Antiarrhythmics in Cardiac Arrest: A Systematic Review and Meta-Analysis

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Introduction

It is widely accepted that antiarrhythmics play a role in cardiopulmonary resuscitation (CPR) universally, but the absolute benefit of antiarrhythmic use and the drug of choice in advanced life support remains controversial.

Aim

To perform a thorough, in-depth review and analysis of current literature to assess the efficacy of antiarrhythmics in advanced life support.

Material and Methods

Two authors systematically searched through multiple bibliographic databases including CINAHL, SCOPUS, PubMed, Web of Science, Medline(Ovid) and the Cochrane Clinical Trials Registry. To be included studies had to compare an antiarrhythmic to either a control group, placebo or another antiarrhythmic in adult cardiac arrests. These studies were independently screened for outcomes in cardiac arrest assessing the effect of antiarrhythmics on return of spontaneous circulation (ROSC), survival and neurological outcomes. Data was extracted independently, compared for homogeneity and level of evidence was evaluated using the Cochrane Collaboration’s tool for assessing the risk of bias. The Mantel-Haenszel (M-H) random effects model was used and heterogeneity was assessed using the I 2 statistic.

Results and Discussion

The search of the literature yielded 30 studies, including 39,914 patients. Eight antiarrhythmic agents were identified. Amiodarone and lidocaine, the two most commonly used agents, showed no significant effect on any outcome either against placebo or each other. Small low quality studies showed benefits in isolated outcomes with esmolol and bretylium against placebo. The only significant benefit of one antiarrhythmic over another was demonstrated with nifekalant over lidocaine for survival to admission (p = 0.003). On sensitivity analysis of a small number of high quality level one RCTs, both amiodarone and lidocaine had a significant increase in survival to admission, with no effect on survival to discharge.

Conclusions

This systematic review and meta-analysis suggests that, based on current literature and data, there has been no conclusive evidence that any antiarrhythmic agents improve rates of ROSC, survival to admission, survival to discharge or neurological outcomes. Given the side effects of some of these agents, we recommend further research into their utility in current cardiopulmonary resuscitation guidelines.

Keywords

Cardiac arrest • Antiarrhythmics • Cardiopulmonary resuscitation • Ventricular fibrillation

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Introduction

Out-of-hospital cardiac arrests (OHCA)s have a reported incidence of 395,000 events in the US with only 5.5% of patients surviving to hospital discharge, whilst in-hospital cardiac arrests (IHCA)s have an estimated incidence of 200,000 in the US with 24.4% surviving to discharge [1,2]. High mortality rates and associated complications such as irreversible neurological disability explain the significant public health burden of cardiac arrest [2,3]. Thus, the need for a standardised approach to resuscitation to improve cardiac and cerebral perfusion during cardiopulmonary resuscitation (CPR) has been recognised for many years, with the aim of improving cardiac arrest outcomes [3].

Pharmacological therapy is universally employed as a resuscitative measure to enhance myocardial perfusion pressure and peripheral blood flow and additionally improve defibrillation success. Antiarrhythmics (AAs) play a role in shock-refractory ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) in the restoration and maintenance of a spontaneous perfusing rhythm during shock termination [4,5]. The American Heart Association (AHA) guidelines recommend the use of AA agents, however there is limited evidence on the associated short-term and long-term outcomes [4–8].

In light of this, we conducted a systematic review and meta-analysis to appraise randomised controlled trials and cohort studies around the efficacy of AAs in adult cardiac arrest, and their effects on short- and long-term patient outcomes.

Methods

Search Strategy

A systematic search was conducted on multiple bibliographic databases including CINAHL, SCOPUS, PubMed, Web of Science, The Cochrane Trials Registry and Medline (Ovid) from the inception of the databases until December 2016. Two independent reviewers used the following combinations of search terms (I) (“Cardiac Arrest”) OR (“Cardiac Arrhythmias”) OR (“Cardiopulmonary Resuscitation”) OR (“Ventricular Tachycardia”) OR (“Ventricular Fibrillation”) OR (“Advanced Life Support”) AND (“Antiarrhythmics”) OR (“Antiarrhythmia agents”) OR (“Amiodarone”) OR (“Lignocaine”) OR (“Lidocaine”) OR (“Magnesium”) OR (“Potassium-channel blockers”). For completeness, a manual reference check of systematic reviews and recent articles was performed to identify any additional studies.

