## Review

# Drug use during adult advanced cardiac life support: An overview of reviews

Hans Vandersmissen [a,c,1], Hanne Gworek [a,c,1], Philippe Dewolf [a,b,c,*], Marc Sabbe [a,b,c]

a Department of Emergency Medicine, University Hospitals of Leuven, Leuven, Belgium
b KULeuven, Department of Public Health and Primary Care, Leuven, Belgium
c KULeuven, Faculty of Medicine, Leuven, Belgium

## Abstract

**Aim**: To conduct an overview of systematic reviews and meta-analyses to summarize the ever-growing evidence on drug use during advanced life support.

**Methods**: We searched Embase, Medline, Cochrane central register of controlled trials and Web of science for systematic reviews and meta-analyses reporting on drug use during advanced life support from inception to March, 2020. Two reviewers independently assessed all abstracts for eligibility, extracted data and assessed risk of bias using the AMSTAR-2 tool. Corrected covered areas were calculated from publication citation matrices to account for potential risk of bias. Data were graphically represented using forest plots.

**Results**: Twenty-two head-to-head drug comparisons from 47 included articles were analysed. Adrenaline significantly increases the incidence of return of spontaneous circulation and survival to hospital discharge, but not the incidence of neurological intact survival. Vasopressin alone or in combination with adrenaline is not superior to adrenaline alone. There is a trend favouring lidocaine over amiodarone in shockable cardiac arrest. The risk of bias assessment of included studies ranged from very low to very high and the overlap between articles was moderate to high.

**Conclusions**: In line with the guidelines, we currently suggest that a standard dose of adrenaline should be administered during resuscitation, however, studies assessing lower doses of adrenaline are pressing. There is no rationale for the combination of vasopressin and adrenaline or vasopressin alone instead of adrenaline. In addition, lidocaine is a valuable alternative for amiodarone and maybe even preferable for shockable cardiac arrest. However more research is necessary.

**Keywords**: Advanced Cardiac Life Support Drug use Adrenaline Amiodarone Lidocaine Outcome

## Contents

## Introduction

The International Liaison Committee on Resuscitation (ILCOR) updates Advanced Life Support (ALS) guidelines every 5 years. They are formed by expert consensus, using state of the art evidence. ILCOR published the latest ALS guidelines in March 2021.[1] These guidelines pay a lot of attention to drug use during cardiac arrest (CA), which has led to more research of these drugs in recent years.

Initial research focused on the return of spontaneous circulation (ROSC) as the primary outcome.[2] These studies demonstrated a significant beneficial effect for several drugs. However, in the last decade, more long-term outcomes were investigated, such as survival to hospital discharge and neurologically intact survival.[8] Unfortunately, the beneficial effect of several drugs is less convincing or even absent for these long-term outcomes.[3] As a consequence, the use of drugs and their dose has been questioned in recent years.[4–6] More primary studies are needed to determine which drugs result in a significant improvement in long-term outcomes.

Meanwhile, a lot of high-quality evidence is available, sometimes with contradicting findings.[3,7,8] As a result, the overview might get lost.

The aim of this overview is to provide a synopsis of systematic reviews and meta-analyses analysing any drug use during CA. It will provide an overview of the highest quality of published evidence for each drug. In addition we were interested if two reviewers, reviewing only systematic reviews and meta-analyses would end up with the same recommendations as the most recent ALS guideline.

## Methods

### Review question

Does, among adults (>18 years), suffering from an in- or out-of-hospital cardiac arrest (I-and OHCA) and regardless of the initial rhythm, the administration of any drug during cardiopulmonary resuscitation or within 15 minutes after ROSC and compared to any other drug or placebo, change survival outcomes (ROSC, hospital discharge or neurological intact survival)?

### Data sources and search strategy

This overview of systematic reviews was registered with PROSPERO on March 10th, 2020 with registration number 172,778 before starting data extraction. A comprehensive search strategy was drafted by the review authors (HV, HG). Subject headings (MeSH), synonyms and free text with various spellings were used.

We searched Medline (Pubmed), Cochrane central Register of Controlled Trials (CENTRAL), Embase and Web of Science from inception to March 16th, 2020. Modified search strategies were used for each database to include specific search filters and terms. We searched PROSPERO for ongoing trials on March 10th, 2020, using the same terms of our search strategy. A detailed search strategy is available in the appendix. (Appendix I. Search strategy)

### Eligibility criteria and study selection

Systematic reviews and/or meta-analyses reporting on drug administration during ALS in adults (>18y) suffering from non-traumatic CA were eligible for inclusion. Drugs had to be administered during CA or within 15 minutes following ROSC. To be eligible for inclusion, either ROSC, survival to hospital discharge or neurological intact survival had to be one of the reported outcomes.

We excluded non-English articles, animal studies, studies in patient subgroups (eg. patients with Brugada, patients with Wolff Parkinson White syndrome, pregnant women), provoked CA (eg. surgery or conversions) and traumatic CA.

Two reviewers (HV, HG) independently assessed all abstracts for eligibility based on the criteria above using Rayyan QCRI.[9] Duplicates were manually excluded. Full texts of all potentially eligible

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│ 18 407 records      │
│ identified through  │
│ database searching  │
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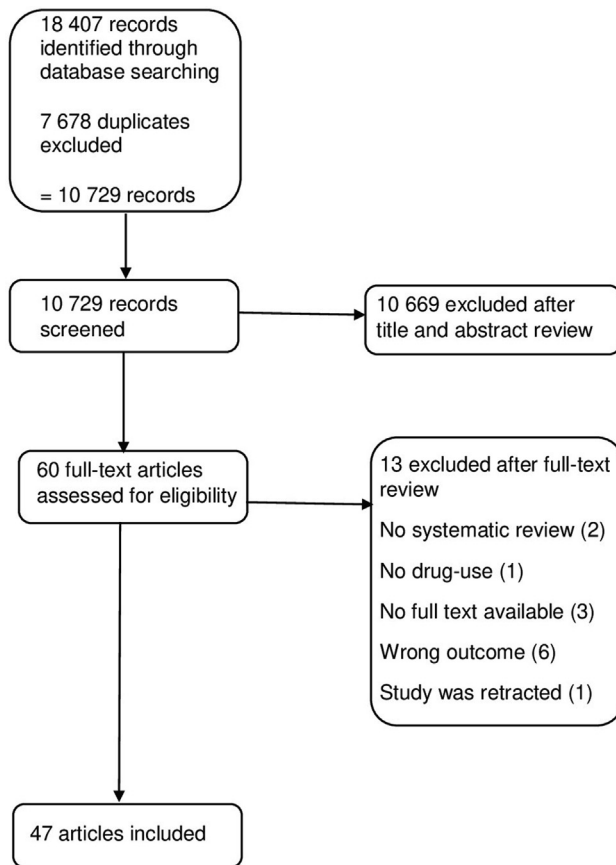
**Fig. 1 – PRISMA flow diagram of study selection.**

studies were independently assessed for inclusion by both reviewers (HV, HG). Any disagreement was resolved by consensus.

### Outcomes

Outcomes of interest were ROSC, survival to hospital discharge and neurological intact survival. Neurological survival has many outcome measures, including cerebral performance category (CPC), Glasgow outcome scale (GOS) and modified Rankin scale score (MRs). The Utstein guidelines on reporting about resuscitation recommend using either CPC or MRs.[10] The outcome measures and cut-offs of each individual study were used.

