Evidence Update Worksheet

Atropine for cardiac arrest
ALS 3206

Worksheet author(s): Tonia Nicholson
Task Force: ALS
Date Submitted to SAC rep for peer review and approval:
SAC rep: Peter Morely

PICOST / Research Question: ***(Attach SAC representative approved completed PICOST template)***
ALS-D-024B
In adult patients in cardiac arrest (asystole, PEA, pulseless VT, and VF) (out-of-hospital, in-hospital), does the use of atropine or atropine in combination with other drugs, compared with not using drugs (or a standard drug regimen), improve outcomes (eg, ROSC, survival)?

Year of last full review: 2010

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
Consensus on Science
Three studies (LOE 4) (total of 12 operating rooms, 2 catheterization laboratories, 2 out-of-hospital cardiac arrest patients, and 4 in-hospital cardiac arrest patients) documented improvement in survival when atropine was given to patients in asystole in combination with epinephrine and following induction with succinylcholine and fentanyl. One study documented improvement in ROSC (14% versus 0%) when atropine was given to adults in asystolic out-of-hospital cardiac arrest in combination with epinephrine and sodium bicarbonate, but none survived to discharge (LOE 3).
Three studies suggested the use of atropine for treatment of cardiac arrest was not associated with any change in survival (LOE 2; LOE 5). Four human studies suggested that the use of atropine was associated with poor survival (LOE 4).

Treatment Recommendation
There is insufficient evidence to support or refute the use of atropine in cardiac arrest to improve survival to hospital discharge.

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST:
((((bradycardia/dt[MeSH Terms]) OR asystole/dt[MeSH Terms]) OR av block/dt[MeSH Terms])) AND atropine[MeSH Terms]

New Search strategy: (for a new PICOST should be outlined here as per Evidence Update Process):
"atropine” OR "atropine" OR "atropin" OR "atropinization" OR "atropinized" OR "hyoscyamine" OR "hyoscyamine" AND ("heart arrest" OR ("heart" AND "arrest") OR "heart arrest" OR ("cardiac" AND "arrest") OR "cardiac arrest")

Database searched: Pubmed 22/04/2023 **(eg Medline Embase Cochrane)**

Time Frame: (existing PICOST) – updated from end of last search (please specify)
Time Frame: (new PICOST) – at the discretion of the Task Force (please specify) Jan 2010 - 2023
Date Search Completed: 22/04/2023
Search Results (Number of articles identified and number identified as relevant):
I67 articles identified. 4 identified as potentially relevant, 1 of these excluded on assessment of full manuscript.

Summary of Evidence Update:
Relevant Guidelines or Systematic Reviews:

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations

RCT:

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
	Study Aim: **Study Type:**	**Inclusion Criteria:**	**Intervention:** **Comparison:**	**1° endpoint:**	**Study Limitations:**

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
1) Atropine Sulfate for Patients with OOH Cardiac Arrest due to Asystole & PEA. SOS-KANTO Study Group: Nagao K, Yago T, Sakamoto T, Koseki K, Igarashi M et al. Published 2011.	**Study Type:** Prospective, multicenter, observational trial of 7,448 adult patients with persistent asystole or PEA after OOHCA in the Kanto area of Japan. Patients were managed according to the Guidelines for CPR from 2000. 1mg of adrenaline was given every 3-5 mins for persistent cardiac arrest. The administration of Atropine was not standardized, but 1mg could also be given every 3-5 mins. 5,048 patients were given adrenaline alone, 1,372 were given adrenaline with atropine.	**Inclusion Criteria:** Age ≥ 18yrs. Cardiac arrest with a non-shockable rhythm.	**1° endpoint:** The primary endpoint was a favourable neurological outcome at 30 days after cardiac arrest (CPC score of 1 or 2). For the patients in asystole, in the multivariable logistic regression analysis, the AOR for epinephrine & atropine compared with epinephrine alone was 0.69 (95%CI 0.19– 2.48; P=0.571) for 30-day favourable neurological outcome. For the patients with PEA, in the multivariable logistic regression analysis the AOR after administration of epinephrine & atropine compared with epinephrine alone was 0.51 (95%CI 0.10–2.48; P=0.040) for 30-day favourable neurological outcome. The secondary endpoints were ROSC, survival to hospital admission and survival at 30 days after cardiac arrest. For asystole, in multivariable logistic regression analysis, AOR for epinephrine & atropine compared with epinephrine alone was: 1.82 (95%CI 1.58–2.09; P<0.001) for ROSC, 1.55 (95%CI 1.31–1.83; P< 0.001)for survival to hospital admission, 1.01 (95%CI 0.59– 1.72; P=0.986) for 30-day survival. So, for asystole this study showed *no* association between administration of atropine and long-term neurological	The study concluded that the administration of atropine had no long-term neurological benefit in adults with out-of-hospital cardiac arrest due to non-shockable rhythms. Atropine is not useful for adults with PEA. (Associated with worse 1°and 2°endpoints) Study Limitations The study was observational & used guidelines from 2000. The time interval from cardiac arrest to administration of atropine was long (call-to-drug-administration interval >30 min). Outcomes might have been different if the drugs had been administered earlier.

			benefit, but atropine appeared to be an independent predictor of ROSC and survival to hospital admission. For PEA, in the multivariable logistic regression analysis the AOR after the administration of epinephrine and atropine compared with epinephrine alone was 0.95 (95%CI 0.73–1.24; P=0.708) for ROSC, 0.87 (95%CI 0.65–1.16; P=0.339) for survival to hospital admission, and 0.40 (95%CI 0.22–0.86; P=0.016) for 30-day survival. Thus for PEA, administration of atropine was an independent predictor of death at 30 days . Neurological outcomes were defined by physicians not connected to this study.	
Study; Author; Year Published 2) The Additive Effect of Atropine Sulfate during Cardiopulmonary Resuscitation in Out- of-hospital Non-traumatic Cardiac Arrest Patients with Non-shockable Rhythm. Yano T, Kawana R, Yamauchi K, Endo G. and Nagamine Y. Published 2019.	**Study Type/Design; Study Size (N)** A retrospective observational study from 2012-2017, of 453 patients with non-traumatic OHCA in Japan. 1-mg of IV epinephrine was administered every 3- 5 minutes. Use of atropine wasn't standardized, but the dose used for asystole or PEA arrest was 1 mg IV, repeated every 3-5 minutes (maximum total of 3 mg) if asystole or PEA arrest persisted. Outcomes were compared between those given epinephrine and atropine (157) and those given epinephrine alone (210).	**Inclusion criteria:** Adults ≥ 18yrs old. Patients arriving at a community hospital in Japan after non-traumatic OHCA with a non-shockable rhythm, between 1st Oct 2012 & 30th April 2017. **Exclusion Criteria:** < 18yrs old; Sustained ROSC before arrival in ED; Initial rhythm in ED shockable; Drug dose unclear; Adrenaline not given; Patient had DNR order.	**Primary Endpoint and Results (include P value; OR or RR; & 95% CI)** The primary outcome was survival to hospital admission (meaning survival until admission after ROSC). After multivariable analysis, Odds ratio (OR) for overall survival to hospital admission for epinephrine only was 0.64 (95% CI: 0.55-0.74, p<0.01), for epinephrine with atropine was 1.33 (95% CI:1.09-1.62). For those with PEA, OR for survival to hospital admission for epinephrine only was 0.62 (95% CI 0.49-0.78; p<0.01) and for epinephrine with atropine was 1.35 (95% CI 0.99-1.83; p=0.06). For those with asystole, OR for survival to hospital admission for epinephrine only was 0.64 (95% CI 0.53-0.76; p<0.01) and for epinephrine with atropine was 1.39 (95% CI 1.10-1.77; p<0.01). Using binominal logistic regression analysis, the OR for survival to hospital admission without administration of atropine was 0.38 (95% CI 0.29-0.50; p<0.01), - After 1mg of atropine was 2.91 (95% CI 1.49-5.67; p<0.01), After 2mg of atropine was 1.54 (95% CI 0.58-4.08; p=0.38), and After ≥3 mg atropine was 0.23 (95% CI 0.09-0.60; p<0.01) Additional outcomes included: 30-day survival (11) and	**Summary/Conclusion Comment(s)** A multivariable logistic regression analysis suggested that administration of atropine (within 2 mg) following epinephrine, was an independent predictor of survival to hospital admission for adults with asystolic OHCA. Results for PEA weren't statistically significant (p=0.06). Limitations 1)Selection bias - the two most experienced emergency physicians have always routinely used atropine following epinephrine, & they could have contributed to the improved OR of ROSC with the addition of atropine. 2) Resuscitation time bias -both groups had a mean call-to-ER arrival interval of longer than 20 mins. Resuscitation outcomes might have been different if the drugs had been administered during

			Favourable neurological outcome at 30 days (Glasgow-Pittsburgh cerebral- performance category of 1 or 2). 11 patients survived to 30 days, including 1 with a favourable neurological outcome, but the sample size was too small to perform a binominal multivariate logistic regression analysis with this variable.	the circulatory phase (approx. 4-10 minutes after cardiac arrest). 3) Propensity score matching (the ideal statistical method) couldn't be used to assess the effect of the addition of atropine. 4) Termination of ACLS efforts was at the attending physician's discretion.
Study; Author; Year Published 3) Guideline Removal of Atropine and Survival after Adult In- Hospital Cardiac Arrest with a Non-Shockable Rhythm. Holmberg M.J, Moskowitz A, Wiberg S, Grossestreuer AV, Yankama T et al. Published 2019.	**Study Type/Design; Study Size (N)** Retrospective, observational study using data from 2006- 2015 from the Get With The Guidelines - Resuscitation registry (GWTG-R) of IHCA in the USA. An interrupted time-series analysis was used to compare survival before (pre-guidelines) & after (post-guidelines) introduction of the 2010 guidelines. A difference-in-difference approach was used to compare the interrupted time-series results between the non-shockable & shockable cohorts to try & account for potential changes in survival unrelated to guideline removal of atropine. Study looked at 20,499 non-shockable and 3,968 shockable cardiac arrests.	**Inclusion criteria:** Adults ≥ 18 years of age. IHCA & documented chest compressions for ≥ 2 mins. Use of atropine at any time during cardiac arrest (timing & dose not available in GWTG-R). **Exclusion criteria:** Visitors Hospital staff	**Primary Endpoint and Results (include P value; OR or RR; & 95% CI)** The ***primary outcome*** was survival to hospital discharge. For the non-shockable cohort, survival rate increased by 0.8% (95%CI: 0.3,1.3, p< 0.01) per yr in the pre-guidelines period & by 0.2% (95%CI: −0.4, 0.8, p = 0.56) per yr in the post-guidelines period (risk difference: −0.6% [95%CI: −1.4, 0.2]per yr, p = 0.14). The immediate change in survival after introducing the guidelines was 1.2% (95%CI: −0.9, 3.3, p = 0.27). For the shockable cohort, survival rate increased by 2.9% (95%CI: 1.1, 4.7,p< 0.01) per year in the pre-guidelines period & by 0.1% (95%CI: −1.6, 1.9, p = 0.89) per year in the post-guidelines period (risk difference −2.7% [95%CI: −5.3, −0.2]per yr, p = 0.04). The immediate change in survival after introducing the guidelines was −2.5% (95%CI: −8.4, 3.3, p = 0.40) The change over time in survival from the pre-guidelines to the post-guidelines period was not significantly different for the non-shockable compared to the shockable cohort (risk difference: 2.0% [95%CI: −0.8, 4.8] per year, p = 0.17) The immediate change in survival after introducing the guidelines was also not different between the cohorts(risk difference 3.5% [95%CI: −2.6, 9.7], p = 0.26). ***Secondary outcomes*** - ROSC & favourable functional outcome (CPC score of 1 or 2). The change over time in ***ROSC*** from pre- to post-guidelines period was not significantly different for the non-shockable compared to the shockable cohort (risk difference: 1.0% [95%CI: −1.4, 3.3] per yr, p = 0.43).	**Summary/Conclusion Comment(s)** The removal of atropine from the 2010 guidelines was not associated with a significant change in survival from IHCA **Limitations** -Study of only patients with IHCA. Study makes a number of assumptions: -No other intervention targeting only shockable or non-shockable rhythms was implemented near the same time as the 2010 guidelines, and adherence to the 2010 guidelines did not differ for non- shockable and shockable arrests. -The survival trend for patients with a non-shockable rhythm would have changed similar to patients with a shockable rhythm in the absence of guideline removal of atropine. -The difference-in-difference approach provides results with relatively large CIs, so study may have been underpowered to detect small differences in outcomes between the groups. -Although there was an attempt to create two

			The immediate change in ROSC between the pre- & post-guidelines period was also not significantly different for the two cohorts (risk difference:1.0% [95%CI: −5.0, 6.9], p = 0.75). Change over time in ***favorable functional outcome*** from pre- to post-guidelines period was not significantly different for the non-shockable compared to the shockable cohort (risk difference: 0.3% [95%CI: −2.8, 3.3] per yr, p = 0.87). The immediate change in favourable functional outcome between the pre- & post-guidelines period was also not significantly different for the two cohorts (risk difference: 5.0% [95%CI: −1.6, 11.5], p = 0.14).	distinct cohorts (non-shockable cardiac arrests with high propensity & shockable cardiac arrests with low propensity to receive atropine), there was some overlap in use of atropine which may have diluted any difference in survival between the non-shockable & shockable cohorts.

