducted Bayesian network and traditional meta-analyses to investigate the relative efficacies of amiodarone, lidocaine, magnesium (MgSO4) and placebo as treatments for pulseless VT or VF. Eleven studies [5200 patients, 7 randomized trials (4, 611 patients) and 4 non-randomized studies (589 patients)], were included in this meta-analysis. The search was conducted, from 1981 to February 2017, using MEDLINE, EMBASE and The Cochrane Library. Estimates were reported as odds ratio (OR) with 95% Credible Interval (CrI). Markov chain Monte Carlo (MCMC) modeling was used to estimate the relative ranking probability of each treatment group based on surface under cumulative ranking curve (SUCRA). Bayesian analysis demonstrated that lidocaine had superior effects on survival to hospital discharge, compared to amiodarone (OR, 2.18, 95% Cr.I 1.26–3.13), MgSO4 (OR, 2.03, 95% Cr.I 0.74–4.82) and placebo (OR, 2.42, 95% Cr.I 1.39–3.54). There were no statistical differences among treatment groups regarding survival to hospital admission/24 h (hrs) and return of spontaneous circulation (ROSC). Probability analysis revealed that lidocaine was the most effective therapy for survival to hospital discharge (SUCRA, 97%). We conclude that lidocaine may be the most effective anti-arrhythmic agent for survival to hospital discharge in patients with pulseless VT or VF.

Introduction

Sudden cardiac arrest is one of the leading causes of death worldwide, with approximately 700,000 events per year in the U.S. and Europe combined.[1,2] For out-of-hospital cardiac arrest (OHCA), the estimated survival to hospital admissions approximately 40%, with survival to hospital discharge even lower, at around 24%.[3–7] Given these dismal rates of survival, which are largely unchanged over the last 5 years, frequent re-evaluation of evidence-based guidelines may be beneficial, and can potentially lead to increased survival. Both the 2015 American Heart Association (AHA) and the 2015 European Resuscitation Council (ERC) guidelines denote amiodarone as the drug of choice in shock-refractory, pulseless VT or VF, with lidocaine used only as an alternative if amiodarone is unavailable (class IIb recommendation)[8,9] Magnesium is not routinely recommended in adults unless polymorphic VT secondary to prolonged QTc is suspected (class III recommendation).[8]

These current recommendations largely stem from two landmark studies, the Amiodarone for Resuscitation After Out-Of-Hospital Cardiac Arrest Due to Ventricular Fibrillation (ARREST) and the Amiodarone versus Lidocaine in Prehospital Ventricular Fibrillation Evaluation (ALIVE) trials, which demonstrated amiodarone's superiority over placebo and lidocaine respectively, in survival to hospital admission in patients with OHCA due to ventricular arrhythmia.[10,11] However, more recent randomized studies have questioned amiodarone's superiority over lidocaine, suggesting a comparable efficacy between the two, in both survival to hospital admission and

Abbreviationslist: AHA, American Heart Association; CrI, Credible Interval; CI, Confidence Interval; CPR, Cardiopulmonary Resuscitation; ERC, European Resuscitation Council; hrs, hours; $MgSO_4$, Magnesium Sulphate; Minutes, mins; MCMC, Markov chain Monte Carlo; OR, odds ratio; OHCA, Out-of-Hospital Cardiac Arrest; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomized controlled trials; ROSC, Return of Spontaneous Circulation; SUCRA, Surface Under Cumulative Ranking Curve; VF, Ventricular Fibrillation; VT, Ventricular Tachycardia; Versus, vs.

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* Corresponding author. Department of Medicine, Robert Packer Hospital, Sayre, PA 18840.
E-mail address: safinmc@gmail.com (S.U. Khan).

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survival to hospital discharge.[6] These new observations mandate a re-evaluation of the body of evidence on effective anti-arrhythmic therapy in shock refractory ventricular arrhythmia.

In keeping with the previously stated guidelines, we hypothesized that amiodarone should be the most effective drug as compared to lidocaine, $MgSO_4$ and placebo. The prior meta-analyses, which called this into question, were hampered by certain limitations.[12,13] A meta-analysis by Huang et al compared anti-arrhythmics which are not currently recommended, included majority of the studies with non-randomized designs, and had significant heterogeneities with regards to baseline characteristics of the study population and timing and cumulative dosing of the drugs.[13] Similarly, Sanfilippo et al included seven studies only and compared amiodarone, lidocaine and placebo by the use of only traditional statistical methods.[12] To test our hypothesis, and to overcome previously stated limitations, we performed a Bayesian network meta-analysis. Bayesian approach is superior to traditional methodology due to its superior estimation of results and its ability to generate a ranking of treatment arms based on the efficacy. Furthermore, it also allows natural and principled way of pooling prior information and calculates the predictive probabilities of future outcomes.[14]

Methods

This meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for protocols (PRISMA) statement and the PRISMA extension statement for network meta-analyses.[15]

Inclusion criteria

Studies were included if they met the following inclusion criteria: i) studies which assessed the effects of amiodarone, lidocaine, $MgSO_4$ or placebo in patients with pulseless VT or VF, ii) studies with adult subjects ≥18 years, which reported outcomes of interest (see below), and iii) full-text articles only.