### Data collection and processing

Two reviewers (HV, HG) independently extracted all data using a pre-formed standardized data collection form. The following data were extracted from the systematic reviews and meta-analyses: title, publication year, drugs used, study design, population, population size, intervention, comparison with different doses and outcomes. The pooled effect outcomes of meta-analyses were extracted either as odds ratios (OR) or risk ratios (RR) with their 95.0% confidence intervals (CI). Only outcomes of ROSC, survival to hospital discharge and neurological intact survival were extracted. Data of both reviewers were subsequently compared, and any disagreement was resolved by consensus and re-examination of the full text. When data was not available in the systematic reviews or meta-analyses, it was extracted from the primary articles.

The extracted data were graphically represented in forest plots for each separate drug comparison. We did not pool any data and did not calculate any summarized effect. We reported and graphically represented the summarized effect measures of the meta-analyses. A separate forest plot was drafted for studies reporting either in OR or in RR. When the intervention and outcome were reversed in the meta-analysis, we inverted both OR or RR and their confidence intervals.

### Quality assessment and data analysis

Two reviewers (HV, HG) independently assessed risk of bias and methodological quality using the AMSTAR-2 tool, an instrument for critical appraisal of systematic reviews.[11] Any disagreement was resolved by consensus.

Finally, we constructed a publication-citation matrix to graphically present overlap of primary articles between systematic reviews (Appendix IV. Publication-citation matrices for each drug comparison). To account for this potential risk of bias, a corrected covered area (CCA) for each publication-citation matrix was calculated as well as for each pair of included systematic reviews or meta-analyses (Appendix V. Corrected covered areas for each pair of individual systematic reviews or meta-analyses). We interpreted the CCA according to pieper et al. Where a CCA of 0.0% to 5.0% should be interpreted as slight overlap, 5.0% to 10.0% as moderate overlap, 10.0% to 15.0% as high overlap and more than 15.0% as very high overlap.[12]

## Results

### Study selection

The initial search identified 10,729 unique records of which 10,669 were excluded based on title and abstract. Sixty articles were reviewed as full text for eligibility, of which 13 were excluded because they did not meet the inclusion criteria. A list of excluded studies and their reason for exclusion is available in the appendix. (Appendix II. List of excluded studies and their reason for exclusion). The remaining 47 systematic reviews and meta-analyses were included. Fig. 1 shows a PRISMA flow diagram of study selection.

### Characteristics of included studies and risk of bias assessment

Forty-seven systematic reviews and meta-analyses were included. Table 1 shows an overview of the most important systematic reviews and meta-analyses. A list of all included studies and their detailed risk of bias assessment can be found in the appendix. (Appendix III. Characteristics of included studies and reference list of primary articles).

### Adrenaline versus placebo

As shown in Fig. 2, eight out of nine meta-analyses reported higher rates of ROSC when using adrenaline.[5,7,13–18] This was in line with four included systematic reviews without meta-analysis. These studies also agree upon a beneficial effect of adrenaline on outcome

**Table 1 – Overview of included systematic reviews and meta-analyses for different drugs.**

| Systematic review/ meta-analysis | Number included trials | Number included patients in total | RoB |
|---|---|---|---|
| Adrenaline versus placebo | | | |
| Atiksawedparit et al. 2014[19] | 15 (1 RCT, 14 OS) | 637 078 | Low RoB |
| Aves et al. 2020[5] | 17 (17 RCT) | 21 510 | Very low RoB |
| Belletti et al. 2018[38] | 28 (28 RCT) | 14 848 | Very low RoB |
| Finn et al. 2019[7] | 26 (26 RCT) | 21 704 | Very low RoB |
| Holmberg et al. 2019[17] | 89 (15 RCT, 67 OS) | 1 562 925 | Very low RoB |
| Huan et al. 2019[18] | 4 (4 RCT) | 8967 | Low RoB |
| Kempton et al. 2019[13] | 5 (5 RCT) | 17 635 | Low RoB |
| Lin et al. 2014[26] | 14 (14 RCT) | 12 246 | Very low RoB |
| Loomba et al. 2015[14] | 14 (1 RCT, 13 OS) | 655 853 | Low RoB |
| Lundin et al. 2016[20] | 88 (48 IS, 40 OS) | 20 086 | High RoB |
| Morales-Cané et al. 2016[15] | 26 (9 RCT, 17 OS) | 762 456 | Moderate RoB |
| Ng et al. 2019[16] | 2 (2 RCT) | 8548 | Very low RoB |
| Pan et al. 2015[23] | NA | NA | Very high RoB |
| Patanwala et al. 2014[25] | 10 (2 RCT, 8 OS) | 436 108 | Low RoB |
| Perkins et al. 2019[8] | 2 (2 RCT) | 8548 | Low RoB |
| Reardon et al. 2013[21] | 9 (1 RCT, 8 OS) | 434 733 | Moderate RoB |
| Shao et al. 2017[22] | 8 (1 RCT, 7 OS) | 1 131 111 | Very high RoB |
| Lidocaine versus placebo | | | |
| Ali et al. 2018[6] | 32 (14 RCT, 16 OS) | 58 546 | Very low RoB |
| Chowdhury et al. 2018[42] | 31 (13 RCT, 18 OS) | 39 914 | Very low RoB |
| Huang et al. 2013[44] | 17 (10 RCT, 7 OS) | 3932 | Low RoB |
| Khan et al. 2017[40] | 11 (7 RCT, 4 OS) | 5200 | Low RoB |
| Lundin et al. 2016[20] | 88 (48 IS, 40 OS) | 20 086 | High RoB |
| Mc Leod et al. 2017[41] | 8 (8 RCT) | 4464 | Very low RoB |
| Ong et al. 2011[47] | 25 (9 RCT, 14 OS) | NA | Moderate RoB |
| Sanfillipo et al. 2016[45] | 7 (3 RCT, 4 OS) | 4381 | Low RoB |
| Lidocaine versus amiodarone | | | |
| Ali et al. 2018[6] | 32 (14 RCT, 16 OS) | 58 546 | Very low RoB |
| Aves et al. 2020[5] | 17 (17 RCT) | 21 510 | Very low RoB |
| Chowdhury et al. 2018[42] | 31 (13 RCT, 18 OS) | 39 914 | Very low RoB |
| Huang et al. 2013[44] | 17 (10 RCT, 7 OS) | 3932 | Low RoB |
| Khan et al. 2017[40] | 11 (7 RCT, 4 OS) | 5200 | Low RoB |
| Lang et al. 2010[46] | 5 (5 RCT) | 1101 | Moderate RoB |
| Lundin et al. 2016[20] | 88 (48 IS, 40 OS) | 20 086 | High RoB |
| Mc Leod et al. 2017[41] | 8 (8 RCT) | 4464 | Very low RoB |
| Ong et al. 2011[47] | 25 (9 RCT, 14 OS) | NA | Moderate RoB |
| Sanfillipo et al. 2016[45] | 7 (3 RCT, 4 OS) | 4381 | Low RoB |
| Magnesium versus placebo | | | |
| Ali et al. 2018[6] | 32 (14 RCT, 16 OS) | 58 546 | Very low RoB |
| Chowdhury et al. 2018[42] | 31 (13 RCT, 18 OS) | 39 914 | Very low RoB |
| Huang et al. 2013[44] | 17 (10 RCT, 7 OS) | 3932 | Low RoB |
| Khan et al. 2017[40] | 11 (7 RCT, 4 OS) | 5200 | Low RoB |
| Lundin et al. 2016[20] | 88 (48 IS, 40 OS) | 20 086 | High RoB |
| Mc Leod et al. 2017[41] | 8 (8 RCT) | 4464 | Very low RoB |
| Ong et al. 2011[47] | 25 (9 RCT, 14 OS) | NA | Moderate RoB |
| Reis et al. 2007[49] | 5 (5 RCT) | 499 | Very high RoB |