Reviewer Comments: ***(including whether this PICOST should have a systematic or scoping review*****)**

The literature search identified 3 observational studies relevant to the question of whether the use of atropine improves outcome after cardiac arrest. One of the studies was prospective and the other two were retrospective. Limitations to the prospective study (Nagao, 2011), are that it used guidelines from 2000, and there was a long time interval from onset of cardiac arrest to drug administration.

For the primary endpoint of favourable neurological outcome at 30 days after cardiac arrest (CPC score of 1 or 2),
for patients in asystole, in the multivariable logistic regression analysis, the adjusted OR (AOR) for epinephrine & atropine compared with epinephrine alone was 0.69 (95%CI 0.19– 2.48; P=0.571).

For the patients with PEA, in the multivariable logistic regression analysis the AOR after administration of epinephrine & atropine compared with epinephrine alone was 0.51 (95%CI 0.10–2.48; P=0.040) for 30-day favourable neurological outcome.

For the secondary outcomes of ROSC, survival to hospital admission, and survival at 30 days, results for patients with PEA all suggested that atropine in addition to epinephrine was associated with worse 30-day survival compared to epinephrine alone, however no difference was found in ROSC or survival to hospital admission.

For asystole, atropine was associated with an improvement in ROSC & survival to hospital admission that were both statistically significant, however no difference in survival at 30 days.

In the first of the retrospective studies (Yano et al), a multivariable logistic regression analysis suggested that administration of atropine (within 2 mg) following epinephrine, was an independent predictor of survival to hospital admission for adults with asystolic OHCA. Results for PEA weren't statistically significant (p=0.06).

The second of the retrospective studies (Holmberg et al) was the only study of IHCA. The results did not suggest a significant change in outcome from IHCA with the removal of atropine from the guidelines in 2010, with the outcomes addressed being survival to hospital discharge, ROSC, and survival with favourable functional outcome.

Reference list: ***(List by ILCOR ref standard (last name first author, year of publication, first page number) and insert hyperlink to all articles identified as relevant (if available on PubMed)***

1. SOS-KANTO Study Group: Nagao K, Yago T, Sakamoto T, Koseki K, Igarashi M et al. Atropine Sulfate for Patients With Out-of-Hospital Cardiac Arrest due to Asystole and Pulseless Electrical Activity. *Circ J* 2011; **75:** 580 – 588. doi: 10.1253/circj.cj-10-0485

2. Yano T, Kawana R, Yamauchi K, Endo G. and Yasuhiro Nagamine Y. The Additive Effect of Atropine Sulfate during Cardiopulmonary Resuscitation in Out- of-hospital Non-traumatic Cardiac Arrest Patients with Non-shockable Rhythm. American Journal Intern Med. 2019 Jun 15; 58(12): 1713–1721. doi: 10.2169/internalmedicine.1932-18

3. Holmberg M.J, Moskowitz A, Wiberg S, Grossestreuer A.V, Yankama T et al. Guideline Removal of Atropine and Survival after Adult In- Hospital Cardiac Arrest with a Non-Shockable Rhythm. *Resuscitation*. 2019 April ; 137: 69–77. doi:10.1016/j.resuscitation.2019.02.002.

Evidence Update Worksheet

Use of advanced airway during cardiac arrest
ALS 3300, 3301, 3302, 3303, 3304

Worksheet author(s): Ari Moskowitz, Luke Andrea
Task Force: ALS
Date Submitted to SAC rep for peer review and approval: Nov 3, 2023
SAC rep: Eric Lavonas

PICOST / Research Questions:

- Population: Adults with cardiac arrest from any cause and in any setting (in-hospital or out-of-hospital)
- Intervention: A specific advanced airway management method during cardiac arrest
- Comparator: A different advanced airway management method or no advanced airway management method during cardiac arrest
- Outcome: Resuscitation process metrics, airway process metrics, ROSC, survival, or survival with favorable neurological outcome at discharge/28 days or longer
- Study Type: Randomized and non-randomized clinical trials, sub-analysis of clinical trials, observational studies with a control group (e.g. cohort studies, case control studies). Additional details below.
- Timeline: January 9, 2019 to August 16, 2023

NOTE: This updated PICOST replaces prior **#3300, #3301, #3302, #3303, and #3304**

Year of last full review: SysRev 2018, EvUp 2019 (Search January 9th, 2019)

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:

We suggest using bag-mask ventilation or an advanced airway strategy during CPR for adult cardiac arrest in any setting (weak recommendation, low to moderate-certainty evidence).

If an advanced airway is used, we suggest a supraglottic airway for adults with out-of-hospital cardiac arrest in settings with a low tracheal intubation success rate (weak recommendation, low certainty of evidence).

If an advanced airway is used, we suggest a supraglottic airway or tracheal intubation for adults with out-of-hospital cardiac arrest in settings with a high tracheal intubation success rate (weak recommendation, very low certainty of evidence).

If an advanced airway is used, we suggest a supraglottic airway or tracheal intubation for adults with in-hospital cardiac arrest (weak recommendation, very low certainty of evidence).

Search strategy: (for a new PICOST should be outlined here as per Evidence Update Process)

Pubmed

(("airway management"[Mesh] OR "Intubation, Intratracheal"[Mesh] OR "airway device" [TIAB] OR "Laryngeal Masks"[Mesh] OR "airway"[TIAB] OR "intubation"[TIAB] OR "supraglottic"[TIAB] OR "Supraglottic airway" [TIAB] OR "SGA" [TIAB] OR "extraglottic" [TIAB] OR "laryngeal"[TIAB] OR

"perilaryngeal"[TIAB] OR "tracheal"[TIAB] OR "i-gel"[TIAB] OR "king tube"[TIAB] OR "Streamlined liner of the pharynx airway"[TIAB] OR "SLIPA"[TIAB] OR "baska"[TIAB] OR "3gLm"[TIAB] OR "cobra tube"[TIAB] OR "cobra LMA"[TIAB] OR "lma"[TIAB] OR "proseal"[TIAB] OR "ILMA"[TIAB] OR "bag-valve mask"[TIAB] OR "bag mask"[TIAB] OR "self inflating bag" OR "Ambu"[TIAB] OR "ambu bag"[TIAB]) AND ("heart arrest"[MESH] OR "cardiac arrest"[MESH] OR eCPR [TIAB] OR "return of spontaneous circulation"[TIAB] OR "ROSC"[TIAB] OR "cardiopulmonary resuscitation"[TIAB] OR "CPR"[TIAB] OR "cardiovascular arrest"[TIAB] OR "asystole"[TIAB] OR "pulseless electrical activity"[TIAB] OR "ventricular tachycardia"[TIAB] OR "ventricular fibrillation"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "Advanced cardiac life support"[TIAB] OR "ACLS"[TIAB] OR "heart massage"[TIAB] OR "out-of-hospital cardiac arrest" [TIAB] OR "in-hospital cardiac arrest" [TIAB] OR “OHCA” [TIAB] OR “IHCA” [TIAB] OR "cardiac massage"[TIAB] OR "chest compression"[TIAB]) NOT ("animals"[TIAB] OR "veterinary medicine"[MESH] OR “sleep” [TIAB] OR “apnea” [TIAB] OR "editorial"[pt] OR "Case Reports"[ptyp]))

Database searched: PubMed
Time Frame: Jan 9th 2010-August 16th, 2023
Date Search Completed: August 16th, 2023
Search Results (Number of articles identified and number identified as relevant):

Total abstracts: 1,041
Total relevant: 59
Total RCTs: 4
Total RCT sub-analysis: 9
Total Observational Studies: 46
Total Other: 0

Summary of Evidence Update:

For the purposes of this evidence update, the PICO will be separated into the following topic areas:

1) Basic vs. advanced airway management
2) Comparison of advanced airway devices (e.g. SGA vs. ETI, comparison of different SGAs)
3) Approach to endotracheal intubation
    a. Direct laryngoscopy vs. alternative endotracheal intubation approaches (e.g. video laryngoscopy)
4) Timing of advanced airway management

A breakdown of relevant studies by question is below:

Question Number	Observational	RCT	RCT sub-analysis	Other
1	13	0	4	0
2	21	2	4	0
3	6	2	0	0
4	6	0	1	0

For the first two topic airways, only data originating from randomized clinical trials (either as a primary analysis or as a secondary analysis of an existing clinical trial) or data from relevant guidelines/systematic reviews will be included in this evidence update. This decision was made as substantial evidence already exists in these topic areas from dedicated randomized clinical trials. Data from observational studies will not be included in this evidence update.

For the second two topics, we will include data from observational studies in addition to data from randomized trials.

After exclusion of observational studies for questions 1 and 2, twenty-five studies were included in full text review:

Question Number	Observational	RCT	RCT sub-analysis	Other
1	0	0	4	0
2	0	2	4	0
3	6	2	0	0
4	6	0	1	0

One additional study for Question #3 was identified outside of the original search and has been included.

Question 1: Basic vs. Advanced Airway Management

Randomized Control Trials					
Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population (inclusion/exclusion)**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
Cerecada-sanchez; 2021(1)	**Aim:** Compare BVM-only airway management to advanced airway management with an iGel SGA during adult, non-traumatic OHCA **Design:** Cluster-randomized trial; 4 BLS units with total n=23 OHCA	Adult OHCA **Inclusion criteria:** Attended to by one of the trained EMTs in the selected BLS units, non-traumatic cardiac arrest, aged >18 years, cardiac arrests assisted by BLS units initially, or cared for by BLS unit unable to perform advanced airway management. **Exclusion criteria:** 1) estimated weight <50 kg, 2) oral cavity opening <2 cm or trismus 3) already being treated by medical or healthcare professionals with advanced airway techniques 4) cardiac arrest due to airway obstruction 5) patients with Return of Spontaneous Circulation (ROSC) upon the arrival of the BLS team 6) obvious signs of death Only patients with capnographic data were analyzed	BVM (n=9) compared with SGA (n=14)	End-tidal CO2 was higher during resuscitation in patients treated with SGA as compared to BVM (mean values 16.3 (±7.1) mmHg in the control group and 27.4 (±15.5) mmHg in the SGA group, p<0.05).	First pass success rate for SGA was 92.9%. 2 instances of vomiting in the SGA group. None in the BVM group.
Malinverni; 2019(2)	**Aim:** Compare chest compression fraction in patients receiving BVM as compared to endotracheal intubation. **Design:** Post-hoc secondary analysis of a single center's data from the CAAM trial; Total N=112 OHCA	Adult OHCA enrolled in the CAAM trial, from a single center. **Inclusion Criteria:** Adult OHCA **Exclusion Criteria:** Suspected massive aspiration, DNR order, known pregnancy or imprisonment.	n=54 in BVM and n=58 in ETI	Chest compression fraction showed no difference overall between the two groups (Median with IQR with BVM vs ETI: 0.880 (0.836–0.902) vs 0.890 (0.850–0.920), p=0.19)	The no flow time associated with ventilation was higher in the BVM group compared to the ETI group (127.5 vs 32 s; p < 0.001)

Baekgaard; 2020(3)	**Aim:** Compare early onset pneumonia in patients receiving BVM as compared to endotracheal intubation. **Design:** Post-hoc secondary analysis from the CAAM trial; Total N=409 OHCA patients who survived to 12 hours	Adult OHCA patients enrolled in CAAM trial and survived to 12 hours. Additional inclusion/exclusion for CAAM trial above.	n=202 BVM and n=407 ETI	No difference in the occurrence of early onset pneumonia) BVM: 53%, ETI: 53%, Odds Ratio 1.0 [0.7-1.5], p = 1.0)	There were no differences between the two groups in terms of ICU length of stay, the incidence of septic or cardiogenic shock, or mechanical ventilator free-days or CPC 1–2 at 28 days. In-hospital mortality was also comparable (BVM: 77%; ETI: 80%, Odds Ratio 1.3 [0.8–2.0], p = 0.40)
Lupton; 2020(4)	**Aim:** To compare patients receiving any AAM to those receiving BVM onl. **Design:** Post-hoc secondary analysis of PART trial; N=2,567	OHCA patients enrolled in PART*. **Inclusion Criteria:** Adult, non-traumatic OHCA. **Exclusion Criteria:** Patient who received initial clinical care with EMS agencies capable of AAM but who were not part of the trial.	n=282 receiving BVM only, n=156 rescue BVM, and n=2,129 receiving some advanced airway	Compared to AAM, BVM-only patients had similar ROSC (odds ratio [OR] = 1.29, 95% confidence interval [CI] = 0.96 to 1.73), but higher 72-hour survival (OR = 1.96, 95% CI = 1.42 to 2.69), survival to discharge (OR = 4.47, 95% CI = 3.03 to 6.59), and neurologically intact survival (OR = 7.05, 95% CI = 4.40 to 11.3).	A secondary analysis of patients who received BVM as rescue after failed AAM revealed similar ROSC (OR = 0.73, 95% CI = 0.47 to 1.12) and 72-hour survival (OR = 1.08, 95% CI = 0.66 to 1.77) but higher survival to discharge (OR = 2.15, 95% CI = 1.17 to 3.95) and neurologically intact survival (OR = 2.64, 95% CI = 1.20 to 5.81) favoring BVM-rescue.