Inclusion Criteria

For a study to be included, the patient population was any adult (over 18 years of age) with a cardiac arrest, either an OHCA or IHCA. All AA agents were considered as an intervention including amiodarone, lidocaine, magnesium, in addition to potassium-channel blockers such as nifekalant and bretylium in comparison to a placebo. Outcomes that were measured included ROSC; short-term survival: survival to hospital admission for OHCA patients, survival to hospital discharge; and neurologic outcomes at discharge. Study designs were limited to randomised controlled trials (RCTs) or prospective/retrospective cohort designs. Two reviewers (AC and BF) assessed and agreed upon each study for inclusion in this systematic review and any discrepancies were discussed with LW and TM.

Data Extraction

Two reviewers (AC and BF) independently extracted data from each article that met the inclusion criteria. The data extracted from each study included the first author’s last name and publication year, the study design, number of participants, patient population, intervention and clinical outcome results. The data collected by each reviewer was then compared for homogeneity and any discrepancies were addressed by discussion with LW and TM.

Level of Evidence and Risk of Bias

Each article was evaluated using the Centre for Evidence Based Medicine (CEBM): Levels of Evidence Introduction Document [9]. These studies were then assessed for risk of bias and methodological quality using the Cochrane Collaboration’s tool for assessing the risk of bias [10]. The results from each study were then grouped into individual AAs.

Statistical Analyses

The combined data was analysed using RevMan5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark). The odds ratio (OR) with 95% confidence interval (CI) was used for dichotomous outcomes, and the weighted mean difference (WMD) with 95% CI for continuous outcomes. The Mantel-Haenszel (M-H) random effects model was used. Heterogeneity was assessed using the I² statistic, with an I² >50% indicating significant heterogeneity. P value of <0.05 provided evidence of significant OR and WMD. We then conducted sensitivity analyses to assess how variance in rhythms and location of cardiac arrest may affect our results. As part of the sensitivity analysis, each outcome was also analysed using only level one RCTs.

Results

Literature Search Results

The initial systematic literature search yielded 1110 citations, of which 340 abstracts were reviewed. Based on a review of their abstract, 54 articles appeared to meet the search criteria. Of these 54 articles, 31 met the inclusion criteria (Figure 1). These 31 articles included eight intervention medications and 42,808 patients (Appendix 1). Each study was then screened for risk of bias and methodological quality (Figure 2). Of these, 11 were high quality level one RCTs, two were low

quality level one RCTs, seven were low quality level two prospective cohort studies and 11 were low quality level three retrospective cohort studies.

**Amiodarone**

Four studies reported on the use of amiodarone versus placebo (n = 27,616) [11–14]. Of these four studies, two reported on return of spontaneous circulation (ROSC) [12,13]. Administration of amiodarone was not associated with an improved ROSC (OR = 1.04; 95% CI 0.87–1.24; I² = 0%; p = 0.68). All four studies reported on survival to admission and survival to discharge. Amiodarone had no significant effect on survival to admission (OR = 1.33; 95% CI 0.91–1.97; I² = 92%; p = 0.14; Figure 3) or survival to discharge (OR = 1.25; 95% CI 0.60–2.58; I² = 97%; p = 0.55; Figure 4). Two studies reported on neurological outcomes in the surviving patients, showing no significant difference with the use of amiodarone (OR = 0.94; 95% CI 0.63–1.40; I² = 0%; p = 0.75) [11,12].