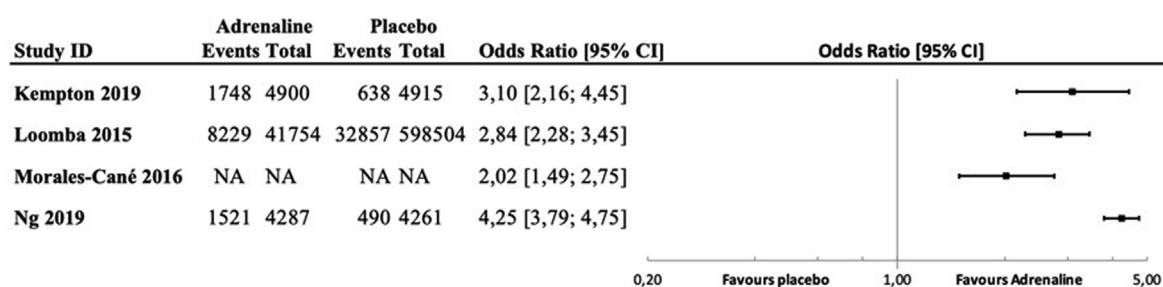RCT = Randomised controlled trial, OS = observational study, IS = interventional study.

ROSC.[20–22,24] For outcome of survival to hospital discharge, six out of ten meta-analyses demonstrated a significant benefit of adrenaline use.[5,7,15–18] On the other hand, Patanwala et al. found a significantly worse survival to hospital discharge when using adrenaline.[25] Four systematic reviews without meta-analysis were not convinced of any beneficial effect of adrenaline use on long-term outcomes.[20–22,24] For neurologically intact survival, none of the included meta-analyses demonstrated a significant beneficial effect.[5,7,13–18,25] Two meta-analyses even reported significantly worse outcome when using adrenaline.[14,16] In addition, three included systematic reviews stated there was no beneficial effect on long term outcomes.[22,24,26]

The results of meta-analyses comparing adrenaline versus placebo are graphically represented using forest plots in the appendix. (Appendix VI. Results of meta-analyses comparing adrenaline versus placebo).

### Adrenaline versus placebo stratified by rhythm

When stratifying for rhythm, four recent meta-analyses demonstrated that adrenaline is more effective to reach ROSC in CA with a non-shockable rhythm.[8,13,15,17] However, the effect is less pronounced for more long-term outcomes, such as survival to hospital discharge.
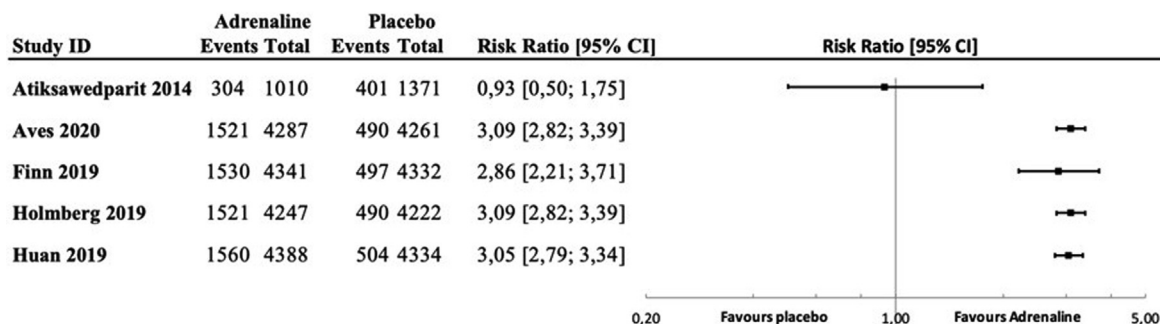
A

| Study ID | Adrenaline Events | Total | Placebo Events | Total | Odds Ratio [95% CI] |
|---|---|---|---|---|---|
| Kempton 2019 | 1748 | 4900 | 638 | 4915 | 3,10 [2,16; 4,45] |
| Loomba 2015 | 8229 | 41754 | 32857 | 598504 | 2,84 [2,28; 3,45] |
| Morales-Cané 2016 | NA | NA | NA | NA | 2,02 [1,49; 2,75] |
| Ng 2019 | 1521 | 4287 | 490 | 4261 | 4,25 [3,79; 4,75] |

Odds Ratio [95% CI] — 0,20 — Favours placebo — 1,00 — Favours Adrenaline — 5,00

B

| Study ID | Adrenaline Events | Total | Placebo Events | Total | Risk Ratio [95% CI] |
|---|---|---|---|---|---|
| Atiksawedparit 2014 | 304 | 1010 | 401 | 1371 | 0,93 [0,50; 1,75] |
| Aves 2020 | 1521 | 4287 | 490 | 4261 | 3,09 [2,82; 3,39] |
| Finn 2019 | 1530 | 4341 | 497 | 4332 | 2,86 [2,21; 3,71] |
| Holmberg 2019 | 1521 | 4247 | 490 | 4222 | 3,09 [2,82; 3,39] |
| Huan 2019 | 1560 | 4388 | 504 | 4334 | 3,05 [2,79; 3,34] |

Risk Ratio [95% CI] — 0,20 — Favours placebo — 1,00 — Favours Adrenaline — 5,00

Fig. 2 – Results of meta-analyses comparing adrenaline versus placebo for ROSC. A. ROSC in Odds Ratio. B. ROSC in Risk Ratio.

| Study ID | HDA Events | Total | SDA Events | Total | Risk Ratio [95% CI] |
|---|---|---|---|---|---|
| Aves 2020 | 35 | 1920 | 29 | 1963 | 0,83 [0,51; 1,35] |
| Finn 2019 | 67 | 2928 | 74 | 2875 | 0,91 [0,65; 1,26] |
| Lin 2014 | 35 | 1920 | 29 | 1963 | 0,83 [0,51; 1,35] |

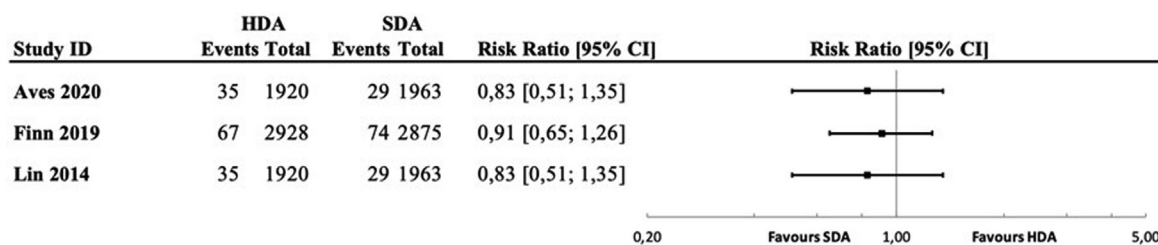Risk Ratio [95% CI] — 0,20 — Favours SDA — 1,00 — Favours HDA — 5,00

Fig. 3 – Results of meta-analyses comparing high dose adrenaline versus low dose adrenaline for neurological intact survival.