BVM= bag-valve mask; ETI = endotracheal intubation; SGA = supraglottic airway; AAM = advanced airway management

***PART inclusion criteria:** adult, nontraumatic, OHCA
PART exclusion criteria: known pregnancy, known prisoners, traumatic arrest etiology, major bleeding or exsanguination, advanced airway insertion prior to participating EMS agency arrival, and preexisting tracheostomy

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)

The literature searched identified one small randomized clinical trial and three post-hoc analyses of previously completed randomized control trials. As noted, observational studies were not reviewed for this question given the existence of large, randomized clinical trials.

The study by Cereceda-Sanchez et. al. was a cluster randomized clinical trial conducted among four basic life support units on the Island of Mallorca. Patients with out-of-hospital cardiac arrest were enrolled and cluster-randomized to receive bag-valve mask only or supraglottic airway placement with an i-Gel. A total of 23 patients were enrolled with 9 in the BVM only group and 14 in the i-Gel group. The primary outcome of end-tidal CO2 was higher in the i-Gel group. There was no statistically significant difference in clinical outcomes.

The remaining post-hoc analyses of completed randomized control trials add little to the comparison of BVM to advanced airway placement. Given their post-hoc nature, all of these studies carry substantial risk of confounding and bias.

Given the above, there is not sufficient new evidence to proceed to a systematic review for this question.

Question 2: Comparison of advanced airway devices (e.g. SGA vs. ETI, comparison of different SGAs)

Randomized Control Trials					
Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population (inclusion/exclusion)**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
PRINCESS; Tjerkaski; 2022(5)	**Aim:** Compare patients in the PRINCESS randomized trial who received intubation against those who received SGA. **Design:** Post-hoc secondary analysis of PRINCESS trial; N for the subanalysis = 328	Patients randomized to intervention arm of PRINCESS. **Inclusion:** Bystander witnessed, adult OHCA. **Exclusion:** Age >80 years, traumatic cardiac arrest, hypothermia at time of cardiac arrest, barrier to placing transnasal cooling catheters, existing DNR order, terminal illness, pregnancy, coagulopathy, need for home supplemental oxygen, EMS response time more than 15 minutes. Patients for whom airway data was missing and patients assigned to the cooling intervention but who did not receive it were excluded.	ETI group (n=259, 79%) and SGA group (n=63)	CPC 1-2 at 90 days (13.5% in SGA and 13.7% in ETI; OR 1.43, 95% CI 0.64–3.01)	No difference in survival at 90 days in ETI vs. SGA group (OR 1.26, 95% CI 0.57–2.55), survival with complete neurologic recovery at 90 days (OR 1.17, 95% CI 0.52–2.73) or hospital admission following sustained ROSC (OR 0.88, 95% CI 0.50–1.52). Faster time to airway in SGA group (8 minutes vs. 4 minutes, p<0.01). Numerous limitations, including biases introduced through selection of advanced airway approach.
SAVE; Lee; 2022(6)	**Aim:** Comparison of ETI to SGA. **Design:** Multicenter, cluster-randomized control trial; Total N=936	**Inclusion:** Nontraumatic OHCA; aged 20 years or older; treated by the participating emergency medical service agencies; required advanced airway management. **Exclusion**: (1) resuscitation deemed inappropriate (rigor mortis or livor mortis), (2) not suitable for ETI (ie, the inability to open the patient's mouth wide enough for laryngoscope insertion), (3) not suitable for SGA (eg, preexisting tracheostomy), (4) cardiac arrest during transportation to the hospital, (5) family's do-not-resuscitate request at the scene, (6) ROSC at the scene and no need for advanced airway support, and (7) airway devices (ETI or SGA) had been established before paramedics arrived.	n=517 ETI and n=419 SGA	Sustained ROSC (>2 hours) was 26.9% (139 of 517 patients) in the ETI group vs 25.8% (108 of 419 patients) in the SGA group. The OR of sustained ROSC was 1.02 (95% CI, 0.98-1.06) for the ETI group compared with the SGA group	The OR of the secondary outcome of prehospital ROSC was 1.04 (95% CI, 1.02-1.07) for the ETI group compared with the SGA group. Other secondary outcomes, including survival to hospital discharge (OR, 1.00; 95% CI, 0.94-1.06) and good neurological outcome (cerebral performance category score ≤2) (OR, 0.99; 95% CI, 0.94-1.03). Limitations: Exclusion of patients not receiving any advanced airway management may result in bias as SGAs are placed earlier in general. Relatively small sample size.

PART; Wang; 2021(7)	**Aim:** Compare CPR metrics in patients receiving SGA vs. ETI **Design:** Post-hoc secondary analysis of PART trial; N=1996 in subanalysis	Patients randomized in PART with CPR quality metrics available. PART inclusion and exclusion described previously.	n=1001 SGA and n=995 ETI	Mean CC fraction (SGA 88% vs. ETI 87%, p = 0.05)	CPR rate (SGA 114 vs. ETI 114 compressions per minute (cpm), p = 0.59) were similar between SGA and ETI. Median number of CC interruptions were: SGA 11 vs. ETI 12 (p = 0.001). Total CC interruption duration was lower for SGA than ETI (LT 160 vs. ETI 181 s, p = 0.002). Limitations: Post-hoc analysis. Nearly half of originally randomized patients without CPR metric data.
AIRWAYS 2; Benger; 2020(8)	**Aim:** Compare long-term cardiac arrest outcomes in patients randomized to ETI vs. SGA. **Design:** Sub-analysis of Airways 2 trial; N=9,296	Patients randomized as part of the AIRWAYS-2 trial. **Inclusion:** Adult, nontraumatic OHCA. **Exclusion**: Prisoner. Previously recruited into the trial. Advanced airway already in place. Small mouth opening.	Follow-up at 3 months: 300/396 (153/194 ETI, 147/202 SGA) Follow-up at 6 months 317/388 (159/190 ETI, 158/198 SGA)	No significant differences were found between the two treatment groups in the primary outcome measure (mRS score at 3 months: odds ratio for good recovery in SGA vs. ETI 0.89, 95% CI 0.69–1.14; 6 months OR 0.91, 95% CI 0.71–1.16).	No differences in Q-5D-5L scores at 3 and 6 month outcomes based on randomization group in the Airways-2 trial. Limitations: Not all patients agreed to follow-up.
PART; Wang; 2019(9)	**Aim:** Comparison of SGA vs. ETI. **Design:** Post-hoc Bayesian re-analysis of PART trial; Total N=3004	Patients randomized in PART trial. Inclusion and exclusion previously described.	SGA n=1505, ETI n=1499	Survival to 72-hours from the index arrest: SGA 275 (18.3%) vs ETI (15.4%). In Bayesian analysis with neutral prior distribution, SGA was better than intubation (risk difference 1.8% [95% credible interval –0.9% to 4.5%], posterior probability 91%)	All below comparisons are SGA vs. ETI. Bayesian neutral prior: - Hospital survival 1.4% [95% CrI –0.4% to 3.4%], posterior probability 93%; - Hospital survival with favorable neurologic status 0.7% [95% CrI –0.5% to 2.1%], posterior probability 86% Bayesian skeptical prior - 72-hour survival risk difference 1.7% [95% CrI –0.9% to 4.3%], posterior probability 89% - Hospital survival 1.3% [95% CrI –0.5% to 3.3%], posterior probability 91% - Hospital survival with favorable neurologic status risk difference (0.6% [95% CrI –0.5% to 2.0%], posterior probability 82%) Limitations: Same limitations as PART trial (low insertion success rate). Limitations of Bayesian analysis with prior distributions based on previous studies (mostly retrospective observational).
Paramedic 2; Deakin; 2021(10)	**Aim:** Compare resuscitation metrics between SGA vs. ETI. **Design:** Post-hoc secondary analysis of Paramedic 2 trial; n=286 in subanalysis	Patients randomized in PARAMEDIC 2 with CPR quality metrics available. **Inclusion:** Adult OHCA. **Exclusion:** Pregnancy. Anaphylaxis or asthma as cause of arrest. Epinephrine prior to EMS arrival.	n=67 SGA and n=78 ETI	Mean compression rate in first 5 minutes (106.9 (13.3) SGA vs 104.2 (16.2) ETI)	No difference in compression rate or fraction between SGA and ETI groups. Limitations: Post-hoc analysis in small cohort of those originally randomized.

OHCA = Out of hospital cardiac arrest ; ETI = Endotracheal Tube; CPC = Cerebral Performance Category; SGA = Supraglottic Airway; DNR = Do Not Resuscitate; EMS = Emergency Medical Services; ROSC = Return of Spontaneous Circulation; OR = Odds Ratio

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)

The literature for this question contains one randomized clinical trial, four post-hoc analyses of previously completed randomized clinical trials, and one analysis of long-term outcome data from a randomized clinical trial. The section did not include observational studies.

The SAVE trial by Lee et. al. was a multicenter cluster randomized clinical trial using emergency medical service agencies in Taiwan. Non-traumatic, out-of-hospital cardiac arrests were included and cluster-randomized to receive endotracheal intubation or supraglottic airway (iGel). They enrolled 936 total patients with 517 receiving ETI and 419 receiving SGA. There was no difference in the primary outcome of sustained ROSC (≥2 hours).

The long-term outcomes from the AIRWAYS-2 trial from Benger et. al. followed the initially randomized patients and showed no statistically significant difference in mRS at 3 or 6 months, but was limited as less than half of the patients who survived agreed to be followed up. The post-hoc secondary analyses of other randomized trials carried substantial risk of bias, contributing little to the comparison of ETI and SGA for advanced airway management in cardiac arrest.

Given the above, there is not sufficient new evidence to proceed to a systematic review for this question.

Question 3: Approach to endotracheal intubation

Randomized Control Trials					
Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population (inclusion/exclusion)**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
Kluj; 2023(11)	**Aim:** To compare two different direct laryngoscopy tools (intubrite vs. macintosh) **Design:** Randomized control trial enrolling 86 patients.	**Inclusion:** Adult OHCA enrolled between 2016 and 2020. **Exclusion:** traumatic arrest, primary use of SGA by the paramedics.	intubrite (42) compared with macintosh (44)	Mean time to first pass success 13.49 seconds with intubrite and 15.55 seconds with macintosh (mean difference of 2.05s for first pass success (p <0.05))	First pass success for intubrite 34/42 (80.9%) vs. 29/44 (64.4%) for macintosh, p=0.08. Limitations: 1) small sample size 2) lack of blinding 3) not clear how primary outcome was measured in patients without successful first pass
Szarpak; 2022(12)	**Aim:** To compare VieScope (direct laryngoscopy with bougie introducer) to direct laryngoscopy with macintosh blade. **Design:** Multicenter, randomized trial enrolling 90 patients	**Inclusion:** Adult OHCA patients with suspected or confirmed COVID-19. **Exclusion:** Patients where the treating team thought direct laryngoscopy would be impossible were excluded.	Vie Scope (45) compared with macintosh (45)	First intubation success rate 93.3% with Vie Scope vs 51.1% with macintosh, OR = 13.39; 95%CI: 3.62, 49.58; *p* = 0.001.	ETI time (time to success) was lower using the Vie Scope® laryngoscope compared with the Macintosh laryngoscope (49 ± 8.5 vs. 97 ± 41 s respectively; mean difference (MD) = −48.00; 95% confidence interval (CI): −60.23, −35.77; p < 0.001). Limitations include: 1) small sample size 2) nonblinded 3) risk of bias as exclusion criteria are subjective