**Lidocaine**

Five studies reported on lidocaine versus placebo (n = 22,285) [12,14–17]. Two reported on ROSC, showing no significant difference with the use of lidocaine (OR = 1.73; 95% CI 0.85–3.51; I² = 84%; p = 0.13) [12,15]. All five studies showed that lidocaine had no impact

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**Figure 1** Study identification algorithm. This diagram outlines the filtering process from the literature search through to study inclusion.

**Figure 2** Screening of bias and methodological quality based on the Cochrane Collaboration’s tool for assessing the risk of bias.
Figure 3 Survival to admission with A) Amiodarone; B) Lidocaine; C) Magnesium; D) Esmolol; E) Bretylium F) Vasopressin.
Figure 4 Survival to discharge with A) Amiodarone; B) Lidocaine; C) Magnesium; D) Esmolol; E) Bretylium F) Vasopressin.
on survival to admission (OR = 1.32; 95% CI = 0.86–2.03; I² = 90%; p = 0.21; Figure 3) and survival to discharge (OR = 1.54; 95% CI = 0.83–2.86; I² = 90%; p = 0.17; Figure 4). Of the 455 patients who survived to discharge in the study by Kudenchuck et al., lidocaine had no impact on neurological outcomes (OR = 0.76; 95% CI = 0.49–1.17; p = 0.21).

Magnesium

Five studies investigated the use of magnesium (n = 485 [18–22]. All five studies reported on ROSC, showing no advantage with the use of magnesium (OR = 1.04; 95% CI = 0.68–1.59; I² = 0%; p = 0.79). Magnesium showed no effect on survival to admission (OR = 1.16; 95% CI = 0.60–2.23; I² = 0%; p = 0.67; Figure 3), survival to discharge (OR = 1.10; 95% CI = 0.57–2.10; I² = 0%; p = 0.78; Figure 4) or survival to one year (OR = 3.59; 95% CI = 0.14–91.35; p = 0.44). The use of magnesium had no beneficial effect on neurological outcomes (OR = 1.52; 95% CI = 0.37–6.33; I² = 0%; p = 0.56).

Esmolol

One study by Driver et al. reported on the use of esmolol against placebo (n = 25) [23]. This study showed a near significant increase in ROSC (OR = 17.59; 95% CI = 0.87–356.81; I² = 0%; p = 0.10; Figure 4). Of the six patients who survived to discharge, esmolol had no effect on neurological outcomes (OR = 1.04; 95% CI = 0.12–151.97; p = 0.43).

Bretylium

Two studies investigated the effect of bretylium compared to placebo (n = 108) [24,25]. Bretylium significantly improved survival to discharge (OR = 4.44; 95% CI = 0.51–39.03; I² = 0%; p = 0.18; Figure 4).

Vasopressin

One study by Gueugniaud et al. assessed the effect of vasopressin versus placebo (n = 2894) [26]. This study showed no effect on ROSC (OR = 0.96; 95% CI = 0.82–1.13; I² = 0.62), survival to admission (OR = 0.96; 95% CI = 0.81–1.15; p = 0.68; Figure 3), survival to discharge (OR = 0.73; 95% CI = 0.43–1.23; p = 0.24; Figure 4), survival to one year (OR = 0.60; 95% CI = 0.33–1.08; p = 0.09) or neurological outcomes in survivors (n = 55; OR = 0.56; 95% CI = 0.19–1.65; p = 0.30).

Amiodarone versus Lidocaine

Seven studies looked at amiodarone versus lidocaine (n = 11,616) [12,14,29,31–34]. There was no difference in ROSC (OR = 0.95; 95% CI = 0.61–1.88; I² = 68%; p = 0.81), survival to admission (OR = 1.18; 95% CI = 0.93–1.50; I² = 66%; p = 0.18), survival to discharge (OR = 0.99; 95% CI = 0.83–1.18; I² = 31%, p = 0.90) or neurological outcome in surviving patients (OR = 1.17; 95% CI = 0.77–1.79; p = 0.45).