Three meta-analyses studied the effect on neurological intact survival but could not find a significant difference, although a similar trend could be observed. [8,13,15] The results of meta-analyses comparing adrenaline versus placebo stratified for rhythm, are graphically represented using forest plots in the appendix. (Appendix VII results of meta-analyses comparing adrenaline versus placebo stratified for rhythm).

### High dose adrenaline (HDA) versus low dose adrenaline (SDA)

Using HDA resulted in slightly higher rates of ROSC compared to SDA. [4,5,7,20,24,26] On the contrary, there was no significant effect on survival to hospital discharge. Fig. 3 shows that for HDA there even was a modest, yet insignificant negative trend for neurological intact survival. [4,5,7,26] Lin et al. stratified for rhythm and did not find any significant result for either rhythm. [26] The results of meta-analyses comparing HDA and SDA are graphically represented using forest plots in the appendix. (Appendix VIII. Results of meta-analyses comparing high dose adrenaline versus low dose adrenaline).

### Vasopressin versus adrenaline

Six meta-analyses compared vasopressin with adrenaline. Overall, no significant beneficial effect was found for either of these drugs. [7,15,17,26–28] Accordingly, none of the five included systematic reviews without meta-analysis reported any benefit of using vasopressin over adrenaline in an unselected patient population. [20,24,29–31] However, for a subgroup of in-hospital CA patients, Layek et al. reported a significant increase in the incidence of ROSC when using vasopressin. [27] On the contrary, Wyer et al. did not find any significant beneficial effect of vasopressin in either subgroup in their systematic review without meta-analysis. [30] The results of meta-analyses comparing vasopressin and adrenaline are graphically represented using forest plots in the appendix. (Appendix IX. Results of meta-analyses comparing vasopressin versus adrenaline).

### Vasopressin and adrenaline versus adrenaline alone

Eight meta-analyses investigating the use of a combination of vasopressin and adrenaline compared to adrenaline alone failed to
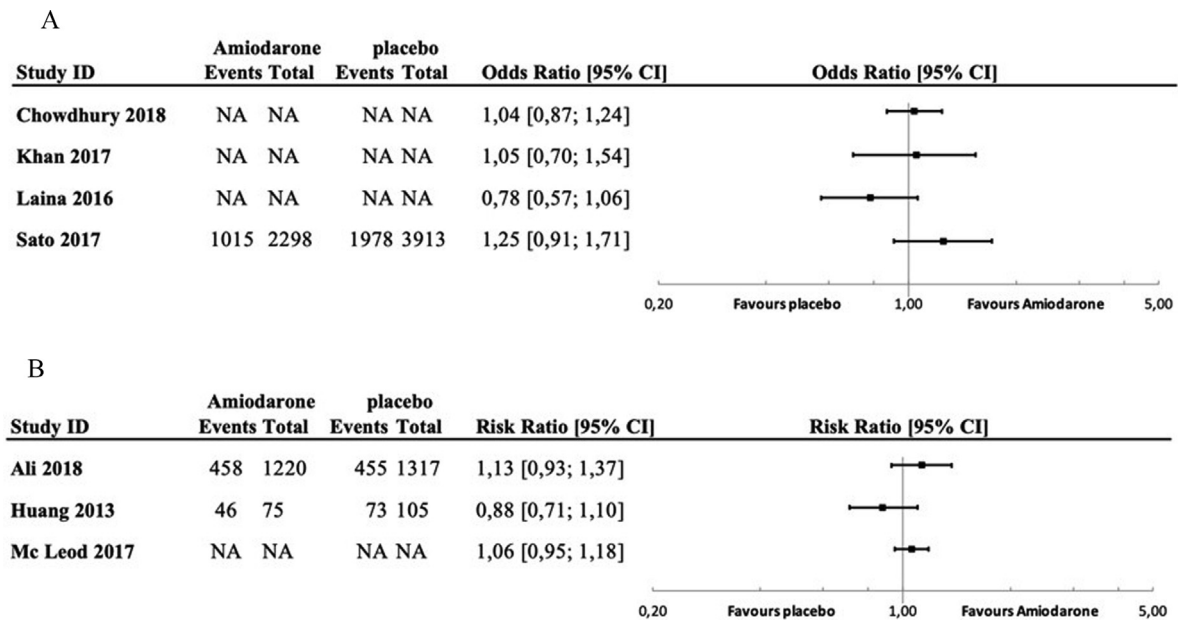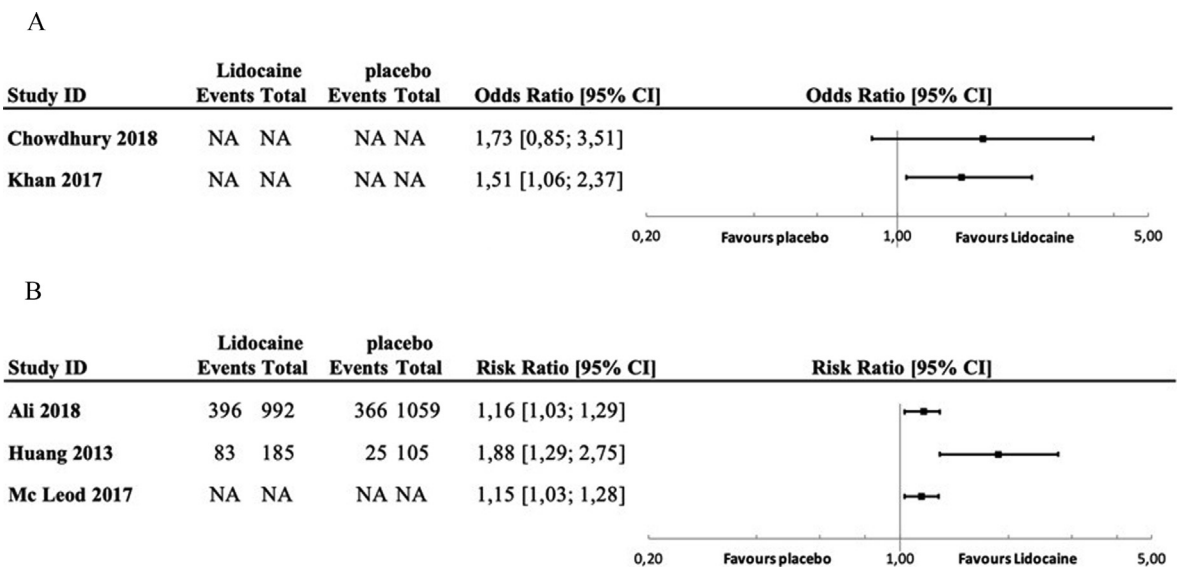
A

| Study ID | Amiodarone Events Total | placebo Events Total | Odds Ratio [95% CI] |
|---|---|---|---|
| Chowdhury 2018 | NA NA | NA NA | 1,04 [0,87; 1,24] |
| Khan 2017 | NA NA | NA NA | 1,05 [0,70; 1,54] |
| Laina 2016 | NA NA | NA NA | 0,78 [0,57; 1,06] |
| Sato 2017 | 1015 2298 | 1978 3913 | 1,25 [0,91; 1,71] |