Kim; 2016 (13)	**Aim:** To compare direct vs. video laryngoscopy. **Design:** Single center, randomized trial including 140 intubations in the ED	**Inclusion:** Adult IHCA or OHCA. Intubation performed by experienced airway manager. **Exclusions:** Traumatic arrest, patients wearing a cervical collar to protect a cervical injury, ETIs with data loss or poor quality of recording	Direct laryngoscopy vs. video laryngoscopy (GlideScope)	Intubation success as defined by no esophageal intubation and no change in operator (DL 92.8% vs.VL 95.8%; p = 0.490)	No difference between the DL and VL: estimated median time 51 (36–67) vs. 42 (34–62) s, respectively (p = 0.143). No difference in esophageal intubation. Longer duration of cardiac compression interruption was found during ETI using DL compared with VL (4.0 vs 0.0 s, respectively; p < 0.001) Limitations include: 1) small sample size 2) single center 3) A number of exclusions may result in bias (e.g. excluding patients who did not undergo intubation)

OHCA = out of hospital cardiac arrest; SGA = supraglottic airway

Observational Studies				
Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population (inclusion/exclusion)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Summary/Conclusion Comment(s)**
Risse; 2023(14)	**Aim:** Comparison of video laryngoscopy against direct laryngoscopy **Design:** Retrospective observational study using the German resuscitation registry; total N 14,387 patients	**Inclusion:** Adult OHCA who underwent ETI. **Exclusion:** Excluded traumatic arrest, use of supraglottic airway, death at scene without CPR.	CPC1/2 status among VL group patients [227/2201 (10.3%) compared with DL 987/12,186 (8.1%); p < 0.001, aOR = 1.34, 95% CI = 1.12–1.60]	OHCA patients undergoing ETI with VL were more likely to survive with good neurologic outcome than those undergoing ETI with DL. Biases may include that use of DL may reflect other resuscitation practices that may be associated with worse outcomes, differences in training for those certified to do DL vs. VL, patients with soiled airway may be more likely to undergo DL, there is no data on patients who did not undergo ETI--so any differences in timing of these two approaches is incompletely understood.
Santou; 2023(15)	**Aim:** Comparison of video laryngoscopy against direct laryngoscopy **Design:** Retrospective observational study using the Japanese national registry with a focus on Hiroshima prefecture; total N 885patients	**Inclusion:** Adult OHCA where an endotracheal tube was placed.	The success rate was 94.1% (490/521) in the VL group and 89.3%(325/364) in the DL group (RR, 1.05;95%CI, 1.01–1.10, P = 0.01).	OHCA patients undergoing ETI with VL were more likely to be successfully intubated than those for whom DL. was used. Biases may include that use of DL may reflect other resuscitation practices that may be associated with worse outcomes, differences in training for those certified to do DL vs. VL, patients with soiled airway may be more likely to undergo DL, there is no data on patients who did not undergo ETI--so any differences in timing of these two approaches is incompletely understood.

Okamoto; 2019(16)	**Aim:** Comparison of video laryngoscopy against direct laryngoscopy **Design:** Analysis of data from the prospective, multicenter, observational second Japanese Emergency Airway Network study (JEAN-2 study); Total N=3,360	**Inclusion:** Adult ED cardiac arrests who underwent ETI. **Exclusion:** Excluded for any intubation other than video laryngoscopy or direct laryngoscopy (example: fiberoptic), intubations where an adjunctive device was used (example: bougie).	First attempt success rate was 78% (480/613) in the VL group and 70% (1913/2747) in the DL group. OR for first attempt success rate with VL compared with DL 1.61 (95%CI 1.26–2.06; P < 0.001). Adjusted OR 1.33 (95%CI 1.03–1.73; P = 0.03).	ED patients undergoing ETI with VL were more likely to be successfully intubated on the first attempt. Biases may include indication/selection bias (they performed a propensity score sensitivity analysis), differences in unmeasured factors like the skill of intubators, and between hospital practice variations (used GEE to account for clustering). They do not have information on timing, or information for those who did not receive intubation, so there is possible resuscitation time bias.
Huebinger; 2020(17)	**Aim:** Comparison of video laryngoscopy against direct laryngoscopy **Design:** Retrospective observational study using the ESO pre-hospital database; total N 22,132 patients	**Inclusion:** Adult OHCA **Exclusion:** Excluded patients with 1) intubation using other approaches besides DL or VL 2) IHCA 3) key missing data	VL FPS was higher than DL (75.7% vs. 69.5%, difference of 6.3%; 95% CI 4.97.6%, p < 0.001), and overall success rate for VL was higher than DL (80.8% v 73.1%, difference of 7.7%; 95% CI 6.4% 9.0%, p < 0.001). Utilizing a mixed model analysis, we found that VL was associated with increased odds of first pass success (aOR 1.5, 95% CI 1.31.6) as well as overall intubation success (aOR 1.6, 95% CI 1.41.7), compared with DL. VL used on first attempt was not associated with increased rate of ROSC (aOR 1.0, 95% CI 0.91.1) or sustained ROSC (aOR 1.0, 95% CI 0.91.1) compared with DL. Additionally, overall VL use was not associated with increased odds of ROSC (aOR 1.0, 95% CI 0.991.1) or sustained ROSC (aOR 1.0, 95% CI 0.91.1) compared with DL.	OHCA patients intubated using VL had higher FPS, but no difference in rates of ROSC. Biases may include that use of DL may reflect other resuscitation practices that may be associated with worse outcomes, differences in training for those certified to do DL vs. VL, patients with soiled airway may be more likely to undergo DL, there is no data on patients who did not undergo ETI--so any differences in timing of these two approaches is incompletely understood.
Bonnette; 2020(18)	**Aim:** Compare bougie assisted with non-bougie assisted intubation during cardiac arrest. **Design:** Subanalysis of the PART trial--only including those who underwent ETI; total N=1,227 included in this subanalysis	Patients enrolled in PART who underwent endotracheal intubation	First-pass ETI success did not differ between Bougie-assisted and non-Bougie ETI (53.1% vs. 42.8%; adjusted OR 1.12, 95% CI: 0.97-1.39). ETI overall success was slightly higher in the Bougie-assisted group (56.2% vs. 49.1%; adjusted OR 1.19, 95% CI: 1.01-1.32). Time to endotracheal tube placement or abandonment was longer for Bougie-assisted than non-Bougie ETI (median 13 vs. 11 min; adjusted HR 0.63, 95% CI: 0.45-0.90). While survival to hospital discharge was lower for Bougie-assisted than non-Bougie ETI (3.6% vs. 7.5%; adjusted OR 0.94, 95% CI: 0.92-0.96), there were no differences in ROSC, 72-h survival or hospital survival or hospital survival with favorable neurologic status.	Use of bougie was associated with slightly higher ETI success, but longer airway placement times and possibly lower survival. Efforts were made to control for various factors including clustering by site and demographics. Confounding by indication may have still biased the results.
Risse; 2020(19)	**Aim:** Comparison of video laryngoscopy against direct laryngoscopy	Patients undergoing non-traumatic OHCA resuscitation with BLS	In the group using VL, 82% rated visualization of the glottis as CL 1&2 versus 55% in the DL group (p = 0.02). Despite better visualization of the larynx, there was no statistically significant difference in successful ETI	Video laryngoscopy resulted in better glottic views. There was better first pass success in the video laryngoscopy group, but this did not reach statistical significance.

	Design: Propspective observational cohort study among 32 paramedics at a single center. EMS personnel on a vehicle equipped with video laryngoscope were asked to use it as first choice: N=97		between VL and DL (GVL 75% vs. DL 68.1%, *p* = 0.63).	

OHCA = out of hospital cardiac arrest; ETI = endotracheal intubation; CPR = cardiopulmonary resuscitation; CPC = cerebral performance category; aOR = adjusted odds ratio; DL = direct laryngoscopy; VL = video laryngoscopy; FPS = first pass success; GEE = generalized estimating equation

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)

The literature review for this question identified six observational studies and three randomized clinical trials.

The observational studies generally explored the comparison between video and direct laryngoscopy during cardiac arrest. Across all five observational studies focused on this question, video laryngoscopy was either superior or neutral for a range of outcome extending from glottic view to hospital survival. All of the observational studies were potentially confounded by indication bias and selection bias, thus should only be considered hypothesis generating. One study, a subanalysis of the PART trial including patients who underwent endotracheal intubation, found that use of bougie was associated with higher overall resuscitation success but longer airway placement times and possibly lower survival.

Two of the randomized trials compared proprietary laryngoscopy tools against direct laryngoscopy in small cohorts. In general, findings favored the proprietary tools over direct laryngoscopy. In one trial at a single center, there was no difference in the primary outcome of intubation success comparing direct and video laryngoscopy when used by experienced operators. Patients who were intubated with direct laryngoscopy had longer overall pause durations as compared to video laryngoscopy.

Given the above, there is sufficient new evidence to proceed to a systematic review for this question.

Question 4: Timing of advanced airway management

Randomized Control Trials					
Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population (inclusion/exclusion**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**

PART; Okubo; 2022(20)	**Aim:** Compare ETI placement to no advanced airway placement, and compare laryngeal tube placement to no advanced airway placement during adult, nontraumatic OHCA. **Design:** Post-hoc secondary analysis from the PART trial; Total N=2,146	OHCA patients enrolled in PART. **Exclusions:** patients with EMS-witnessed out-of-hospital cardiac arrest, unknown age, unknown time of advanced life support EMS arrival, unknown time of the first laryngeal tube or endotracheal intubation attempt, negative value in an interval between advanced life support arrival and time of the first laryngeal tube or endotracheal intubation attempt, unknown time of time-dependent covariates (shock delivery after advanced life support arrival, epinephrine administration, and departure from the scene), negative values in intervals between advanced life support arrival and the time-dependent covariates, or unknown survival to hospital discharge status	923 laryngeal tube compared to 923 matched at risk patients A laryngeal tube is a specific type of SGA that was used during the PART trial. 776 ETI compared to 766 matched at risk patients	Timing of laryngeal tube insertion attempt was not associated with survival to hospital discharge: 0 to lesser than 5 minutes (RR=1.35, 95% CI 0.53 to 3.44); 5 to lesser than 10 minutes (RR=1.07, 95% CI 0.66 to 1.73); 10 to lesser than 15 minutes (RR=1.17, 95% CI 0.60 to 2.31); or 15 to lesser than 20 minutes (RR=2.09, 95% CI 0.35 to 12.47) after advanced life support arrival. Timing of ETI was also not associated with survival to hospital discharge: 0 to lesser than 5 minutes (RR=0.50, 95% CI 0.05 to 4.87); 5 to lesser than10 minutes (RR=1.20, 95% CI 0.51 to 2.81); 10 to lesser than15 minutes (RR=1.03, 95% CI 0.49 to 2.14); 15 to lesser than 20 minutes (RR=0.85, 95% CI 0.30 to 2.42); or more than/equal to 20 minutes (RR=0.71, 95% CI 0.07 to 7.14).	**Relative secondary endpoints:** Timing of laryngeal insertion and timing of ETI insertion were not associated with neurologic outcomes at hospital discharge or 72-hour survival. **Study limitations:** Limited by post-hoc nature of the study design and introduction of selection bias.

ETI = endotracheal intubation; SGA = supraglottic airway; OHCA = out-of-hospital cardiac arrest; EMS = emergency medical services

Observational Studies				
Author; Year Published	**Study aim; Study design; Study Size (N)**	**Patient Population (inclusion/exclusion)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Summary/Conclusion Comment(s)**
Nakagawa; 2022(21)	**Aim:** To evaluate the association between the timing of advanced airway management and neurological outcomes. Time considered on a linear scale of 1-minute increments. **Design:** Retrospective observational study using the Japanese national registry; Total N=182,913.	Patient population was OHCA who underwent advanced airway management (SGA or ETI). **Inclusion:** OHCA, underwent advanced airway management. **Exclusion:** age < 8 years, age ≥ 118 years, unknown initial electrocardiogram rhythm, missing time variables and negative or outlying data (emergency call-to-patient contact interval > 30 min, patient contact-to-hospital arrival interval > 90 min, patient contact-to-advanced airway management performance >30 min), patients who achieved a return of spontaneous circulation before EMS contact	Shockable initial rhythms: 1-minute unit increases in time from patient contact to the initiation of advanced airway management with an SGA or ETI were negatively associated with CPC 1–2 at one month (aOR, 0.92; 95% CI, 0.90–0.93). Non-shockable initial rhythms: 1-minute unit increases in time from patient contact to the initiation of advanced airway management with an SGA or ETI were negatively associated with CPC 1–2 at one month (AOR, 0.96; 95% CI, 0.95–0.96).	Increases in time from patient contact to the initiation of advanced airway management was associated with worse neurologic outcomes. Hypothesis generating only, and subject to a number of biases (eg resus time bias). Note that delays in airway management may reflect delays in other elements of care as well.
Daorattanachai; 2021(22)	**Aim:** To compare survival to hospital discharge (and neurologically favorable survival) between early (≤2min) and late (>2min) endotracheal intubation for cardiac arrest in the ED. **Design:** Retrospective observational study in a single emergency department; Total N=416.	Patient population was adult ED cardiac arrests with non-shockable rhythms that had been intubated. **Inclusion:** adult patients ≥18 years old, cardiac arrest in the emergency department, an initial non-shockable rhythm, intubated during CPR. **Exclusion:** do not attempt resuscitation order, intubation prior to cardiac arrest, out of hospital intubation, no advanced airway placed during the arrest, referral of patient to a different hospital after resuscitation, missing data on advanced airway.	Survival to discharge occurred in 23 (11.00%) of those who were intubated early (≤2 minutes after the start of chest compressions) and 14 (6.80%) of those who were intubated late (>2 minutes after the start of chest compressions) (p = 0.168). When adjusted for potential confounders, AOR = 1.28; 95% CI, 0.59–2.76. Discharge with favorable neurologic function (CPC of 1-2) occurred in 13 (6.25%) of those who were intubated early and 6 (2.91%) of those who were intubated late (p = 0.157). When adjusted for potential confounders, AOR = 1.68; 95% CI, 0.52–5.45. ROSC occurred in 106 (50.72%) of those who were intubated early and 98 (47.34%) of those who were intubated late (p = 0.094).	No difference in survival between early (≤2 minutes after the start of chest compressions) and late (>2 minutes after the start of chest compressions) intubation during cardiac arrest with non-shockable rhythms in the ED Limitations: Numerous potential biases, including resuscitation time bias. Small sample size from a single center.