Data sources and searches

Authors M.A.S. and H.R. independently conducted data search using PubMed/MEDLINE, EMBASE and Cochrane Central Register of Controlled Clinical Trials from 1981 to February 2017 using the following key words: "anti-arrhythmic therapy," "amiodarone," "lidocaine," "magnesium," "cardiac arrest," "ventricular tachycardia," "ventricular fibrillation," and "shockable rhythm." The electronic search was supplemented by manual review of the bibliographies contained in the obtained articles. The whole process was supervised by third author (S.U.K) and any discrepancies were resolved after discussion and agreement. Fig. 1 illustrates the PRISMA-based selection process of the included studies.

Data extraction and quality assessment

Data collection was conducted using a standardized collection form that incorporated study design, sample size, and characteristics and outcomes of the study. Risk of bias assessment was done at the study level. Quality assessment of randomized

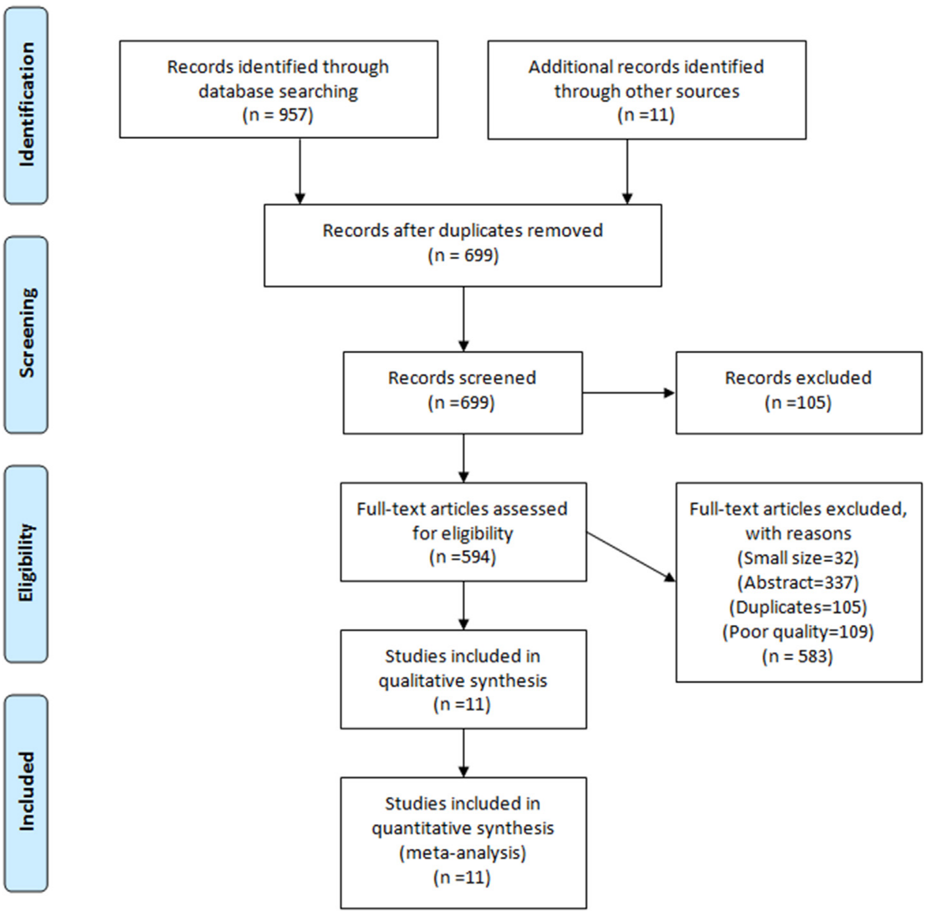

Fig. 1. Search strategy: Study selection process using preferred reporting items for systematic reviews and meta-analyses (PRISMA).

controlled trials (RCTs) and observational data was done using the Cochrane bias risk assessment tool and the Newcastle-Ottawa scale, respectively.[16,17] In case of Allegra et al, detailed information about the allocation concealment was missing, while random sequence generation was not entirely clear in Fatovich et al and Dorian et al.[11,18,19] However, as all of them had randomized prospective design, we considered unclear selection bias for these studies. Double blinding was adequate in all the trials and the risk of outcome assessment bias was extremely low. In general, all the RCTs merit good methodological quality on Cochrane quality assessment tool (Supplement Table 1). Conversely, the observational studies are affected by high risk of allocation and performing bias, therefore, the Newcastle-Ottawa scale was used for the assessment of observation studies (Supplement Table 2). Total of eight domains were checked and each domain carried one point. A total of ≥6 points were required to meet the criteria for good methodological quality. All of the included studies met the set criteria. Authors M.A.S. and H.R. independently performed data extraction and quality assessment of the included studies, with any discrepancies resolved by mutual agreement.