B

| Study ID | Amiodarone Events Total | placebo Events Total | Risk Ratio [95% CI] |
|---|---|---|---|
| Ali 2018 | 458 1220 | 455 1317 | 1,13 [0,93; 1,37] |
| Huang 2013 | 46 75 | 73 105 | 0,88 [0,71; 1,10] |
| Mc Leod 2017 | NA NA | NA NA | 1,06 [0,95; 1,18] |

**Fig. 4 – Results of meta-analyses comparing amiodarone versus placebo for ROSC. A. ROSC in Odds Ratio. B. ROSC in Risk Ratio.**

A

| Study ID | Lidocaine Events Total | placebo Events Total | Odds Ratio [95% CI] |
|---|---|---|---|
| Chowdhury 2018 | NA NA | NA NA | 1,73 [0,85; 3,51] |
| Khan 2017 | NA NA | NA NA | 1,51 [1,06; 2,37] |

B

| Study ID | Lidocaine Events Total | placebo Events Total | Risk Ratio [95% CI] |
|---|---|---|---|
| Ali 2018 | 396 992 | 366 1059 | 1,16 [1,03; 1,29] |
| Huang 2013 | 83 185 | 25 105 | 1,88 [1,29; 2,75] |
| Mc Leod 2017 | NA NA | NA NA | 1,15 [1,03; 1,28] |

**Fig. 5 – Results of meta-analyses comparing lidocaine versus placebo for ROSC. A. ROSC in Odds Ratio. B. ROSC in Risk Ratio.**

demonstrate any significant beneficial effect for any outcome. On the contrary, more recent studies even demonstrated a slightly negative, however insignificant, trend for long-term outcomes.[5,7,15,17,26,32–34] In contrast, Sillberg et al. reported trends of increased ROSC incidence favouring an adrenaline/vasopressin combination. Nevertheless, this result was not confirmed for more long-term outcomes.[35] Mentzelopoulos et al. found the adrenaline/vasopressine combination to be significantly superior to adrenaline alone for both ROSC incidence and survival to hospital discharge in asystolic CA. Furthermore, they also found that vasopressin might have better long-term outcomes than adrenaline when drugs were administered within 20

minutes of CA.[33] Zhang et al. reported a beneficial effect of the combination in Asian populations, but not in other regions.[34] Lundin et al. also mentioned a significantly increased ROSC incidence when using an adrenaline/vasopressin combination in a specific subgroup of patients with acidosis.[20]

Two meta-analyses stratified for rhythm, but neither found any significant difference in any outcome.[5,15] The results of meta-analyses comparing vasopressin and adrenaline are graphically represented using forest plots in the appendix. (Appendix X. Results of meta-analyses comparing an adrenaline/vasopressin combination versus adrenaline alone).
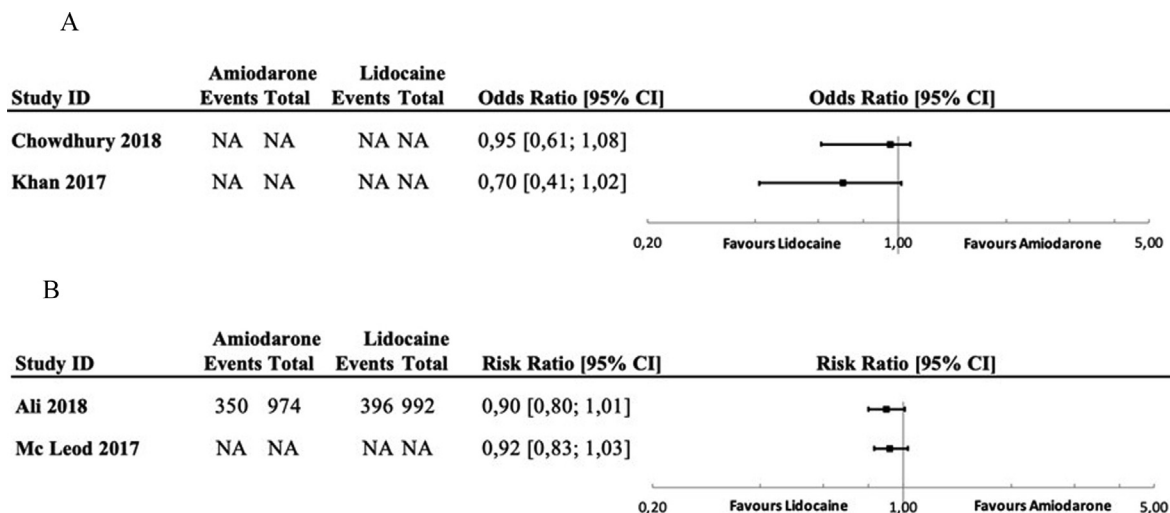
A

| Study ID | Amiodarone Events Total | Lidocaine Events Total | Odds Ratio [95% CI] | Odds Ratio [95% CI] |
|---|---|---|---|---|
| Chowdhury 2018 | NA NA | NA NA | 0,95 [0,61; 1,08] | |
| Khan 2017 | NA NA | NA NA | 0,70 [0,41; 1,02] | |

0,20　　　Favours Lidocaine　　1,00　　Favours Amiodarone　　5,00

B

| Study ID | Amiodarone Events Total | Lidocaine Events Total | Risk Ratio [95% CI] | Risk Ratio [95% CI] |
|---|---|---|---|---|
| Ali 2018 | 350 974 | 396 992 | 0,90 [0,80; 1,01] | |
| Mc Leod 2017 | NA NA | NA NA | 0,92 [0,83; 1,03] | |

0,20　　　Favours Lidocaine　　1,00　　Favours Amiodarone　　5,00

**Fig. 6 – Results of meta-analyses comparing amiodarone versus lidocaine for ROSC. A. ROSC in Odds Ratio. B. ROSC in Risk Ratio.**

### Vasopressin, adrenaline and methylprednisolone versus adrenaline alone

The combination of vasopressin, adrenaline and methylprednisolone was significantly better compared with adrenaline alone in achieving ROSC.[15,20] Lundin et al. even mentioned that the combination is beneficial for survival to hospital discharge as well as neurologically intact survival.[20] However, this was based on only 2 RCT, both performed by Mentzelopoulos et al. One RCT, including 99 Greek CA patients, showed a significant increase in ROSC and survival to hospital discharge.[36] The second RCT, including 268 adult IHCA patients, found a significantly superior effect of the combination on ROSC and neurologically intact survival.[37] Belletti et al. found the combination the most likely of all treatments to be the best in their network ranking meta-analysis.[38]

### Amiodarone versus placebo

Eight meta-analyses investigated the effects of amiodarone compared to placebo.[6,39–45] Three of them only looked at shockable rhythms.[6,39,40] Studies which included irrespective of rhythm, however, also mainly investigated VFib/VT. Khan et al. and Mcleod et al. performed a network meta-analysis.[40,41] HYPERLINK "SPS: refid::bib40_bib41"

The results of meta-analyses for ROSC are presented in Fig. 4. Despite some reported higher survival to hospital admission incidence, none of the meta-analyses and systematic reviews demonstrated any significant effect for the outcomes of interest.[6,39–45] The results of meta-analyses comparing amiodarone and placebo are graphically represented using forest plots in the appendix. (Appendix XI. Results of meta-analyses comparing amiodarone versus placebo).