Lidocaine versus Bretylium

Three studies investigated lidocaine versus bretylium (n = 486) [35–37]. There was no difference in ROSC (OR = 1.78; 95% CI = 0.95–3.34; I² = 43%; p = 0.07), survival to admission (OR = 0.98; 95% CI = 0.37–2.60; p = 0.97) or survival to discharge (OR = 1.14; 95% CI = 0.46–2.82; I² = 28%; p = 0.78).

Lidocaine versus Nifekalant

Four studies compared lidocaine with nifekalant (n = 317) [29,38–40]. These studies showed no significant increase in ROSC (OR = 2.92; 95% CI = 0.63–13.47; I² = 76%; p = 0.12). However, there was a significant increase in survival to admission with nifekalant (OR = 2.91; 95% CI = 1.44–5.87; I² = 34%; p = 0.003). There was no significant difference in survival to discharge (OR = 1.48; 95% CI = 0.75–2.91; I² = 0%; p = 0.26) or neurological outcomes in surviving patients (OR = 2.40; 95% CI = 0.36–15.94; p = 0.36).

Lidocaine versus Sotalol

One study by Kovoor et al. investigated lidocaine versus sotalol (n = 129) [41]. There was no difference in ROSC (OR = 0.60; 95% CI = 0.28–1.27; p = 0.18), survival to admission (OR = 0.44; 95% CI = 0.17–1.15; p = 0.09), survival to discharge (OR = 0.44; 95% CI = 0.08–2.38; p = 0.34) or neurological outcomes in survivors (n = 7; OR = 0.14; 95% CI = 0.00–4.47; p = 0.27).

Sensitivity Analysis

All results of the sensitivity analysis are included in Appendix 2. The sensitivity analysis of level one RCTs revealed that amiodarone had a significant improvement in survival to admission (OR = 1.32; 95% CI = 1.13–1.55; I² = 0%; p = 0.0006) and a non-significant improvement in survival to discharge (OR = 1.18; 95% CI = 0.98–1.44; I² = 0%; p = 0.09). However, in OHCA patients there were no changes to ROSC (OR = 1.06; 95% CI = 0.89–1.27; I² = 0% or neurological outcomes (OR = 0.94; 95% CI = 0.63–1.40; I² = 0%; p = 0.75). Lidocaine in level one RCTs was shown to have a significant improvement in ROSC (OR = 1.26; 95% CI = 1.05–1.51; I² = 0%; p = 0.01) and survival to admission (OR = 1.37; 95% CI = 1.15–1.63; I² = 0%; p = 0.005), yet no improvement in survival to discharge (OR = 1.16; 95% CI = 0.94–1.42; I² = 0%; p = 0.17) or neurological outcomes (OR = 0.76; 95% CI = 0.49–1.17; I² = 0%; p = 0.21). In a level one RCT, bretylium had a non-significant increase in survival to admission (OR = 3.17; 95% CI = 0.75–13.51; I² = 0%; p = 0.12), although it had statistically significant results prior to sensitivity analysis.
For IHCAs, amiodarone had a no significant improvement in ROSC compared to lidocaine (OR = 0.41; 95% CI = 0.15–1.08; I² = n/a; p = 0.07) and lidocaine was superior to bretylium (OR = 2.78; 95% CI = 1.04–7.45; I² = n/a; p = 0.04). Lidocaine improved survival to admission compared to nifekalant (OR = 2.91; 95% CI = 1.44–5.87; I² = n/a; p = 0.003).

Discussion

This is the most comprehensive review to date, combining 42,808 cardiac arrests from 31 studies to assess the efficacy of AAs on outcomes post cardiac arrest. The included studies took place in a wide variety of settings, with the majority assessing OHCA, and examined a range of different agents. To be included, the AA had to be compared to a control group, another AA, ‘standard therapy’ or placebo.