Outcome measures

The primary focus was the efficacy of amiodarone, lidocaine, $MgSO_4$, and placebo with regards to survival to hospital discharge. Secondary outcomes assessed were survival to hospital admission/24 h and return of spontaneous circulation (ROSC). Due to the lack of uniform calibration tools and insufficient data, neurological improvement could not be analyzed. Survival to hospital admission/24 h was defined as patients who arrived to the hospital alive, were formally assigned a hospital bed, and survived for at least a subsequent 24 h. The definitions of survival to hospital discharge and ROSC are self-explanatory.

Statistical analysis

The network meta-analysis, which is an extension of traditional pair-wise meta-analysis, was conducted by Bayesian statistical approach.[14] The Bayesian network meta-analysis allows for combining of data related to multiple treatment groups simultaneously, pooling of direct and indirect elements of the evidence in a single estimate with the benefit of greater power and precision for rare events, and comparison of the interventions without a direct connection on the basis of indirect information. The Bayesian approach allows greater flexibility to use complex models with a more natural interpretation and can also rank treatments according to their comparative effectiveness. Outcomes were pooled using the random effects model (informative priors), and for all estimates, convergence was achieved at 40,000 iterations.[20] An informative priors model is particularly useful when data is sparse, as it allows for the assessment of between-study heterogeneity variances, based on a report by Turner et al.[21]

Estimates were presented as an odds ratio (OR) with corresponding 95% credible interval (Cr.I) ranging from the 2.5th to the 97.5th centiles of posterior distribution. Markov chain Monte Carlo (MCMC) modeling was used to estimate the relative ranking probability of each treatment group.[22] "Rankograms" are provided, which represent a comparative hierarchy of treatment effects based on surface under cumulative ranking curve (SUCRA).[23] A SUCRA is taken as a numerical representation of the probability of effectiveness, i.e., a SUCRA of 90% correlates to a 90% effectiveness of that treatment, as compared to other interventions. Thus, the larger the SUCRA value, the better the treatment. The network analysis was carried out using NetMetaXL 1.6.1 (Canadian Agency for Drugs and Technologies in Health, Ottawa, Canada) and winBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

A sensitivity analysis restricted only to RCTs and patients with OHCA was conducted in addition to the primary analyses. A pair-

Table 1
Reports baseline characteristics of the studies along with outcome measures.

Study (design)	arms	n (Intervention/ Control)	Age (mean)	Male (%)	CAD (%)	Witnessed arrest (%)	Bystander initiated CPR (%)	Survival to discharge (%)	Survival to hospital admission/24 h. (%)	ROSC (%)
Allegra et al, 2001 (RCT)[18]	IV 2 g $MgSO_4$/Placebo (NS)	58/58	65/65	57/47	NR	39/40	NR	4/4	16/17	22/18
Dorian et al, 2002 (RCT)[11]	IV Amiodarone (5 mg/kg of estimated body weight)/ Lidocaine (1.5 mg/kg)	180/167	68/66	76/81	61/59	76/78	26/28	5/3	23/12	NR
Harrison et al, 1981 (PS)[25]	IV 100 mg Lidocaine bolus/No Lidocaine	62/54	62/64	50/42	NR	NR	NR	11/2	21/17	NR
Hassan et al, 2001 (RCT)[28]	IV (2 g or 8 mM) $MgSO_4$ repeated with further 2 g if persistent VF after 6 shocks/Placebo (NS)	52/53	65/66	71/70	NR	93/88	47/59	4/2	17/13	17/13
Herlitz et al, 1997 (RS)[24]	IV 50 mg Lidocaine could be repeated up-to 200 mg/No Lidocaine	185/105	69/65	81/86	NR	90/85	24/13	14/8	38/18	44/24
Kudenchek et al, 1999 (RCT)[10]	IV Amiodarone 300 mg/Placebo (Polysorbate 80)	246/258	66/65	76/79	64/59	70/77	66/59	13/13	44/34	NR
Kudenchek et al, 2016 (RCT)[6]	IV Amiodarone 150 mg/IV 60 mg Lidocaine/Placebo (NS)	974/993/1059	63/63/62	78/82/80	NR	61/70/7	61/59/60	24/47/21	46/47/40	36/40/34
Skrifvars et al, 2004 (PS)[29]	IV Amiodarone 300 mg ± 150 mg after 3 shocks/No Amiodarone	75/105	61/66	72/79	NR	91/76	56/44	28/42	51/64	61/69
Thel et al., 1997 (RCT)[30]	2 g $MgSO_4$ bolus followed by 8 g infusions over 24 h/Placebo	76/80	63/68	61/54	37/44	74/76	NR	21/21	13/11	54/60
Fatovich et al, 1997 (RCT)[19]	IV 5 g $MgSO_4$/Placebo (NS bolus)	31/36	64/65	81/86	NR	NR	65/50	3/0	43/50	22/22
Rea et al, 2006 (RS)[31]	As per 2000 AHA guidelines: Amiodarone/Lidocaine	74/79	62/64	49/61	21/18	66/74	42/36	62/68	53/57	NR