### Lidocaine versus placebo

Six meta-analyses investigated the effects of lidocaine compared to placebo.[6,40–42,44,45] Khan et al. and Mc Leod et al. performed a network meta-analysis.[40,41] Ali et al. and Khan et al only included studies with shockable rhythms.[6,40] As illustrated in Fig. 5, four meta-analyses found a significant increase in ROSC incidence if lidocaine was used over placebo.[6,40,41,44] For survival to hospital discharge, only Khan et al. was able to find a significant beneficial effect in their network meta-analysis.[40] However, the other five meta-analyses also demonstrated a favourable trend towards lidocaine use.[6,41,42,44,45] For neurological intact survival, no significant result or trend could be observed. Lundin et al. showed no beneficial effect for lidocaine versus placebo for the outcomes ROSC and survival to discharge.[20] Ong et al., however, demonstrated an increased rate of survival to hospital discharge after the administration of lidocaine in patients with VF.[47]

The results of meta-analyses comparing lidocaine and placebo are graphically represented using forest plots in the appendix. (Appendix XII. Results of meta-analyses comparing lidocaine versus placebo).

### Amiodarone versus lidocaine

Six meta-analyses compared amiodarone with lidocaine.[6,40–42,44,45] For ROSC as shown in Fig. 6, all meta-analyses demonstrated a non-significant favourable trend towards lidocaine.[6,40–42] For survival to hospital discharge, only Khan et al. found lidocaine to be significantly superior to amiodarone in shockable rhythms.[40] None of the meta-analyses found any significant result for neurological intact survival. Two systematic reviews without meta-analysis found no difference in survival to discharge when comparing amiodarone and lidocaine.[46,47] Ong et al. also failed to prove a difference in survival with intact neurological outcome in patients with pVT or VFib.[47]

The results of meta-analyses comparing amiodarone and lidocaine are graphically represented using forest plots in the appendix. (Appendix XIII. Results of meta-analyses comparing amiodarone versus lidocaine).

### Magnesium versus placebo

None of the seven meta-analyses could find any significant effect for all outcomes of interest. Although, a very slight favourable trend

towards magnesium was observed for survival to hospital discharge and neurological intact survival.[6,40–42,44,48,49] Two systematic reviews showed no differences in ROSC incidence following magnesium administration.[20,47] Lundin et al. did not find any beneficial effect on survival to hospital discharge.[20]

The results of meta-analyses comparing magnesium versus placebo are graphically represented using forest plots in the appendix. (Appendix XIV. Results of meta-analyses comparing magnesium versus placebo).

### Thrombolytics versus placebo

Two meta-analyses compared thrombolytics with placebo. Li et al. found a significant beneficial effect for all outcomes of interest.[50] For ROSC and survival to hospital discharge, Wang et al. also found a favourable trend.[51] Tay et al. concluded that thrombolytics were more effective in pre-hospital settings, especially in patients with a thrombotic event.[52] Lundin et al. reported higher rates of ROSC, but no differences in survival to hospital discharge.[20]

The results of meta-analyses comparing thrombolytics versus placebo are graphically represented using forest plots in the appendix. (Appendix XV. Results of meta-analyses comparing thrombolytics versus placebo).

### Beta-blockade versus placebo

Chowdhury et al. reported a non-significant favourable trend towards beta-blockade, although this is based on one study by Driver et al.[42] In 2019, Gottlieb et al. performed a meta-analysis investigating beta-blockade versus placebo in shock refractory VF/VT with a larger sample size. They found a significant beneficial effect for all outcomes.[53] In contrast, Lundin et al. described no differences in rates of ROSC and intact neurological survival.[20] Miraglia et al. concluded recently that there is limited evidence for esmolol use in refractory VF/VT.[54]

The results of all meta-analyses comparing beta-blockade versus placebo are graphically represented using forest plots in the appendix. (Appendix XVI. Results of meta-analyses comparing beta-blockade versus placebo).

### Comparisons of other drugs

The head-to-head comparisons of other drugs in our included systematic reviews and meta-analyses can be found in the appendix. (Appendix XVII. Comparisons of other drugs).

## Discussion

Overviews of systematic reviews are most frequently employed where multiple systematic reviews already exist on related topics and aim to systematically synthesize the results. They can be a useful tool to support decision-making by clinicians and developers of clinical guidelines. They can also play a valuable role if evidence exists but is conflicting. While the evidence synthesized within an overview may be used to generate new insights and understanding, it is important to note that overviews are fundamentally a method of bringing together, summarizing and enhancing accessibility of existing evidence.[63] For all interventions, with

available data, results are presented as comparisons. Most reviews compared an intervention with placebo or standard care. However, there were few direct comparisons between different forms of the same intervention, and even fewer comparisons between different interventions.

ILCOR recommends, in their general adult CA algorithm, the systematic use of adrenaline, with and without a shockable first rhythm. They also recommend amiodarone, but only within the shockable rhythm approach.[1] Our findings are, as one could predict, very similar to the recent ILCOR ALS guidelines.[1] We do believe that adrenaline currently still has its place in ALS protocols. However, there is growing evidence that the use of adrenaline in adults with OHCA does not result in survivors with an improved neurologic outcome.[3] A standard dose of adrenaline increases ROSC, survival to hospital admission and discharge incidence compared with placebo. However, there was no difference in neurologic outcome at discharge observed. As previously stated in the Paramedic2 trial, adrenaline has multiple and complex adrenergic effects with a nonlinear dose–response relationship.[3] Higher doses improve coronary perfusion but also disrupt cerebrovascular autoregulation, and thus, possibly, can lead to further neurologic damage.[3] At this stage, we suggest that there is an urgent need for studies investigating lower doses of adrenaline. Other alternatives such as a continuous infusion or a maximum dosage should be considered. Fisk et al. found in their retrospective study that a standard dose of adrenaline (1 mg) is not beneficial over a lower dose of adrenaline (0.5 mg) for all outcomes.[55] The Canadian Resuscitation Outcomes Consortium will perform a RCT to evaluate a low cumulative dose (maximum 2 mg) compared with the current standard dose (NCT03826524). Most of the systematic reviews could not perform an adequate meta-analyses due to the heterogeneous population. RCT focusing on more homogeneous populations and evaluating ROSC and neurologic short- and long term outcomes need to be designed. This will enable future systematic reviews to meta-analyze consistent data across trials to improve the certainty of pooled effects.

Although the adrenaline/vasopressin combination did not improve outcomes when compared to adrenaline alone, a combination with methylprednisolone seemed significantly better in reaching ROSC and survival to hospital discharge than adrenaline alone. However, these results were only based on 2 RCT investigating IHCA.[36,37] Further research is needed to determine the methylprednisolone effect on all outcomes.

Antiarrhythmic drugs are administered in the prehospital setting primarily for their immediate effects, namely to terminate VFib/VT in order to restore and stabilize an organized rhythm. Our results indicate that lidocaine is equally or even more effective than amiodarone for shockable rhythms. This is based on the results of 9 systematic reviews and meta-analyses with a borderline non-significant increase in ROSC incidence following lidocaine administration.[6,40–42,44–47] Nonetheless, it must be mentioned that the only common reference used in this overview and the ILCOR guidelines is the meta-analysis of Ali et al.[6] In contrast to our study design, ILCOR also included RCT and guidelines. This is a known limitation of an overview of reviews. We might have missed important information from recent RCT. The European Resuscitation Council Guidelines for Resuscitation of 2018 were not included in this overview yet. They concluded that the beneficial effects on ROSC were similar for amiodarone and lidocaine.[56] In addition, the optimal time at which one of these drugs should be given remains unknown. It is likely that their efficacy is progressively decreasing with delayed administration.