Two level one [11,12] and two level three [13,14] papers assessed amiodarone compared to standard practice or a placebo, combining 27,616 patients. On meta-analysis they showed administration of amiodarone had no significant effect on the incidence of ROSC, survival to admission, survival to discharge or neurological outcome. On secondary analysis of level one papers only, the two remaining studies did find a significant increase in survival to admission and the only level one paper to assess the outcome found a higher rate of ROSC. No other sensitivity analyses were possible, as none of these studies assessed IHCAs and only included VF/VT rhythms. One of these papers [13] has previously been criticised for its divergent baseline characteristics [7]. Whilst the amiodarone group did have higher rates of ‘witnessed’ arrests and were more likely to receive more bystander CPR, these characteristics would be likely to skew the results in favour of the intervention group. Despite having been independently verified as positive predictors of CA outcomes [42,43], such bias is not apparent in their results.

Two level one [12,16] and three level two studies [14,15,17] compared lidocaine to a control group, incorporating 22,285 cardiac arrests. There was no significant effect of lidocaine administration on the incidence of ROSC, survival to hospital, survival to discharge or neurological outcomes. However on secondary analysis of level one papers alone, lidocaine significantly improved ROSC rates and survival to admission. There remained no improvement in survival related to discharge or neurological outcome. As with amiodarone, no other sensitivity analyses were possible.

Two level one [12,31] and five level three papers [14,29,32–34] compared amiodarone to lidocaine, with 11,616 arrests analysed. Overall there was no significant difference between the two medications in ROSC, survival to admission, survival to discharge or neurological outcome. There were no significant differences after sensitivity analysis accounting for level of evidence or arrest location. All the studies only included VT/VF rhythms.

Five level one papers assess the utility of magnesium during cardiac arrest, including 485 cardiac arrests [18–22]. Overall there was no effect on ROSC, survival to admission, survival to discharge or neurological outcomes. There were no significant differences after sensitivity analysis accounting for level of evidence, arrest location or initial rhythm.

Limited numbers of studies assessed the effects of other novel AAs in cardiac arrest. These were mostly low quality or small high quality studies, such as the results must be interpreted with caution. The use of esmolol in one small study (n = 25) showed an increased survival to ROSC, with no effect on survival to admission, survival to discharge or neurological outcomes [23]. In two small studies (n = 108) bretylium significantly improved survival to admission, with no significant increase in survival to discharge [24,25]. However, three small studies found bretylium to be no better than lidocaine [35–37]. One large high quality RCT showed no effect with the addition of vasopressin to normal resuscitation protocols [26].

On meta-analysis we have found either no or conflicting evidence of superiority between different AAs, with the exception of nifekalant. Early data suggests that potassium channel blockers may be more effective than lidocaine, but they still have no proven benefit in placebo-controlled trials.

In four low quality retrospective studies, nifekalant demonstrated a significantly improved survival to admission [29,38–40]. There was no benefit in ROSC, survival to discharge or neurological outcomes.

International guidelines continue to recommend use of amiodarone, which was introduced on the basis that it increases the chance of ROSC and survival to admission for patients in refractory VF or VT rhythms [4,44]. This understanding is largely based on the findings of the ARREST [11] and ALIVE [31] trials. The ARREST trial was the first to show an early benefit for amiodarone; survival to hospital increased. The ALIVE study provided support to the concept that amiodarone increased survival to hospital, performing superiorly to lidocaine. Neither paper found an increase in survival to discharge.

Most recently, the ROC-ALPS [12] paper did suggest amiodarone was superior to placebo in increasing ROSC and survival to hospital but found no difference between amiodarone and lidocaine, contradicting ALIVE’s findings. The only consistent finding amongst all the highest quality level one papers has been that there is no survival benefit to discharge or improvement in neurological outcomes. The reasons that AAs may facilitate the process of resuscitation itself, but not improve survival would in itself be an interesting area for further research.

It is these ongoing developments regarding the utility of AAs that have additionally led to significant evolution of the ACLS Algorithm over years [45]. The timing of pharmacological administration of antiarrhythmics during the stages of the resuscitation protocol has greatly shifted from being a later consideration to being administered on the third shock in VT or VF [46]. Thus, the variability of administration time in each study should be recognised as a limitation when evaluating the overall efficacy of antiarrhythmics.