AHA = American heart association, CAD = coronary artery disease, CPR = cardiopulmonary resuscitation, hr. = hours, NS = normal saline; PS = prospective study, RCT = randomized controlled trial; RS = retrospective study; IV = intravenous; ROSC = return of spontaneous circulation.

wise analysis was conducted using Comprehensive Meta-Analysis software, version 3.0 (Biostat, Englewood, NJ). All tests were performed at a 5% significance level. Heterogeneity was assessed using Q statistics and I^2. I^2 >50% was considered a high degree of heterogeneity.

Results

The initial search of electronic data base yielded a total of 957 articles. The manual review of the bibliographies identified additional 11 studies. After removal of the duplicates, 699 articles were screened. Additional 105 studies were excluded because of incorrect patient population (not trials of ventricular arrhythmia) and unclear outcomes of interests. Finally, 594 articles were assessed for eligibility and an extensive and diligent review process involving exclusion of abstracts, poor quality studies and studies comparing different anti-arrhythmic agents ultimately led to the selection of 11 studies. Of the 11 included studies (n = 5200), 7 were RCTs (n = 4, 611), 2 were prospective observational studies (PS) studies (n = 296), and 2 had retrospective observational designs (RS) (n = 293). Ten of the 11 trials studied OHCA, with only 1 trial focused on in-hospital cardiac arrest.[22] Except for ROSC, where data was compiled using only seven studies (5 RCTs, 1 PS, and 1 RS), all other outcomes were compiled using all 11 studies. Across included studies, the mean age of subjects ranged from 61 to 68 years, with male gender predominating over the female. Notably, there was significant variation in cumulative dosages of anti-arrhythmics given across the studies. Table 1 presents a brief account of characteristics, baseline information, and outcomes reported for the included studies. Figs. 2 and 3 present forest plots and rankograms respectively, for all outcomes studied. Traditional meta-analysis results are included in the Supplementary material.

For survival to hospital discharge, the amiodarone versus (vs) placebo, lidocaine vs placebo, and amiodarone vs lidocaine comparisons were compiled using three studies, whereas the $MgSO_4$ vs placebo comparison was compiled using 4 studies. The event rate for survival was 21% (329/1526) in the amiodarone arm, 36% (541/1470) in the lidocaine arm, 9% (21/214) in the $MgSO_4$ arm, and 18% (329/1801) in the placebo arm. Bayesian analysis revealed that lidocaine was significantly better than amiodarone in improving survival to hospital discharge (OR, 2.18; 95% Cr.I. 1.26–3.13), $MgSO_4$ (OR, 2.03; 95% Cr.I. 0.74–4.82) and placebo (OR, 2.42; 95% Cr.I. 1.39–3.54). Probability analysis favored lidocaine as the best treatment (SUCRA, 97%) for survival to hospital discharge followed by $MgSO_4$ (SUCRA, 42%) and amiodarone (SUCRA, 40%). Traditional analysis revealed comparable results for amiodarone vs lidocaine (OR, 1.04; 95% CI, 0.85–1.26; P-value = 0.67; I^2 = 0), as well as all other treatment arms (Supplement Fig. 1).

For survival to hospital admission/24 h, the amiodarone vs placebo, lidocaine vs placebo, and amiodarone vs lidocaine comparisons were compiled using 3 studies, whereas the $MgSO_4$ vs placebo comparison was compiled using 4 studies. The event rate for survival was 43% (666/1530) in the amiodarone arm, 41% (613/1470) in the lidocaine arm, 25% (55/214) in the $MgSO_4$ arm, and 36% (664/1804) in the placebo arm. There were no statistical differences between amiodarone and lidocaine (OR, 1.05; 95% Cr.I. 0.75–1.46) and between $MgSO_4$ and placebo (OR, 0.98; 95% Cr.I. 0.58–1.64). Both amiodarone (35%) and lidocaine (42%) showed non-significant improvement as compared to $MgSO_4$. Traditional analysis demonstrated that lidocaine was significantly superior to placebo (OR, 1.68; 95% CI, 1.03–2.75; P-value = 0.04; I^2 = 0)