Okubo; 2022(23)	**Aim:** To evaluate the association between the timing of prehospital advanced airway management and 1-month survival. **Design:** Retrospective observational study using the Japanese national registry; Total N=424,260 Ultimately analyzed 175,102 who received an advanced airway.	Patient population was adult OHCA who underwent advanced airway management. **Inclusion:** age ≥18, cardiac arrest before EMS arrival, cardiac arrest for which EMS providers attempted resuscitation, cardiac arrest attended by an emergency life-saving technician. **Exclusion:** age outliers (≥120 years), unknown initial rhythms, inappropriate resuscitation interval variables, unknown time-dependent or time-independent covariates [interval between initiation of CPR by EMS providers and successful placement of advanced airway device for those who received an advanced airway, interval between initiation of EMS CPR and first shock delivery by EMS providers for those with shockable rhythms, interval between initiation of EMS CPR and epinephrine administration by EMS providers for those who received epinephrine, interval between initiation of EMS CPR and prehospital ROSC for those who had prehospital ROSC, interval between emergency call and initiation of EMS CPR, and interval between initiation of EMS CPR and hospital arrival], and if the interval between emergency call to initiation of EMS was CPR ≥30 minutes.	Advanced airway placement within the first 15 minutes was associated with better 1-month survival for nonshockable rhythms. No statistically significant association for shockable rhythms. Shockable rhythms; risk ratios and 95% confidence intervals of 1-month survival for advanced airway placement as compared to no advanced airway placement: ▪ 1.01 (0.89–1.15) between 0 and 5 minutes ▪ 1.06 (0.98–1.15) between 5 and 10 minutes ▪ 0.99 (0.87–1.12) between 10 and 15 minutes ▪ 0.74 (0.59–0.92) between 15 and 20 minutes ▪ 0.61 (0.37–1.00) between 20 and 25 minutes ▪ 0.73 (0.26–2.07) between 25 and 30 minutes Nonshockable rhythms; risk ratios and 95% confidence intervals of 1-month survival for advanced airway placement as compared to no advanced airway placement: ▪ 1.12 (1.00–1.27) between 0 and 5 minutes ▪ 1.34 (1.25–1.44) between 5 and 10 minutes ▪ 1.39 (1.26–1.54) between 10 and 15 minutes ▪ 1.20 (0.99–1.45) between 15 and 20 minutes ▪ 1.18 (0.80–1.73) between 20 and 25 minutes ▪ 0.63 (0.29–1.38) between 25 and 30 minutes ▪ 0.44 (0.11–1.69) after 30 minutes Association was not seen on the outcome of neurologically favorable survival (CPC 1-2) for either rhythm.	Improved survival to 1 month with advanced airway management within the first 15 minutes of the arrest compared to those who did not receive advanced airway management. The association was not seen after 15 minutes. No impact on neurologic outcomes, or for patients with shockable rhythms. Limitations: Well done observational study, using risk-set matching within specified time periods to reduce resuscitation time bias.

Fukuda; 2021(24)	**Aim:** To determine if time to advanced airway management is associated with outcomes after OHCA. **Design:** Retrospective observational study using the Japanese national registry; Total N=164,223	Patient population was adult OHCA. **Inclusion:** age ≥18 years, OHCA who underwent advanced airway management by EMS in the prehospital setting. **Exclusion:** cardiac arrest witnessed by EMS personnel, patients for whom physicians were involved in prehospital ALS, patients who received advanced airway management before emergency call or EMS contact, patients who received advanced airway management after ROSC or hospital arrival, patients who did not receive timely in-hospital treatment (i.e., transport time > 60 min), and patients with missing, incomplete, or inconsistent data.	Each 1-minute unit increase in time from the emergency call (ie. each minute in delay) to successful advanced airway placement (with SGA, ETI, or laryngeal tube) was associated with worse neurologic outcomes (AOR for CPC 1-2 at 1-month, 0.90; 95% CI, 0.90–0.91), worse 1-month overall survival (AOR for survival at 1-month, 0.92; 95% CI, 0.92–0.93) and worse prehospital ROSC (AOR for prehospital ROSC , 0.96; 95% CI, 0.96–0.97).	Increased time from emergency call to advanced airway placement (SGA, ETI, or laryngeal tube) resulted in decreased neurologically favorable 1-month survival, overall 1-month survival, and prehospital ROSC. Limitations: Well done observational study, using risk-set matching to avoid resuscitation time bias. Exclusion of patients not receiving AAM from the primary analysis is a limitation.
Nakagawa, 2021(25)	**Aim:** Evaluate the association between time to ETI placement and neurologic outcomes at 1 month. **Design:** Retrospective observational study using the Japanese national registry; Total N=14,969	Patient population was OHCA aged 15 years or older. **Inclusion:** age 15 years or older, witnessed by laypersons, ETI undertaken in the prehospital setting. **Exclusion:** unknown initial rhythm, missing or negative or outlying (>99th percentile) time values.	Shockable initial rhythm (n=1,102): Each 1-minute unit increase in time from patient contact to ETI placement (ie. each minute in delay) was associated with worse neurologic outcomes (AOR for CPC 1-2 at 1-month, 0.91; 95% CI, 0.86–0.96) and ROSC (AOR for ROSC, 0.90; 95% CI, 0.87–0.93). Non-shockable initial rhythm (n=13,867): Each 1-minute unit increase in time from patient contact to ETI placement (ie. each minute in delay) was associated with worse neurologic outcomes (AOR for CPC 1-2 at 1-month, 0.92; 95% CI, 0.89–0.96) and ROSC (AOR, 0.91; 95% CI, 0.90–0.92).	Increased time from patient contact to ETI placement resulted in decreased neurologically favorable 1-month survival and ROSC. Limitations: No attempt to manage resuscitation time bias.
Benoit, 2019(26)	**Aim:** Identify the association between the timing of prehospital advanced airway placement and the minute to minute of achieving ROSC. **Design:** Observational cohort study using data from the Resuscitation Outcomes	Patient population was adult, non-traumatic OHCA (patients enrolled in PRIMED). **PRIMED inclusion criteria:** adults ≥18 years old with nontraumatic, OHCA being treated by EMS **PRIMED exclusion criteria:** incarcerated patients, pregnant patients, known DNR order, arrest due to exsanguination or severe burns, existing tracheostomy, use of mechanical CPR device other than the impedance threshold	A statistically significant negative association between the time to advanced airway placement and the hazard of ROSC was observed, such that increasing intervals between EMS arrival and airway placement were associated with decreasing probabilities of ROSC. Model results are shown in figures with continuous hazard ratios and associated 95% confidence intervals; the time from EMS arrival to advanced airway placement is presented as a continuous exposure variable.	Earlier EMS advanced airway placement is associated with increased probability of ROSC. Limitations: Excluded those who were never exposed (never received an advanced airway) opens risk of selection bias. There is also resuscitation time bias since short arrests with no advanced airway would be excluded. Strict inclusion criteria limit generalizability.

	Consortium (ROC) Prehospital Resuscitation using an Impedance Valve and Early versus Delayed (PRIMED) trial; Total N=7,547	device being tested in the trial. **Additional study inclusion:** all patients who received ETI or placement of a SGA by EMS, including patients enrolled during the run-in period of the original trial. **Additional study exclusion:** unwitnessed arrests, EMS witnessed arrests, and patients who had an advanced airway placed after ROSC.		

ETI = endotracheal intubation; SGA = supraglottic airway; OHCA = out-of-hospital cardiac arrest; EMS = emergency medical services; ROSC = return of spontaneous circulation; CPC = cerebral performance category; AAM = advanced airway management; CPR = cardiopulmonary resuscitation

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)

The literature review for this question identified six observational studies and one post-hoc analysis of a randomized clinical trial.

The observational studies focused on the out-of-hospital population (only one study differed, examining arrests in the emergency department), with results that favored early advanced airway management. Outcomes, which included survival, neurologically favorable survival, and return of spontaneous circulation, all either favored earlier advanced airway or were neutral. All of these observational studies are at risk of selection bias due to limiting the inclusion criteria to those who received an advanced airway. One study performed risk set-matching, but all others did not account for resuscitation time bias.

In the post-hoc analysis using data from the randomized PART trial, timing of advanced airway placement was not associated with survival for either laryngeal tube (a type of supraglottic airway) or endotracheal tube placement.

There is not sufficient new evidence for a systematic review on the topic of this question.

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Evidence Update Worksheet

CPR-related cognitive activity, consciousness, awareness and recall and its management
ALS 3004

Worksheet author(s): Rebecca L West, Jasmeet Soar, Sarah Rudd, Wolfgang Wetsch, Bernd Böttiger

[Updated search by Sarah Rudd Librarian/Information Specialist, Bristol UK].

No COIs

Task Force: ALS
Date Submitted to SAC rep for peer review and approval:
SAC rep:

PICOST / Research Question:

The PICOST (Population, Intervention, Comparator, Outcome, Study Designs and Timeframe)

Population: Adults in any setting with consciousness during CPR

Intervention: **Sedation, analgesia, or other intervention to prevent consciousness**

Comparators: No specific intervention for consciousness

Outcomes: Any clinical outcome. Arrest outcomes and psychological wellbeing post arrest

Other relevant outcomes identified from the review where included such as rescuer outcomes including, rescuer distress, and trauma.

Study Designs: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were all eligible for inclusion. For the purpose of the scoping review, we also included Case reports and case series, Grey literature and unpublished studies (e.g., conference abstracts, trial protocols). Articles based around the Lazarus phenomenon and cough CPR as well as narrative articles referring to near death experiences and consciousness were excluded but noted for discussion.

Timeframe: All languages were included providing an English title or abstract was given. Search between 26 January 2020 up to 21 September 2023

Year of last full review: 2021

Published scoping review:

West RL, Otto Q, Drennan IR, Rudd S, Böttiger BW, Parnia S, Soar J. CPR-related cognitive activity, consciousness, awareness and recall, and its management: A scoping review. Resusc Plus. 2022 May 9;10:100241. doi: 10.1016/j.resplu.2022.100241. PMID: 35586308; PMCID: PMC9108988.

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:

CoSTR 2021 summary:

'This is a new topic, and there is insufficient evidence to warrant progressing to a Systems Review of interventions for CPR-induced consciousness. Given the interest in this topic, the task force considered the available evidence and made the following good practice statements: In settings in which it is feasible, rescuers may consider using sedative or analgesic drugs (or both) in very small doses to prevent pain and distress to patients who are conscious during CPR (good practice statement). Neuromuscular-blocking drugs alone should not be given to conscious patients (good practice statement). The optimal drug regimen for sedation and analgesia during CPR is uncertain. Regimens can be based on those used in critically ill patients and according to local protocols (good practice statement).'

Current Search Strategy: CPR terms: Awareness; Consciousness; Recall

Search used in previous review:

'We searched Medline, Embase, EMcare and CINAHL (via EBSCO) from inception to 26 Nov 2020 with a repeat search conducted on 21 October 2021. Search filters were used to limit to adults and humans. We also screened reference lists of included papers. Grey literature (including local protocols) was identified by asking ILCOR colleagues to share articles, no specific separate additional search for grey literature was conducted.'