One may state that we still have no answer to what matters the most: providing the right antiarrhythmic drug at the right time for the right group of patients. Future research focusing on early administration in select patients may help to further elucidate the role of antiarrhythmic drugs in OHCA.

The ILCOR guidelines made a weak recommendation for the use of thrombolytics in suspected PEs during CA. Although at present, there is insufficient evidence for this recommendation, we certainly understand the importance from a clinical perspective. As we did not include RCT and guidelines, therefore we are possibly lacking recent evidence concerning thrombolytics use.

Five RCT referred to the ILCOR guidelines, which are included in the systematic reviews and meta-analyses of our overview of reviews. [57-61] The 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science considered an increased risk of bleeding after thrombolysis, but major bleeding complications did not occur more often.[62]

Our study design has some flaws. A limitation of overviews of systematic reviews is the overlap of the same primary articles used in meta-analyses. As a consequence, certain primary articles included in multiple systematic reviews or meta-analyses can have more impact on the results of our analysis than single used primary studies. This risk of bias was addressed for by drafting publication-citation matrices and calculating CCA. However, it is still under discussion how to interpret and account for this CCA. Attention must be paid for certain comparisons, certainly when overlap is high to very high.

Although trial inclusion and patient characteristics of the studies were similar, there was a time interval of over 3 decades between the first and last included trial. This may result in a substantial variability such as in CPR protocols, defibrillation protocols, and quality of provided CPR differences. As this was inconsistently reported across the included randomized trials, we were not able to assess the possible influences on the relative efficacy of antiarrhythmic drugs used during OHCA resuscitation. In addition, there were also important differences in post-resuscitation care such as the use of targeted temperature management and percutaneous coronary intervention.

Almost all indirect comparisons for each drug yielded only a low or very low evidence quality, with confidence intervals that may include substantial benefit or substantial harm for most comparisons.

## Conclusion

Standard dose adrenaline still has a place in resuscitation protocols. There is sufficient evidence that there is no place anymore for high dose adrenaline, as it may worsen neurological outcome. Furthermore, vasopressin alone or in combination with adrenaline does not seem to have beneficial effects and is therefore not recommended. Lidocaine seems to be a valuable alternative for amiodarone but it is still under discussion which one is the agent of choice in shockable. Large RCT are necessary to confirm these findings. Several studies concerning the use of methylprednisolone, magnesium, beta-blockade and thrombolytics suggest promising results. However, they often had a small sample size or a specific patient population. This overview provides a useful summary of systematic reviews and meta-analyses investigating drug use during ALS. It may therefore be a useful tool to find summarized data and potential research gaps. Nonetheless, great

caution should be taken comparing results of separate meta-analyses since an overview is not a comparative design, but rather a summary of data.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgement

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2021.100156.

REFERENCES

[1] Soar J, Böttiger BW, Carli P, Couper K, Deakin CD, Djärv T, Lott C, Olasveengen T, Paal P, Pellis T, Perkins GD, Sandroni C, Nolan JP. ILCOR/ERC European Resuscitation Council Guidelines 2021: Adult advanced life support. Resuscitation 2021;161:115–51.

[2] Kleinman ME, Perkins GD, Bhanji F, et al. ILCOR Scientific Knowledge Gaps and Clinical Research Priorities for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: A Consensus Statement. Circulation 2018;137:e802–19.

[3] Perkins GD, Chen J, Deakin CD, et al. A Randomized Trial of Epinephrine in Out-of-Hospital CA. N Engl J Med 2018;379:711–21.

[4] Vandycke C, Martens P. High dose versus standard dose epinephrine in CA - a MA. Resuscitation 2000;45:161–6.

[5] Aves T, Chopra A, Patel M, Lin S. Epinephrine for Out-of-Hospital CA: An Updated SR and MA. Crit Care Med 2020;48:225–9.

[6] Ali MU, Fitzpatrick-Lewis D, Kenny M, et al. Effectiveness of antiarrhythmic drugs for shockable CA: A SR. Resuscitation 2018;132:63–72.

[7] Finn J, Jacobs I, Williams TA, Gates S, Perkins GD. Adrenaline and vasopressin for CA. The Cochrane database of SRs 2019.

[8] Perkins GD, Kenna C, Ji C, et al. The effects of adrenaline in out of hospital CA with shockable and non-shockable rhythms: Findings from the PACA and PARAMEDIC-2 randomised controlled trials. Resuscitation 2019;140:55–63.

[9] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid. A. Rayyan - a web and mobile app for SRs. SR 2016;5.

[10] Jacobs I, Nadkarni V, Bahr J, et al. CA and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). Resuscitation 2004;63:233-49.

[11] Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for SRs that include randomised or non-randomised studies of healthcare interventions, or both. BMJ clinical evidence 2017.

[12] Pieper D, Antoine SL, Mathes T, Neugebauer EAM, Eikermann M. SR finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol 2014;67:368–75.

[13] Kempton H, Vlok R, Thang C, Melhuish T, White L. Standard dose epinephrine versus placebo in out of hospital CA: A SR and MA. American J Emergency Med 2019;37:511–7.

[14] Loomba RS, Nijhawan K, Aggarwal S, Arora RR. Increased ROSC at the expense of neurologic outcomes: Is prehospital epinephrine for out-of-hospital CA really worth it? J Crit Care 2015;30:1376–81.

[15] Morales-Cané I, Valverd-Leon MDR, Rodriguez-Borrego MA. Epinephrine in CA: SR and MA. Revista Latino-Americana de Enfermagem 2016;24 e2821.

[16] Ng KT, Teoh WY. The Effect of Prehospital Epinephrine in Out-of-Hospital CA: A SR and MA. Prehospital Disaster Medcine 2019;34:532–9.

[17] Holmberg MJ, Issa MS, Moskowitz A, et al. Vasopressors during adult CA: A SR and MA. Resuscitation 2019;139:106–21.

[18] Huan L, Qin F, Wu Y. Effects of epinephrine for out-of-hospital CA: A SR and MA of randomized controlled trials. Medicine 2019;98 e17502.

[19] Atiksawedparit P, Rattanasiri S McEvoy M, Graham CA, Sittichanbuncha Y, Thakkinstian A. Effects of prehospital adrenaline administration on out-of-hospital CA outcomes: a systematic review and meta-analysis. Critical Care 2014;18:463.

[20] Lundin A, Djärv T, Engdahl J, et al. Drug therapy in CA: a review of the literature. European Heart J Cardiovascular Pharmacotherapy 2016;2:54–75.

[21] Reardon PM, Magee K. Epinephrine in out-of-hospital CA: A critical review. World J Emergency Med 2013;4:85–91.

[22] Shao H, Li CS. Epinephrine in Out-of-hospital CA: Helpful or Harmful? Chin Med J 2017;130:2112–6.

[23] Pan J, Zhu JY, Kee HS, Zhang Q, Lu YQ. A Review of Compression, Ventilation, Defibrillation, Drug Treatment, and Targeted Temperature Management in Cardiopulmonary Resuscitation. Chin Med J 2015;128:550–4.

[24] Larabee TM, Liu KY, Campbell JA, Little CM. Vasopressors in CA: a SR. Resuscitation 2012;83:932–9.