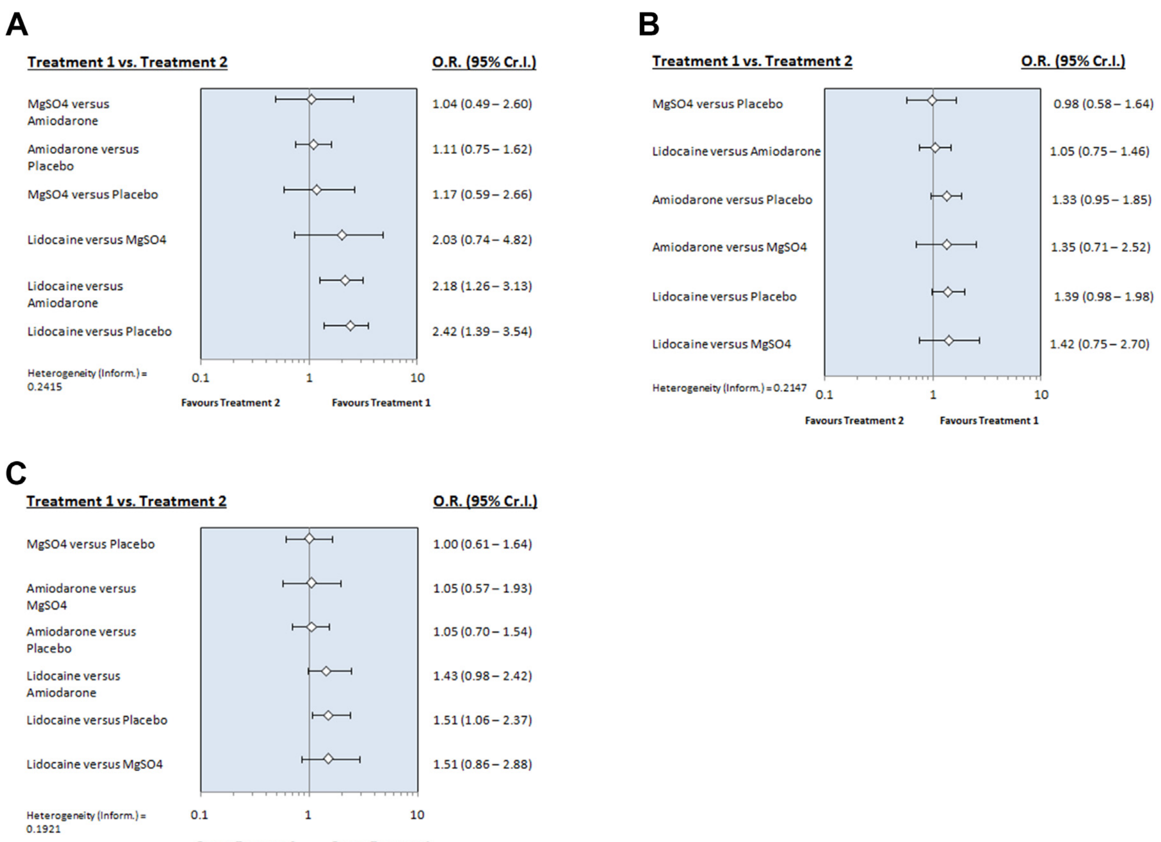

Fig. 2. Forest plot display of odds ratio (OR) with 95% credible intervals (Cr.I.) for target interventions. Endpoints are A) survival to hospital discharge; B) survival to hospital admission/24 h; and C) return of spontaneous circulation.

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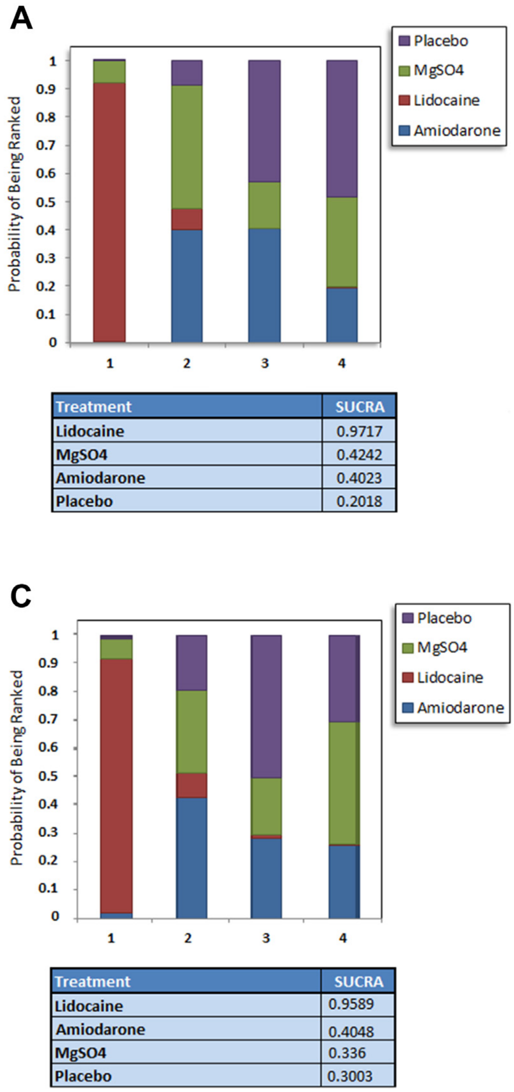