((((“awareness”[MeSH Terms] OR
“awareness”[All Fields]) AND (“cardiopulmonary
resuscitation” [MeSH Terms]
OR (“cardiopulmonary” [All Fields] AND
“resuscitation”[All Fields]) OR “cardiopulmonary
resuscitation”[All Fields] OR
“cpr”[All Fields])) OR (“awareness”[MeSH
Terms] OR “awareness”[All Fields])) OR
((“awareness”[MeSH Terms] OR “awareness”[
All Fields]) AND (“cardiopulmonary
resuscitation”[MeSH Terms] OR (“cardiopulmonary”[
All Fields] AND “resuscitation”[
All Fields]) OR “cardiopulmonary
resuscitation”[All Fields]))) AND ((((“heart
massage”[MeSH Terms] OR (“heart”[All
Fields] AND “massage”[All Fields])
OR “heart massage”[All Fields]) OR
((“heart”[MeSH Terms] OR “heart”[All
Fields] OR “cardiac”[All Fields]) AND
compression[All Fields])) OR ((“heart
arrest”[MeSH Terms] OR (“heart”[All
Fields] AND “arrest”[All Fields]) OR
“heart arrest”[(All Fields]) OR (“cardiopulmonary
resuscitation”[MeSH Terms]
OR (“cardiopulmonary”[All Fields]
AND “resuscitation”[All Fields]) OR
“cardiopulmonary resuscitation”[ll Fields]
OR “cpr”[All Fields]))) OR (“cardiopulmonary
resuscitation”[MeSH Terms] OR
(“cardiopulmonary”[All Fields] AND
“resuscitation”[All Fields]) OR “cardiopulmonary
resuscitation”[All Fields])).

New updated search strategy:
CPR terms; Awareness; Consciousness; Recall

((((“awareness”[MeSH Terms] OR
“awareness”[All Fields]) AND (“cardiopulmonary
resuscitation” [MeSH Terms]
OR (“cardiopulmonary” [All Fields] AND
“resuscitation”[All Fields]) OR “cardiopulmonary
resuscitation”[All Fields] OR
“cpr”[All Fields])) OR (“awareness”[MeSH
Terms] OR “awareness”[All Fields])) OR
((“awareness”[MeSH Terms] OR “awareness”[
All Fields]) AND (“cardiopulmonary
resuscitation”[MeSH Terms] OR (“cardiopulmonary”[
All Fields] AND “resuscitation”[
All Fields]) OR “cardiopulmonary
resuscitation”[All Fields]))) AND ((((“heart
massage”[MeSH Terms] OR (“heart”[All
Fields] AND “massage”[All Fields])
OR “heart massage”[All Fields]) OR
((“heart”[MeSH Terms] OR “heart”[All
Fields] OR “cardiac”[All Fields]) AND
compression[All Fields])) OR ((“heart
arrest”[MeSH Terms] OR (“heart”[All
Fields] AND “arrest”[All Fields]) OR
“heart arrest”[(All Fields]) OR (“cardiopulmonary
resuscitation”[MeSH Terms]
OR (“cardiopulmonary”[All Fields]
AND “resuscitation”[All Fields]) OR
“cardiopulmonary resuscitation”[ll Fields]
OR “cpr”[All Fields]))) OR (“cardiopulmonary
resuscitation”[MeSH Terms] OR
(“cardiopulmonary”[All Fields] AND
“resuscitation”[All Fields]) OR “cardiopulmonary
resuscitation”[All Fields])).

Database searched: Medline, Embase, CINAHL
Time Frame: All years and all languages were included as long as there is an English abstract

Time Frame: (new PICOST) – New literature from the 26/1/2020 to present **Date Search Completed:** 21/09/2023.

Search Results: 747 returned, 594 after duplicates, 19 relevant studies identified, 4 excluded due to being a part of the previous scoping review.

15 new papers since the previous scoping review were identified (these 15 included the 2021 CoSTR summary[3] paper).
One further expert guideline paper was identified during reading of papers[15].

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews (n=4):

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	No. of articles identified	Key findings	Treatment recommendations
Dąbrowski (2023)[1]. Analgesic use in patients during cardiopulmonary resuscitation.	Rapid review	1.How often does the return of consciousness occur during CPR? 2.What is the incidence of chest injuries in patients during CPR? 3.What painkillers and sedatives are used to improve treatment?	**32**	Only a small number of studies made it difficult to assess prevalence. More studies dealing with chest trauma during resuscitation, but no study considered use of analgesia. No standardized therapeutic approach for the use of analgesia / sedatives however local protocols exists.	With the incidence of rib / sternal fractures being significant there seems to be a need for systematic diagnostic imaging post resuscitation. No generally accepted guidelines for analgesia / sedation during resuscitation however local protocols commonly use Ketamine, Fentanyl and midazolam.
West (2022)[2]. CPR-related cognitive activity, consciousness, awareness and recall, and its management: A scoping review [A summary of this Scop Rev is included in the 2021 ILCOR Summary CoSTR publication][3]	Scoping Review	Care of patients who are conscious or aware during CPR.	8 observational studies and 26 case reports	Two types of cogitative awareness identified: 1)Visible signs of consciousness, 2)perception of lucidity. Prevalence varied between 0.23-0.9% of resuscitation with 48-59% of rescuers reporting some experience of it . CPRIC was associated with professional rescuers, shock-able rhythm, witnessed arrest and held a higher incidence of ROSC and survival to discharge. Few studies on the use of analgesia / sedation but it use did not appear to reduce development in PTSD in survivors.	Little evidence but ILCOR good practice released: In settings in which it is feasible, rescuers may consider using sedative or analgesic drugs (or both) in very small doses to prevent pain and distress to patients who are conscious during CPR (good practice statement). Neuromuscular-blocking drugs alone should not be given to conscious patients (good practice statement). The optimal drug regimen for sedation and

					analgesia during CPR is uncertain. Regimens can be based on those used in critically ill patients and according to local protocols.
Howard (2022)[4]. Pre-hospital guidelines for CPR induced consciousness: Scoping review.	Scoping review	Identify prehospital CPRIC guidelines and compare them, highlighting common pharmacological management trends, and discuss the factors that might impact CPRIC guidelines, and the management trends identified.	23 pre-hospital guidelines and 1 good practice statement	20 different ways to treat CPRIC identified. Midazolam most frequently used (61%), with doses varying from 1mg - 2.5md IV (2mg - 10mg IM) followed by Ketamine (48%) in doses varying from 10mg - 200mg IV and Fentanyl (39%)in doses varying from 25mcg - 100mcg IV.	Recommendation that future research be focused on development of a consensus management statement.
Parnia (2022)[5]. Guidelines and standards for the study of death and recalled experiences of death—a multidisciplinary consensus statement and proposed future direction:	Guideline	Establish current knowledge regarding death, consciousness and the recalled experience of death (RED)and to propose an appropriate definition and framework for the study of RED.	NA	Many different experiences currently labelled under the term near death experiences. New classification suggests reported experiences must include 6 components: relation with death, sense of transcendence, ineffability, positive transformative effects, severity of illness that leads to LOC, absence of other coma related experiences. These new experienced are proposed to be called RED - Recalled experience of death. RED is defined as a specific cognitive experience occurring during a period of LOC in relation to a life-threatening	The literature that cites NDEs can now be divided into the following 3 categories:(1) classical - original experience described in 1975. (2) authentic - classical NDE but with the addition of newer categories and themes that have been discovered since 1975 and (3) mislabelled NDEs - heterogeneous group of experiences that have no relation to death or life-threatening illness but have also been labelled NDE. The term RED should be used instead of NDE in relation to the study of

				event, including cardiac arrest	experiences in relation to death

RCT: No RCTs were identified

Nonrandomized Trials, Observational Studies (n=5):

Study Acronym; Author; Year Published	**Study Type/Design; Study Size (N)**	**Patient Population**	**Primary Endpoint and Results (include P value; OR or RR; & 95% CI)**	**Summary/Conclusion Comment(s)**
Jaffe (2021)[6]. Psychological outcomes and awareness during CPR in cardiac arrest survivors.	Case control study N=116	Cardiac arrest survivors form Cardiac arrest registry or from NYU Langone medical center (New York)	GAD-7, PHQ-9 and SSS PTSD used to assess psychological outcomes. CPRIC assessed using reported memories and awareness. Assessment of timeline then made. Cardiac arrest survivors with awareness showed higher rates of sever to moderate depression than those without awareness (50% Vs 30.6% P=0.049) and higher rates of PTSD (43.2% Vs 27.8% P=0.107) but no difference in sever anxiety.	Cardiac arrest survivors may experience depression, anxiety and PTSD. Mechanism is unclear, but there may be a relationship between memories / awareness and negative psychological outcomes.
Gregory (2021)[7] An exploration of UK paramedics' experiences of cardiopulmonary resuscitation induced consciousness.	Mixed method, cross sectional survey N=293	Paramedics registered with HPCP and working in the UK at the time of the survey.	57% stated witnessing CPRIC. 50% of those cases witnessed CPRIC was said to have interfered with resuscitation on first experience of it but fell to 31% by the third experience of it. Most common reasons for interference were patient resisting clinical interventions, increased rhythm and pulse checks, distress, confusion and reluctance to perform CPR.	CPRIC incidence similar to other studies. Interference may be related to clinician exposure rather than any specific characteristic.
Carty (2022)[8]. Pre-hospital practitioner awareness and	Cross sectional study	Emergency medical technicians, Paramedics, advanced paramedics	93% of respondents involved in at least one OHCA. 57% of those admitted to witnessing	Many practitioners had personal experience with CPRIC with a wide range of reported manifestations. In some cases it

experience of CPR induced consciousness.	N=232 responding to survey N=7 interviewed		CPRIC. Most common initial rhythm was VF or pulseless VT. 65% of those who had witnessed CPRIC stated compression were interrupted at least once due to CPRIC. 88% of cases showing signs of CPRIC transported to ED and 63% of those had achieved ROSC.	resulted in interruptions to CPR. There was an apparent link between CPRIC and higher levels of ROSC. The study shows the need for CPRIC educational support for practitioners. The use of ketamine, midazolam and fentanyl are used by some organizations but there is no evidence to suggest risk or benefit.
Sterz (2023)[9] Lapses of the heart	Prospective controlled study N=126	All patients admitted to Department of Emergency Medicine of the Medical University of Vienna due to CA, whose communicative abilities were restored and who agreed to participate in the study.	76% responded that their impressions during cardiac arrest were nothing or blackout. 20 (16%) gave a detailed account of resuscitation. 5 (4%) scored 7 or more on the Greyson NDE scale. 11 of the 20 had their resuscitation started within 1 minute of arrest.	Reported CPRIC was of high significance to patients that experienced it, and many changed their views on life and death.
Parnia (2023)[10] AWAreness during resuscitation II	Multi centre prospective N-=567 and cross-sectional N= 126	Prospective study: In hospital cardiac arrests during 2010-2015 during 9:00-17:00 Mon - Friday. Inclusion: >=18, In hospital cardiac arrests lasting >=5 minutes. Exclusion: out of hospital cardiac arrests. Cross sectional: Cardiac arrest survivors identified by public database. Inclusion: >=18, cardiac arrest self-reported cognitive experiences.	Primary outcome: visual or auditory awareness From the prospective study: 37.6% of participants achieved ROSC, (53) 9.3% survived to discharge, 28/53 completed the interview. 11 (39%) if those reported memories and / or perceptions of the cardiac arrest. 6 (21%) had transcendent experiences using the NDE scale. No reports of external signs of consciousness. 4 themes occurred: Post emergence from coma during CPR (CPRIC) (7%), in post resuscitation period (7%), dream/dream like experiences (11%), recalled experience of death (21%)	People undergoing cardiac arrest may have awareness, cognitive experiences and consciousness despite absent outwards signs of consciousness. The study reinforces the need to study psychological outcomes in cardiac arrest survivors and supports the idea that PTSD / other negative psychological outcomes may be associated with cardiac arrest emergence form consciousness.

			From the cross sectional study: Themes the same as above plus a 5th - delusions. Of the 28 survivors with the combined tablet / headphones no body describe explicit recall or the images and auditory stimuli. 1 (3.5%) correctly identified the correct fruit from the auditory stimuli alone. Interpretable EEG was obtained from 53 subjects. Absence of cortical brain activity dominant (47%) but seizure like activity (5%) also emerged. Near normal / physiological EEG was also demonstrated. This declined after 50 minutes of CPR.	