Many theories have developed surrounding the absence of perseverance of amiodarone’s short-term benefits. One
suggestion has been that delays in administration may render it ineffective because in the later ‘phases’ of cardiac arrest the original cellular mechanisms of arrhythmia may no longer be reversible pharmacologically as metabolic processes predominate [7,47]. Indeed some papers report significant associations between early administration and survival to admission in groups receiving AAs, moreso than those receiving placebo; they conclude that early AAs use may confer greater benefit [12,16]. The recent ROC-ALPS study reported a significant increase in survival to discharge with AAs if the arrest was witnessed by emergency medical services [12]. Some studies don’t observe such effects however [13].

This theory could be tested by comparing an OHCA with IHCAs, where the in-hospital time to AAs is often considerably less given earlier response times, pre-existing vascular access and a greater number of initial responders [48–50]. However, to date we found no placebo or ‘standard practice’ controlled amiodarone study assessing in-hospital arrests; this may be a useful point for future research. The closest is the study by Pollack et al. who assessed the transition of practice as amiodarone was introduced to in-hospital arrests [33]. They hypothesised that as a ‘superior’ AA was introduced, a survival benefit would be seen in those patients receiving the medication. No such benefit eventuated despite specifically analysing their data to assess for an ‘ARREST-like’ short-term survival benefit. Given that there was no survival benefit conferred by amiodarone vs lidocaine in IHCAs or OHCA, such an in-hospital placebo controlled trial could be considered viable and ethically appropriate.

It has also been pointed out that AAs raise the defibrillation [11,51–53]. Early and successful defibrillation when attempted in conjunction with CPR within three to five minutes of collapse has been shown to increase survival rates [4]. This poses the question of whether administering AAs may, in some cases, impede the success rate of a key intervention which has proven benefits. Others have suggested that lidocaine administration in certain patients may be associated with asystole and prevent successful defibrillation [16]. Despite this, as we have already highlighted, some studies have shown early benefits to defibrillation with amiodarone use.

We recognise that previous reviews postulate that there may be marginal benefits in survival to discharge that are too small to be detected by individual studies or through meta-analysis to date. They claim that even a small benefit could be clinically significant given the magnitude of annual cardiac arrests [6]. Whilst logically sound, we believe it’s equally important to consider the potential adverse effects from AAs. Several larger studies were powered to detect adverse drug reactions associated with trial pharmacotherapy. ARREST highlighted that the incidence of hypotension and bradycardia were significantly increased in those receiving Amiodarone [11]. This may also result in the need for pacing as demonstrated in Resuscitation Outcomes Consortium-Amiodarone, Lidocaine or Placebo Study (ROC-ALPS) [12]. This group has theorised the lack of survival benefits in AA use might be explained by adverse impacts of these medications counterbalancing any beneficial impacts [11]. Some have suggested the solvent solution used in some amiodarone formulations may be responsible for some of these side-effects, and could be avoided by the use of alternative agents [54–56]. However the ROC-ALPS study utilised one of these new formulations but did not to report on hypotension and bradycardia in their paper or supplementary material; however a greater number of amiodarone patients required temporary pacing. Side effects profiles may be improving, but these are by no means risk-free medications.

By principle, any intervention with known serious adverse effects warrants reconsideration if there are no proven benefits of administration. Whilst we acknowledge there may be short-term survival benefit of amiodarone use, there is also substantial potential for harm caused by the routine use of AAs. Increasing survival to hospital admission, without survival to discharge can be viewed as serving to increase invasive and costly medical intervention for these patients; this could be traumatic both for the patient and their family who often get little contact with them in an acute, intensive therapy setting [57,58]. Alternatively, if patients are admitted and regain consciousness, the patient may gain some valuable time with their loved ones. Although they may not have a higher chance of survival to discharge, perhaps there is merit to lengthening their last hours of life.