Treatment	SUCRA
Lidocaine	0.9717
MgSO4	0.4242
Amiodarone	0.4023
Placebo	0.2018

Treatment	SUCRA
Lidocaine	0.8209
Amiodarone	0.7264
MgSO4	0.253
Placebo	0.1997

Treatment	SUCRA
Lidocaine	0.9589
Amiodarone	0.4048
MgSO4	0.336
Placebo	0.3003

Fig. 3. Rankogram with corresponding surface under the cumulative ranking curve (SUCRA). The larger is the SUCRA, the better is the treatment. Endpoints are A) survival to hospital discharge; B) survival to hospital admission/24 h; and C) return of spontaneous circulation.

(Supplement Fig. 2). MCMC modeling ranked lidocaine as the best treatment modality (SUCRA, 82%), followed by amiodarone (SUCRA, 72%), $MgSO_4$ (SUCRA, 25%), and placebo (SUCRA, 20%) for survival to hospital admission/24 h.

For achievement of ROSC, two studies compared amiodarone and placebo, 2 studies compared lidocaine and placebo, 1 study compared amiodarone and lidocaine, and 4 studies compared $MgSO_4$ and placebo. Thirty-seven percent of patients (396/1049) attained ROSC with amiodarone, 41% (479/1167) with lidocaine, 32% (69/214) with $MgSO_4$, and 35% (537/1492) with placebo. Bayesian analysis revealed comparable outcomes among amiodarone, $MgSO_4$, and placebo. However, patients treated with lidocaine had a higher rate of achieving ROSC as compared to placebo (OR, 1.51; 95% Cr.I. 1.06–2.37), with a trend favoring lidocaine over both amiodarone (OR, 1.43; 95% Cr.I. 0.98–2.42) and $MgSO_4$ (OR, 1.51; 95% Cr.I. 0.86–2.88). This trend was consistent with traditional analysis; however, statistical significance was not achieved (Supplement Fig. 3). MCMC modeling ranked, lidocaine as the best treatment (SUCRA, 95%), with amiodarone (SUCRA, 40%) and $MgSO_4$ (SUCRA, 33%) as the second and third best treatments respectively, for achieving ROSC.

A sensitivity analysis was conducted on the included RCTs for OHCA due to ventricular arrhythmia. Bayesian estimates are reported in Table 2. Table 3 reports the probability analysis ranking for each drug for the desired outcome. Six trials [total (n = 4151); amiodarone (n = 1396); lidocaine (n = 1160); $MgSO_4$ (n = 138); placebo (n = 1457)] were included in the sensitivity analysis.[6,10,11,23–25] Lidocaine was superior to both amiodarone (OR, 2.42; 95% Cr.I. 1.25–3.39) and placebo (OR, 3.01; 95% Cr.I. 1.60–4.30) in survival to hospital discharge. For survival to hospital admission/24 h, lidocaine improved the outcome significantly compared to $MgSO_4$ (OR, 1.43; 95% Cr.I.1.06–2.00). There were no significant differences among treatment arms with regards to ROSC. MCMC modeling ranked lidocaine as the best treatment for both survival to hospital discharge and ROSC.

Discussion

There is a considerable controversy in the published literature with regards to first line anti-arrhythmic agent for ventricular arrhythmia. This mandates the re-assessment of comparative efficacies of anti-arrhythmic regimens. To facilitate this process, we

Table 2
Sensitivity analysis is based on the randomized trials, evaluating the anti-arrhythmic drugs in out of hospital cardiac arrest due to ventricular arrhythmia. Estimates are reported as odds ratio (OR) with 95% credible interval (Cr.I).

Comparisons	Survival to hospital discharge	Survival to hospital admission/24 h	Return of spontaneous circulation
	OR (95% Cr.I.)	OR (95% Cr.I.)	OR (95% Cr.I.)
Amiodarone vs. Placebo	1.24 (0.85–1.93)	1.33 (0.69–2.48)	1.07 (0.49–2.12)
MgSO4 vs. Amiodarone	1.43 (0.30–6.24)	1.55 (0.86–2.96)	1.10 (0.57–2.43)
Lidocaine vs. MgSO4	1.68 (0.38–7.24)	**1.43** (1.06–2.00)	1.07 (0.71–1.58)
MgSO4 vs. Placebo	2.12 (0.49–8.90)	1.15 (0.85–1.72)	1.19 (0.81–1.80)
Lidocaine vs. Amiodarone	**2.42** (1.25–3.39)	1.07 (0.65–1.88)	1.17 (0.69–2.28)
Lidocaine vs. Placebo	**3.01** (1.60–4.30)	1.24 (0.83–1.75)	1.26 (0.83–1.88)

Bold values indicate statistically significant outcomes.

reviewed the published literature to date to compare the efficacy of amiodarone, lidocaine, $MgSO_4$, and placebo, with a primary end-point of survival to hospital discharge and secondary end-points of survival to hospital admission/24 h and ROSC.