[25] Patanwala AE, Slack MK, Martin JR, Basken RL, Nolan PE. Effect of epinephrine on survival after CA: a SR and MA. Minervaanestesiologica 2014;80:831–43.

[26] Lin S, Callaway CW, Shah PS, et al. Adrenaline for out-of-hospital CA resuscitation: a SR and MA of randomized controlled trials. Resuscitation 2014;85:732–40.

[27] Layek A, Maitra S, Pal S, Bhattacharjee S, Baidya DK. Efficacy of vasopressin during cardio-pulmonary resuscitation in adult patients: a MA. Resuscitation 2014;85:855–63.

[28] Aung K, Htay T. Vasopressin for CA: a SR and MA. Arch Intern Med 2005;165:17–24.

[29] Koshman SL, Zed PJ, Abu-Laban RB. Vasopressin in CA. Ann Pharmacotherapy 2005;39:1687–92.

[30] Wyer PC, Perera P, Jin Z, et al. Vasopressin or epinephrine for out-of-hospital CA. Ann Emerg Med 2006;48:86–97.

[31] Biondi-Zoccai GG, Abbate A, Parisi Q, et al. Is vasopressin superior to adrenaline or placebo in the management of CA? A MA. Resuscitation 2003;59:221–4.

[32] Jing XL, Wang DP, Li X, et al. Vasopressin and epinephrine versus epinephrine in management of patients with CA: A MA. Signa Vitae 2010;5:20–6.

[33] Mentzelopoulos SD, Zakynthinos SG, Siempos I, Malachias S, Ulmer H, Wenzel V. Vasopressin for CA: MA of randomized controlled trials. Resuscitation 2012;83:32–9.

[34] Zhang Q, Liu B, Zhao L, et al. Efficacy of vasopressin-epinephrine compared to epinephrine alone for out of hospital CA patients: A SR and MA. American J Emergency Med 2017;35:1555–60.

[35] Sillberg VA, Perry JJ, Stiell IG, Wells GA. Is the combination of vasopressin and epinephrine superior to repeated doses of epinephrine alone in the treatment of CA-a SR. Resuscitation 2008;79:380–6.

[36] Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, et al. Vasopressin, epinephrine, and corticosteroids for in-hospital CA. Arch Intern Med 2009;169:15–24.

[37] Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital CA: a randomized clinical trial. JAMA 2013;310:270–9.

[38] Belletti A, Benedetto U, Putzu A, et al. Vasopressors During Cardiopulmonary Resuscitation. A Network MA of Randomized Trials. Crit Care Med 2018;46:e443–51.

[39] Sato S, Zamami Y, Imai T, et al. MA of the efficacies of amiodarone and nifekalant in shock-resistant ventricular fibrillation and pulseless ventricular tachycardia. Sci Rep 2017;7:12683.

[40] Khan SU, Winnicka L, Saleem MA, Rahman H, Rehman N. Amiodarone, lidocaine, magnesium or placebo in shock refractory ventricular arrhythmia: A Bayesian network MA. Heart & lung : the journal of critical care 2017;46:417–24.

[41] McLeod SL, Brignardello-Petersen R, Worster A, et al. Comparative effectiveness of antiarrhythmics for out-of-hospital CA: A SR and network MA. Resuscitation 2017;121:90–7.

[42] Chowdhury A, Fernandes B, Melhuish TM, White LD. Antiarrhythmics in CA: A SR and MA. Heart Lung Circulation 2018;27:280–90.

[43] Laina A, Karlis G, Liakos A, et al. Amiodarone and CA: SR and MA. Int J Cardiol 2016;221:780–8.

[44] Huang Y, He Q, Yang M, Zhan L. Antiarrhythmia drugs for CA: a SR and MA. Crit Care 2013;17:R173.

[45] Sanfilippo F, Corredor C, Santonocito C, et al. Amiodarone or lidocaine for CA: A SR and MA. Resuscitation 2016;107:31–7.

[46] Lang ES, Bronwing K. Ventricular tachyarrhythmias (out-of-hospital CAs). Clinical Evidence 2010;12:216.

[47] Ong ME, Pellis T, Link MS. The use of antiarrhythmic drugs for adult CA: a SR. Resuscitation 2011;82:665–70.

[48] Chen F, Lin Q, Chen G, Wang X, Lin S. Does Intravenous Magnesium Benefit Patients of CA? a MA. Hong Kong J Emergency Med 2012;19:103–9.

[49] Reis AG, Paiva EFd, Schvartsman C, Zaritsky AL. Magnesium in cardiopulmonary resuscitation: critical review. Resuscitation 2008;77(1):21–5.

[50] Li X, Fu QL, Jing XL, et al. A MA of cardiopulmonary resuscitation with and without the administration of thrombolytic agents. Resuscitation 2006;70:31–6.

[51] Wang Y, Wang M, Ni Y, Liang B, Liang Z. Can Systemic Thrombolysis Improve Prognosis of CA Patients During Cardiopulmonary Resuscitation? A SR and MA. J Emergency Med 2019;57:478–87.

[52] Tay SY. Thrombolysis as a therapeutic modality in CA. Hong Kong J Emergency Med 2004;11:26–34.

[53] Gottlieb M, Dyer S, Peksa GD. Beta-blockade for the treatment of CA due to ventricular fibrillation or pulseless ventricular tachycardia: A SR and MA. Resuscitation 2020;146:118–25.

[54] Miraglia D, Miguel LA, Alonso W. The evolving role of esmolol in managment of pre-hospital refractory ventricular fibrillation; a scoping review. Arch Acad Emergency Med 2020;8 e15.

[55] Fisk CA, Olsufka M, Yin L, et al. Lower-dose epinephrine administration and out-of-hospital CA outcomes. Resuscitation 2018;124:43–8.

[56] Soar J, Perkins GD, Maconochie I, et al. European Resuscitation Council Guidelines for Resuscitation: 2018 Update – Antiarrhythmic drugs for CA. Resuscitation 2019;14:99–103.

[57] Böttiger BW, Böhrer H, Bach A, Motsch J, Martin E. Bolus injection of thrombolytic agent during cardiopulmonary resuscitation for massive pulmonary embolism. Resuscitation 1994;28:45–54.

[58] Böttiger BW, Arntz HR, Chamberlain DA, et al. Thrombolysis during resuscitation for out-of-hospital CA. N Eng J Med 2008;359:2651–62.

[59] Yousuf T, Brinton T, Ahmed K, et al. Tissue Plasminogen Activator Use in CA Secondary to Fulminant Pulmonary Embolism. J Clin Med Res 2016;8:190–5.

[60] Kurkciyan I, Meron G, Sterz F, et al. Pulmonary embolism as a cause of CA: presentation and outcome. Arch Intern Med 2000;160:1529–35.

[61] Janata K, Holzer M, Kurkciyan I, et al. Major bleeding complications in cardiopulmonary resuscitation: the place of thrombolytic therapy in CA due to massive pulmonary embolism. Resuscitation 2003;57:49–55.

[62] Soar J, Berg KM, Andersen LW, et al. Adult Advanced Life Support: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation 2020;156:A80–A119.

[63] Hunt H, Pollock A, Campbell P, Estcourt L, Brunton G. An introduction to overviews of reviews: planning a relevant research question and objective for an overview. Syst Rev 2018;7:39.