Our review builds on the work completed by others, which have included subsets of the information presented here [6–8]. This paper does, however, have a number of advantages. We present the range of current evidence for the majority of AAs, rather than one or two of the most common agents. Our analysis includes a number of studies that seem to have eluded prior search strategies. In addition, we have adapted our analysis to correct for errors made by prior groups. One prior meta-analysis contained errors in its statistical analysis, pertaining to use of fixed-effects models in grouping diverse studies [7]. As such their results ought to be interpreted with great caution as they were not analysed to be applicable to the new populations. Another review grouped the results of studies comparing amiodarone with both placebo and a range of alternative AAs [8]. The significant heterogeneity present in these ‘control’ groups make the results that analysis invalid in reference to the question ‘does amiodarone improve survival’.

Limitations

Since the mid-1990s global resuscitation councils have had consensus statements over appropriate measure of the outcomes of resuscitation and recommend outcomes be reported as early (ROSC, survival to admission), intermediate (survival to discharge) and long-term (survival to six months or more) [59]. Many studies we include consistently did not report on long-term outcomes, and as such we are unable to provide any evidence for the longer term harms or benefits of AAs.

Many of these studies also utilised other surrogate endpoints to measure the utility of AAs; common measures
included length of CPR, number of shocks delivered, number of ‘trial’ AA boluses used and further episodes of arrest or arrhythmia after admission to name but a few. Whilst groups using these measures have justified their use, we did not to include them in our analysis. These resuscitation factors have much potential for variance as they were inconsistently defined by different groups. In addition, the intrinsic potential pitfalls with utilising surrogate endpoints have been extensively discussed for many years [60–62]. There may be a reasonable theoretical basis for assuming each of these endpoints might confer benefit to patients, but observed changes in surrogate endpoints reported by various papers here do not translate into clinically significant survival benefits in large studies or meta-analysis. Furthermore, it is difficult to qualify the impact of potential confounding aetiology of the underlying arrhythmia, which could have a variety of causes including ischaemic, non-ischaemic, congenital, idiopathic.

Resuscitation and the examination of the contributions made by its different elements during cardiac arrest are intrinsically challenging to study scientifically [59,63,64]. Furthermore, the heterogeneity and progression of the underlying arrhythmia mechanism may additionally be a confounding factor affecting survival rates. This warrants further sensitivity analysis on antiarrhythmic administration in VF compared to Monomorphic VT. If particular arrhythmia mechanisms are proven to benefit from AAs, this warrants development of the ACLS algorithm into further subcategories stemming from ‘shockable’ and ‘non-shockable’. However, distinguishing the underlying rhythm proves extremely difficult, given VT often degenerates into VF and studies can only be limited to monitored settings.

Whilst there are groups who have spent the time and effort to design rigorous trials examining the effects of AAs, there remains insufficient RCT data to make level 1a recommendations on systematic review. Particularly, the analyses of newer AAs should be interpreted with caution – there is, to date, a paucity of evidence of these agents. Studies of new agents in CPR should endeavour to utilise placebo controls given the lack of proven benefit of other agents available for comparison.

Conclusion

We found no conclusive evidence that any antiarrhythmic improves rates of ROSC, survival to admission, survival to discharge or neurological outcomes. In short, no one antiarrhythmic delivered during resuscitation has been shown to improve patients’ outcomes.

Our review particularly emphasises the lack of benefit of AAs in improving medium term outcomes in the manner they are currently utilised. This is a significant and pertinent finding. Whilst the use of AAs during in hospital arrests is likely to remain a case-by-case decision as guided by senior clinicians, the default use of amiodarone during CPR algorithms does not seem to be supported by evidence. It remains plausible that there may be greater benefit with early AA administration, but there is not currently adequate evidence assessing this question.

As colleagues we must consider the potential benefits and harms of AA use and the ethical implications of increasing survival to hospital without improvement in longer-term survival. The evidence surrounding newer and novel AAs is too limited to draw any conclusions about their clinical use.

Conflict of Interest

The authors have no conflicts of interest to declare.

Uncited Reference

[65].

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.hlc.2017.07.004.

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