In this Bayesian network meta-analysis, we report that lidocaine is significantly superior to amiodarone, as well as all other treatment modalities, in regards to survival to hospital discharge. MCMC modeling ranked lidocaine as the most effective drug for survival to hospital discharge. The superiority of lidocaine was consistent even in the sensitivity analysis based on RCTs assessing OHCA due to ventricular arrhythmias. These findings are novel and contradict the outcomes of prior land mark trials and meta-analyses.[10–13]

The ARREST and ALIVE trials were the pioneer randomized studies, which provided the strongest evidence in favor of amiodarone in OHCA due to shockable ventricular arrhythmias.[10,11] The ARREST trial (n = 504) reported that after a mean 5 ± 2 electrical shocks, patients who received amiodarone had a higher rate of survival to hospital admission compared to placebo (adjusted OR, 1.6; 95% confidence interval (CI), 1.1–2.4; p = 0.02).[10] Subsequently, the ALIVE trial (n = 347) reported that at a mean 7 ± 3 min (mins) time to arrival of first responders and a mean 25 ± 8 min time of drug dispatch to administration, patients who received amiodarone had a higher rate of survival to hospital admission compared to lidocaine (OR, 2.17; 95% CI, 1.21–3.81; p = 0.009).[11] Largely based on these two studies, the AHA currently recommends amiodarone as the first-line anti-arrhythmic drug to be given in shock-refractory ventricular arrhythmias.[8] One of the major limitations of both of these trials was the insufficient statistical power to detect differences in survival to hospital discharge. A recent large study by Kudenchuk et al, with over 3000 subjects, attempted to counter this limitation and demonstrated comparable outcomes between amiodarone and lidocaine (percent point difference 0.7; 95% CI, −3.2–4.7; p = 0.70) and between amiodarone and placebo (percent point difference 3.2; 95% CI, −0.4–7.0; p = 0.08) in survival to hospital discharge.[6] Interestingly, amiodarone failed to show statistical superiority over lidocaine with regards to survival to hospital admission (percent point difference 1.3; 95% CI, −2.1–4.8; p = 0.44). When compared to placebo, both amiodarone and lidocaine had higher rates of survival to hospital admission.

On the same note, the impact of anti-arrhythmic therapy in survival to hospital discharge was assessed in the meta-analysis by Huang et al, which comprised of ten RCTs and 7 observational studies.[13] This meta-analysis reported that neither amiodarone (risk ratio (RR), 0.82; 95% CI, 0.54–1.24; p = 0.35) nor $MgSO_4$ (RR, 1.07; 95% CI, 0.62–1.86; p = 0.85) were able to improve survival to hospital discharge over placebo. In this study, lidocaine was found to have significant improvement over placebo in survival to hospital discharge (RR, 2.26; 95% CI, 0.93to 5.52; p = 0.07), although no difference was found between amiodarone and lidocaine (RR, 1.01; 95% CI, 0.65–1.55; p = 0.97). Similarly, a recent pair-wise meta-analysis by Sanfilippo et al, which compared amiodarone, lidocaine and placebo, demonstrated identical outcomes between amiodarone and lidocaine in survival to hospital discharge (OR, 1.06; 95% CI, 0.87–1.30; p = 0.56).[12]

Neither of these studies was able to demonstrate statistically significant differences between amiodarone and lidocaine for survival to hospital discharge. Although this focused review builds on the information provided by good quality RCTs and observational studies of the relevant treatment arms, we have tried to minimize the major biases (selection, attrition and allocation) generated by non-randomized studies by performing a sensitivity analyses restricted to RCTs only, a common limitation cited in previous meta-analyses. And since Bayesian approach is superior to traditional approach, our results depict the superiority for lidocaine with greater power and precision and carry more authenticity than the prior reviews. Therefore, we consider that our findings are of clinical importance, and hint toward equivalent or perhaps even improved efficacy of lidocaine over amiodarone in survival to hospital discharge.

Our Bayesian approach, supplemented by traditional analysis, showed similar outcomes between lidocaine and amiodarone and between $MgSO_4$ and placebo for survival to hospital admission/24 h. These findings are in-line with the previous reports: Sanfilippo et al (amiodarone vs lidocaine: OR, 1.02; 95%CI, 0.86–1.21, p = 0.81) and Huang et al [(amiodarone vs lidocaine: OR, 1.28; 95%CI, 0.57–2.86, p = 0.55), ($MgSO_4$ vs placebo: OR, 1.07; 95%CI, 0.62–1.86, p = 0.81)](12,13).The role of amiodarone in improving survival to hospital admission was only first established by the ARREST trial (10). Prior to this landmark trial, lidocaine had historically been the preferred anti-arrhythmic, in conjunction with defibrillation, for shock-refractory ventricular arrhythmia. This was in spite of the often conflicting evidence for the effects of lidocaine; some studies showed benefit over no anti-arrhythmic, while other studies showed no difference.[24,25] This common use of lidocaine was likely due to its predictable pharmacokinetics, as well as ease of administration.[26,27] Furthermore, bradycardia and hypotension are classically associated with amiodarone and not with lidocaine, a fact which probably also contributed to lidocaine's historic preferential

Table 3
Probability analysis is based on the randomized trials, ranking the anti-arrhythmic drugs in out of hospital cardiac arrest due to ventricular arrhythmia. Treatments are ranked based on surface under cumulative ranking curve (SUCRA). The greater the value of SUCRA, the better is the treatment.