Case studies, grey literature (n=5):

Study Acronym; Author; Year Published	**Article Type, Demographics**	**Key observations**	**Summary / conclusion**
Woollacott (2021)[11] Verified account of near-death experience in a physician who survived cardiac arrest	Case Study 58 year old F	Cardiac arrest under general anaesthetic. Describes hearing the anaesthetist shouting, a stillness in the chest, beeping from the cardiac monitors. Her experiences post arrest were assessed using the NDE scale, with a score of 23/32 . 6 perceptions she held in relation to the cardiac arrest were verified by the team post event.	Near death experiences / awareness during CPR can have a huge impact / change in the patient's beliefs and spirituality. Suggesting that near death experiences are a gateway to higher or expanded awareness.
Czerwonka (2021)[12] Not a normal resuscitation with ventricular fibrillation-	Case Study 49 year old	VF arrest, immediate CPR by 2 nearby doctors. During CPR the patient showed eye opening, purposeful movements, eye	Rapid reaction by qualified rescuers aided in the resuscitation success and the likelihood of CPRIC. Although there are recommendations on sedation after

Awareness during cardiopulmonary resuscitation		tracking, biting on laryngoscopy and verbal expressions, giving him a technical GCS 11. 15mg of Midazolam and 2 lots of 0.6mg of Fentanyl was given due to the suspected CPRIC. After Amiodarone, adrenaline and defibrillation ROSC was gained. A diagnosis of STEMI with full occlusion of the RCA was made in hospital, 2 stent were inserted and he discharged 11 days later	ROSC this vary, and recommendations / guidance on sedation during the resuscitation are scarce and there are no RCTs on the subject. The patient had no recollection of events, but it is uncertain whether this was due to induced amnesia with midazolam or possible reduced cerebral perfusion. However it is recognized that this is a traumatic situation for both patient and rescuers and debriefing / psychological support should be offered to rescuers and also form part of the rescue and treatment chain
Martial (2022)[13] Studying death and near-death experiences requires neuroscientific expertise	Commentary	The paper by Parnia contains inaccurate statements bordering on a misunderstanding of the brain death concept. People who experience NDEs are inherently people who have not been dead and have not met brain death criteria which opposes Parnia's paper. There is no evidence to suggest NDEs from cardiac arrests differ from other life threatening conditions as stated in the paper. Important studies regarding what happens in the dying brain have been omitted in Parnia's paper.	Near death research merits a framework but the guidelines and standards paper by Parnia[5] does not contribute to the scientific understand of near death experiences and the dying process and shows a lack of neuroscientific understanding
Wilson (2023)[14] Some people are aware during CPR	New Scientist article	References to AWARE II study: awareness rate of 39%. After 40 minutes of CPR, almost half of the people had brainwaves that appeared nearly normal.	One clinician suggested the findings suggest doctors should give more consideration to sedating people undergoing CPR. However, a second sedatives could lower the chances of a successful resuscitation and that there is not enough evidence yet**.**
Howard (2023)[15]	Guideline	Expert guideline based on Delphi process	Definition of CPRIC is consciousness with no spontaneous circulation, can be interfering with CPR efforts (eg, pushing rescuers away, pulling out cannula) or non-interfering. Suggests drug treatments (eg, low dose ketamine) and longer resuscitation attempt (≥ 45 minutes)
Silvestri (2023)[16]	Scoping review protocol	This paper recognizes the lack of current consensus guidelines and sets out the framework for a scoping review of the pre-hospital evidence which will be carried out in the near future.	

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)

There remains insufficient evidence to conduct a systematic review on this topic as there are no interventional studies.

There is a small amount of new data since our previous scoping review. In our opinion, there is insufficient new information to justify another scoping review at this time. The 2021 Good Practice Statements remain valid:

- **In settings in which it is feasible, rescuers may consider using sedative or analgesic drugs (or both) in very small doses to prevent pain and distress to patients who are conscious during CPR (good practice statement).**
- **Neuromuscular-blocking drugs alone should not be given to conscious patients (good practice statement).**
- **The optimal drug regimen for sedation and analgesia during CPR is uncertain. Regimens can be based on those used in critically ill patients and according to local protocols (good practice statement).**

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Evidence Update Worksheet

Asthma in Cardiac Arrest
ALS 3408

Worksheet author(s): Kate Berg
Task Force: ALS
Date Submitted to SAC rep for peer review and approval:
SAC rep: Eric Lavonas

PICOST / Research Question: In adult cardiac arrest due to asthma, does any modification of treatment, as opposed to standard care (according to treatment algorithm), improve outcome?

Year of last full review: full review 2010, EvUp 2021

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
There are no RCTs that specifically evaluate or compare adjuvant treatment with standard treatment for cardiac arrest in asthmatic patients. Most of the literature comprises case reports and case series.

Evidence from 3 non–cardiac arrest case series involving 35 patients suggests that asthmatic patients are at risk for gas trapping during cardiac arrest, especially if their lungs are ventilated with high tidal volumes and/or rapid rates (LOE 5). One volunteer adult study demonstrated that increasing PEEP caused increased transthoracic impedance (LOE 5).

Seven case series involving 37 patients suggested increased ease of ventilation and ROSC with lateral chest compressions at the base of the ribs (LOE 4). In a single case report, lateral chest compressions were associated with cardiac arrest and poor cardiac output (LOE 4). Three single case reports (2 intraoperative and 1 ED) involving cardiac arrest caused by asthma suggested improvement in ease of ventilation and ROSC with thoracotomy and manual lung compression (LOE 4).

Treatment Recommendation (2010)

There is insufficient evidence to suggest any routine change to cardiac arrest resuscitation treatment algorithms for patients with cardiac arrest caused by asthma.

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
("asthma"[MeSH Terms] OR "asthma"[All Fields] OR "asthmas"[All Fields] OR "asthma s"[All Fields]) AND ("heart arrest"[MeSH Terms] OR ("heart"[All Fields] AND "arrest"[All Fields]) OR "heart arrest"[All Fields] OR ("cardiac"[All Fields] AND "arrest"[All Fields]) OR "cardiac arrest"[All Fields])
New Search strategy: (for a new PICOST should be outlined here as per Evidence Update Process)

Database searched: PubMed
Time Frame: Jan 1, 2021-April 11 2023
Date Search Completed: April 11, 2023
Search Results (Number of articles identified and number identified as relevant): 43 found; 1 2021 ERC guidelines paper included. No observational studies and no RCTs identified.

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
European Resuscitation Council	**Guidelines 2021: Cardiac arrest in special circumstances**[1]	Cardiac arrest from asthma or COPD	19 observational studies, 0 RCTs	Patients with severe asthma exacerbations have been found to have very high airway pressures, suggesting high risk of gastric insufflation with mask ventilation, so early intubation suggested; early attention to hypoxemia and airway sstablishment suggested; checking or signs of tension pneumothorax suggested; disconnect from positive pressure ventilation and use manual pressure to deflate if severe air trapping suspected; case reports of ECPR being successful were noted	Administer high concentration oxygen. Ventilate with respiratory rate (8_10 min_1) and sufficient tidal volume to cause the chest to rise. Intubate the trachea if able to do so safely. Check for signs of tension pneumothorax and treat accordingly. Disconnect from positive pressure ventilation if relevant and apply pressure to manually reduce hyper-inflation. Consider IV fluids. Consider E-CPR in accordance with local protocols if initial resuscitation efforts are unsuccessful.

RCT:

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
	Study Aim: **Study Type:**	**Inclusion Criteria:**	**Intervention:** **Comparison:**	**1° endpoint:**	**Study Limitations:**

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	Study Type:	**Inclusion Criteria:**	**1° endpoint:**	

Reviewer Comments: No new studies identified. The ERC guidelines from 2021 include guidance for cardiac arrest in the setting of asthma exacerbation, but these are based on very limited evidence, mostly from studies included in prior reviews. There is insufficient new evidence to warrant a new systematic review.

Reference list:

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Evidence Update Worksheet

Antiarrhythmics during and after cardiac arrest
ALS 3201, 3514

Worksheet author(s): Alexandra Rose GOSLING, Shinichiro OHSHIMO, Peter KUDENCHUK, Jasmeet SOAR

Task Force: ALS
Date Submitted to SAC rep for peer review and approval: 8 February 2024
Presented to ALS Task Force on 8 February 2024.

COI: JS, SO, RG - No COI. PJK - PI, Lead Investigator for ROC-ALPS (2016) and ARREST (1999) RCTs.

PICOST / Research Question:
P- Among adults in any setting (in-hospital or out-of-hospital) with cardiac arrest and a shockable rhythm at any time during cardiopulmonary resuscitation (CPR) or immediately after return of spontaneous circulation (ROSC),
I- does administration of antiarrhythmic drugs (e.g., amiodarone, lidocaine, other),
C – compared with another antiarrhythmic drug or placebo or no drug,
O - change outcomes of survival to hospital discharge with good neurological outcome, survival to hospital discharge, ROSC and recurrence of pVT/VF?

Year of last full review: (*insert year where this PICOST was most recently reviewed) 2018*

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:

Treatment recommendations
We suggest the use of amiodarone or lidocaine in adults with shock refractory VF/pVT (weak recommendation, low-quality evidence).

We suggest against the routine use of magnesium in adults with shock-refractory VF/pVT (weak recommendation, very low-quality evidence).

The confidence in effect estimates is currently too low to support an ALS Task Force recommendation about the use of bretylium, nifekalant, or sotalol in the treatment of adults in cardiac arrest with shock-refractory VF/pVT.

The confidence in effect estimates is currently too low to support an ALS Task Force recommendation about the use of prophylactic antiarrhythmic drugs immediately after ROSC in adults with VF/pVT cardiac arrest.

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST

New Search strategy: (for a new PICOST should be outlined here as per Evidence Update Process)
Database searched: Medline, Embase

PubMed search 1 Jan 2017 to 14 July 2023: 930 titles

(("Heart Arrest"[Mesh] OR heart arrest[tiab] OR cardiac arrest[tiab] OR sudden cardiac death[tiab] OR cardiovascular arrest[tiab] OR cardiopulmonary arrest[tiab] OR cardiopulmonary failure[tiab] OR "Resuscitation"[Mesh] OR resuscitation[tiab] OR "Cardiopulmonary Resuscitation"[Mesh] OR cardiopulmonary resuscitation[tiab] OR cpr[tiab] OR code blue[tiab] OR code 99[tiab] OR "Advanced Cardiac Life Support"[Mesh] OR advanced cardiac life support[tiab] OR acls[tiab] OR pulseless electrical activity[tiab] OR "Ventricular Fibrillation"[Mesh] OR ventricular fibrillation[tiab] OR asystole[tiab] OR pulseless ventricular tachycardia[tiab] OR in-hospital cardiac arrest[tiab]) AND ("Anti-Arrhythmia Agents"[Mesh] OR amiodarone[tiab] OR lidocaine[tiab] OR procainamide[tiab] OR Nifekalant[tiab] OR bretylium[tiab] OR magnesium[tiab] OR esmolol[tiab] OR sotalol[tiab])) AND (("2017/01/01"[Date - Publication] : "3000"[Date - Publication])) Sort by: Most Recent

EMBASE search 1 Jan 2017 to 14 July 2023: 753 titles

((((((((((((('heart'/exp OR heart) AND ('arrest'/exp OR arrest) OR 'cardiac'/exp OR cardiac) AND ('arrest'/exp OR arrest) OR sudden) AND ('cardiac'/exp OR cardiac) AND ('death'/exp OR death) OR 'cardiovascular'/exp OR cardiovascular) AND ('arrest'/exp OR arrest) OR cardiopulmonary) AND ('arrest'/exp OR arrest) OR cardiopulmonary) AND ('failure'/exp OR failure) OR 'resuscitation'/exp OR resuscitation OR cardiopulmonary) AND ('resuscitation'/exp OR resuscitation) OR cpr OR 'code'/exp OR code) AND ('blue'/exp OR blue) OR 'code'/exp OR code) AND 99 OR advanced) AND ('cardiac'/exp OR cardiac) AND ('life'/exp OR life) AND ('support'/exp OR support) OR acls OR pulseless) AND electrical AND ('activity'/exp OR activity) OR ventricular) AND ('fibrillation'/exp OR fibrillation) OR 'asystole'/exp OR asystole OR pulseless) AND ventricular AND ('tachycardia'/exp OR tachycardia) OR 'in hospital') AND ('cardiac'/exp OR cardiac) AND ('arrest'/exp OR arrest) AND ('anti arrhythmia' AND agents OR 'amiodarone'/exp OR amiodarone OR 'lidocaine'/exp OR lidocaine OR 'procainamide'/exp OR procainamide OR nifekalant OR 'bretylium'/exp OR bretylium OR 'magnesium'/exp OR magnesium OR 'esmolol'/exp OR esmolol OR 'sotalol'/exp OR sotalol OR lignocaine OR 'lignocaine'/exp OR phenytoin OR 'phenytoin'/exp OR metoprolol OR 'metoprolol'/exp) AND [2017-2023]/py

Search Results (Number of articles identified and number identified as relevant):

930 PubMed titles
753 Embase titles

47 relevant articles identified (45 PubMed, 2 Embase):
21 Guidelines/systematic reviews
6 Secondary analyses of ROC ALPS RCT
20 Non-RCTs