Drugs	Survival to hospital discharge	Survival to hospital admission/24 h.	Return of spontaneous circulation
	SUCRA (%)	SUCRA (%)	SUCRA (%)
Lidocaine	87	62	77
$MgSO_4$	61	20	57
Amiodarone	39	91	40
Placebo	10	25	25

use. These side effects have persistently been an observed issue across various published trials.[6,10,11] Even in the latest trial by Kudenchuk et al, there was a higher incidence of bradycardia, need for cardiac pacing, and hypotension with amiodarone as compared to lidocaine.[6] These side effects occur even with the use of new aqueous formulations of amiodarone with capitol, which previously were thought to have less potential for causing hypotension. Since, in spite of these drawbacks, amiodarone remains the current anti-arrhythmic of choice; our review of evidence, supported by our Bayesian and rank probability analyses, suggests a revision of amiodarone's accepted superior efficacy.

For ROSC, both our Bayesian and traditional analyses favor lidocaine over amiodarone. These findings are in line with Kudenchuk et al, where a greater number of lidocaine recipients achieved ROSC as compared to amiodarone (39.9% vs 35.9%; $p = 0.07$) and placebo.[6] Our comparisons of amiodarone, lidocaine and $MgSO_4$ are also consistent with previously published report.[13]

Our study is limited by several factors. Our meta-analysis includes both RCTs and non-randomized cohort studies, causing methodological heterogeneity. This is a common limitation cited in previous meta-analyses on this topic primarily because there are so few high-quality RCTs comparing anti-arrhythmic agents. We attempted to compensate for this limitation by performing a sensitivity analysis only on RCTs. There was also noticeable heterogeneity in regards to baseline characteristics of study subjects, associated co-morbidities, underlying cardiac diagnoses, and prognosis. Furthermore, although the algorithms used in each study for the treatment of ventricular arrhythmias were in line with current guidelines for that time (1989–2016), there was still substantial procedural variability among included studies, namely bystander cardiopulmonary resuscitation (CPR) initiation, time to arrival of first responders, quality and duration of CPR, response time to the first defibrillatory shock, dose of anti-arrhythmic given and protocol violations. The continued evolution of post-ROSC in-hospital care can very likely impact survival to hospital discharge as well. Such factors can have a significant influence on the results of even a well-designed trial, particularly if the sample size is small. Part of this heterogeneity is expected and can be explained by the time period of each included study. Although the standard current practices of the time were used in all studies, this undoubtedly changes through the years. Finally, publication bias was not assessed due to the small number of included studies, which is another potential limitation.

In summary, in the context of an overall absence of sufficient RCTs with head-to-to head comparisons of various anti-arrhythmic drugs, we attempted to overcome this limitation by utilizing a Bayesian analysis to generate indirect evidence on the efficacy of these drugs. Our analyses demonstrate that lidocaine is either superior or at least equal in efficacy to amiodarone, $MgSO_4$ and placebo. Probability analysis ranked $MgSO_4$ inferior to both lidocaine and amiodarone. Current review provides some future implications. So far the published literature failed to demonstrate the long term survival benefit of any anti-arrhythmic agent. This is because there is an overall low number of available, high-quality studies; those that are available have limited sample sizes and therefore low event rates. Our meta-analysis is the first comprehensive report, supported by the largest sample size of the comparison groups and superior statistical methodology to endorse lidocaine for survival to hospital discharge. These observations certainly call for further randomized trials to be undertaken, especially ones that are adequately powered to delineate desired outcomes. Although previous studies have failed to demonstrate clinical benefit of other drugs, such as the potassium channel blockers sotalol or ibutilide, it is important to note that those studies were limited by non-randomized comparisons, major biases, non-uniform drug administrations, and insufficient treatment dosages. It would therefore not be unreasonable to further study these alternate drugs and their role in shock-refractory ventricular arrhythmias, albeit in properly designed trials. Lastly, since 2000, the AHA guidelines have not changed, and were reiterated in the most recent update in 2015, despite the fact that the strength of exiting evidence in support of amiodarone is not robust. Based on our review, revision of the guidelines regarding amiodarone is warranted, while lidocaine can be considered as the first line agent.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hrtlng.2017.09.001.

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