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Amiodarone and/or Lidocaine (plus others)					
Wang Q et al. Comparison the efficacy of amiodarone and lidocaine for cardiac arrest: A network meta-analysis Medicine (Baltimore). 2023 Apr 14;102(15):e33195	Meta-analysis	**Population**: CA patients **Intervention:** IV amiodarone or lidocaine or amiodarone combined lidocaine or placebo **Outcome:** survival to hospital discharge, survival to hospital admission/24h, favorable neurological outcome **Study design:** RCTs and retrospective studies	• 9 studies (10,980 patients) • 5 RCTs, 4 non-RCTs • 8 valuated survival to hospital admission/24h • 9 studies evaluated survival to hospital discharge • 4 studies reported favourable neurological outcome. • 6 studies reported the dose of amiodarone (150–300 mg) 3 studies reported the dose of lidocaine (60 mg or 1.5 mg/kg)	• Amiodarone (OR 2.28, 95% CrI 1.61-3.27) and lidocaine (OR 1.53, 95% CrI 1.05-2.25) superior to placebo re survival to hospital admission/24h • Amiodarone (OR 2.19, 95% CrI 1.54–3.14) and lidocaine (OR 1.58, 95% CrI 1.09–2.32) was superior to placebo re survival to discharge • Amiodarone (OR 2.43, 95% CrI 1.61–3.68) and lidocaine (OR 1.62, 95% CrI 1.04–2.53) was superior to placebo re favourable neurological outcome	Amiodarone and lidocaine are superior to placebo in discharge rates for cardiac arrest patients. Amiodarone should be listed as first line drug for cardiac arrest.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Zeppenfeld K et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death Eur Heart J 2022 Oct 21;43(40):3997-4126	ESC Guideline 2022	Antiarrhythmic drugs	1155 referenced articles	• Isoprotereno l infusion, verapamil or quinidine for acute treatment of an electrical storm or recurrent ICD discharges should be considered in idiopathic VF (2a) • Quinidine should be considered for chronic therapy to suppress an electrical storm or recurrent ICD discharges in idiopathic VF (2a) • Isoprotereno l infusion should be considered for recurrent VF in ERS patients (2a) • Quinidine in addition to an ICD should be	Isoproterenol, verapamil, quinidine, amiodarone, beta blockers recommended in management of electrical storm and recurrent VF, but should be guided by underlying pathology.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				considered for recurrent VF in ERS patients (2a) • Isoprotereno l may be considered in SQTS patients with an electrical storm (2b) • IV amiodarone treatment should be considered for patients with recurrent PVT/VF during the acute phase of ACS (2a) • Antiarrhyth mic therapy with beta-blockers in combination with IV amiodarone is recommend ed in patients with SHD and electrical storm unless contraindicat ed (B)	

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				IV beta blocker treatment is indicated for patients with recurrent PVT/VF during STEMI unless contraindicated (B)	
Ono K et al. JCS/JHRS 2020 Guideline on Pharmacotherapy of Cardiac Arrhythmias. J Arrhythm. 2022 25;38(6):833-973.	Japanese Circulation Society Guidelines			Sections IX and X address VF and cardiac arrest.	Equivalent 2a recommendations for Nifekalant and Amiodarone, 2 b for lidocaine, 3 for Mg. Consider Beta blocker or Stellate ganglion block in persistent VF. 2 b recommendation for lidocaine or beta blocker after ROSC
Srisurapanont K et al. Comparing Drugs for Out-of-hospital, Shock-refractory Cardiac Arrest: Systematic Review and Network Meta-analysis of Randomized Controlled Trials West J Emerg Med. 2021 Jul 19;22(4):834-841	Systematic review and network meta-analysis	Atraumatic OHCA with refractory VF or pVT in patients > 8 years old where at least one study group received a medication and reported on ROSC, survival to hospital admission or discharge or neurological outcome.	• 18 RCTs (6,582 patients) 12 medications used: magnesium (2 RCTs), buffer (1 RCT), amiodarone (4 RCTs), nifekalant (1 RCT), lidocaine (5 RCTs). bretylium (2 RCTs), epinephrine (9 RCTs),	• Norepinephrine was the only drug to show a significant improvement in ROSC (OR 8.91 95% CI 1.88-42.29) Amiodarone improved survival to hospital admission (OR 1.53 95% CI 1.01-2.32)	• No medication was associated with improved survival to hospital discharge from OH refractory VF/pVT cardiac arrest. • Norepinephrine associated with improved ROSC Amiodarone was associated with an increased likelihood of survival to hospital admission

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
			vasopressin (2 RCTs), sotalol (1 RCT), norepinephrine (1 RCT), methoxamine (1 RCT) and placebo (6 RCTs)		
Zhao H et al. Amiodarone and/or lidocaine for cardiac arrest: Bayesian network meta-analysis. Am J Emerg Med 2020;38:2185-93	Bayesian network meta-analysis – studies from inception to 1/21/2020 evaluating survival to discharge, survival to hospital admission/24 h and favorable neurological outcome	• Primary endpoint survival to discharge • Secondary endpoints survival to hospital admission/24 h and favorable neurological outcome • Amiodarone, lidocaine, placebo and combinations of same	• 9 studies (10,972 patients) meeting criteria: Dx refractory VF/VT cardiac arrest (in and out of hospital), age ≥18 yrs, assessed amiodarone, lido, amio+lido or placebo and full text articles • Included 4 RCTs, 4 RS (retrospective studies) and 1 PS (prospective study). • Cochrane bias risk assessment	• Head-to-head studies Survival to hospital admission/24h – 8 studies: • Lidocaine (Lido OR 3.12 (95% CI) 1.08, 9.98)) and amiodarone (Amio OR 2.96 (95% CI) (1.02, 8.53)) each individually better vs combination of the two drugs • NSD between amiodarone vs lidocaine (Amio OR 0.95 95% CI (0.67,1.34)) • NSD Amio vs placebo (Amio OR 1.34 95% CI (0.95, 1.90))	• In head-to-head studies lido and amio significantly better than placebo in survival to hospital discharge; amiodarone more effective than placebo in favorable neurological outcome; lido and amiodarone individually more effective than lido plus amio in survival to hospital admission/24h • Amiodarone and lidocaine are superior to the combination of the two drugs in admission rates and superior to placebo in discharge rates. • The probability analysis revealed that lidocaine is the most effective agent for hospital admission and survival to discharger. • Regarding favorable neurological outcome, amiodarone is superior to placebo.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
			& Newcastle-Ottawa scale used to access quality of RCT & observational studies • Primary endpoint survival to hospital discharge; secondary endpoints survival to hospital admission/24 h and favorable neurological outcome (modified Rankin scale 0-3) • Bayesian network meta-analysis performed • Pooled outcome measures determined using random effects model	• NSD Lidocaine vs placebo (Lido OR 1.42 95% CI (0.97, 2.06)) • NSD Amiodarone plus lidocaine vs placebo (Amio+Lido OR 0.45 95% CI (0.15, 2.35)) Survival to discharge -9 studies: • Amio vs placebo (Amio OR 1.18 95% CI (1.03, 1.35)) • Lido vs placebo (Lido OR 1.22 95% CI (1.06, 1.41)) • NSD Amio vs amio plus lidocaine (Amio OR 2.25 95% CI (0.93, 5.44) • NSD Amio vs lidocaine (Amio OR 0.96 (0.86,1.07)) • NSD Amio plus lido vs lido (Amio+lido OR 0.43 (0.18,1.03))	• The probability analysis revealed that amiodarone was superior to lidocaine and placebo in neurological outcome.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				• NSD Amio plus lido vs placebo (Amio+lido OR 0.52 (0.21, 1.27)). Favorable neurological survival - 4 studies: • Amio vs placebo (Amio OR 1.2 95% CI (1.02,1.41)) • NSD amio vs lidocaine (Amio OR 1.09 (0.92, 1.29)) • NSD Lido vs placebo (Lido OR 1.1 (0.93,1.30)) • Markov chain Monte Carlo modeling (MCMC) was used to estimate relative ranking probability of treatments – lidocaine was most effective for survival to hospital admission and discharge; amiodarone as	

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				most effective for favorable neuro outcome • These findings are different from those of 2 previous meta-analyses. One of these - a conventional meta-analysis - concluded that amiodarone and lidocaine had the same beneficial effect on survival to hospital admission, and both were better than placebo. It also concluded that there was no significant difference among the three interventions in survival to hospital discharge. The second study – a network meta-analysis - concluded that lidocaine had the best effect in survival to hospital discharge, with no significant	

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				difference in survival to hospital admission. • In a retrospective study comparing amiodarone with lidocaine (without a placebo comparison) we performed a Bayesian network meta-analysis to obtain more evidence. The proportions of patients surviving to hospital admission and discharge were not different between patients who received lidocaine, amiodarone, or a combination of the two drugs. However, the combination regimen was the least effective in our study, even less effective than placebo. This may be	

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				because only one study with 41 patients was included. Another reason may be that amiodarone and lidocaine have different pharmacological mechanisms, and the combination of the two drugs could increase side effects and inhibit the sinoatrial and atrioventricular nodes.	
Ludwin K et al. Effect of amiodarone and lidocaine on shock-refractory cardiac arrest: A systematic review and meta-analysis. Kardiol Pol 2020;78:999-1007	Systematic review and meta-analysis	• Amiodarone vs lidocaine	• Studies were included if they met the following criteria: 1) randomized and quasi-randomized controlled trials, cohort and cross-sectional studies; 2) intravascular access; 3) comparison of	• An insignificantly higher number of cases with return of spontaneous circulation was observed in the amiodarone group compared with the lidocaine group (OR, 1.03; 95% CI, 0.87–1.21; P = 0.75). • A similar relationship was observed for survival to hospital	• No statistically significant survival benefit of resuscitation with amiodarone compared with lidocaine.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
			amiodarone and placebo, lidocaine and placebo, or amiodarone and lidocaine; 4) reporting at least return of spontaneous circulation (ROSC) outcome; 5) adult patients with cardiac arrest • 682 unique references → 8 selected • 1° outcome of this systematic review was ROSC. • 2° outcome was survival to hospital discharge and survival to hospital discharge with favorable neurological	discharge (OR, 1.12; 95% CI, 0.92–1.38; P = 0.26), as well as survival with favorable neurological outcome (OR, 1.11; 95% CI, 0.89, 1.39; P = 0.35).	

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
			outcome. Favorable neurological outcome was defined as the patient discharged home or for rehabilitation, Cerebral Performance Categories Scale score of 1 or 2, or a modified Rankin Scale score of 1 or 2 • 8 studies selected (5 retrospective observational and 3 randomized) but authors mistook Daya IV vs IO ALPS substudy as updated ALPS for the main ALPS analysis		
Ali MU, et al. Effectiveness of antiarrhythmic drugs for shockable cardiac arrest: A	Systematic review and meta-analysis (Medline, Embase, and	P: shockable cardiac arrest in adults I: antiarrhythmic drugs	14 RCTs and 17 observational studies	For the critical outcomes of survival to hospital discharge and discharge with	The high level evidence supporting the use of antiarrhythmic drugs during CPR for shockable cardiac arrest is limited

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
systematic review. Resuscitation 2018:132:63-72	Cochrane Library)	C: other antiarrhythmic drugs or placebo O: survival to hospital discharge; discharge with good neurological function; ROSC T: from inception to August 15, 2017		good neurological function, none of the anti-arrhythmic drugs showed any difference in effect compared with placebo, or with other anti-arrhythmic drugs. For the outcome of return of spontaneous circulation, the results showed a significant increase for lidocaine compared with placebo (RR = 1.16; 95% CI, 1.03–1.29, p = 0.01).	and showed no benefit for critical outcomes. Original ILCOR SR.
Chowdhury A et al. Antiarrhythmics in Cardiac Arrest: A Systematic Review and Meta-Analysis. Heart Lung Circ 2018;27:280-290	Systematic review and meta-analysis (CINAHL, SCOPUS, PubMed, Web of Science, Medline(Ovid) and the Cochrane Clinical Trials Registry)	P: adult cardiac arrests (OHCA and IHCA, over 18 yo) I: 8 antiarrhythmic drugs (amiodarone, lidocaine, magnesium, esmolol, nifekalant, bretylium, vasopressin,	31 studies (13 RCTs; 7 prospective cohort studies; 11 retrospective cohort studies; n= 42,808)	For any outcome, amiodarone, lidocaine and magnesium showed no significant effect either against placebo or each other. For ROSC, esmolol showed a near significant	There has been no conclusive evidence that any antiarrhythmic agents improve rates of ROSC, survival to admission, survival to discharge or neurological outcomes.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
		sotalol) C: other antiarrhythmic drugs or placebo O: ROSC; survival to hospital admission for OHCA patients, survival to hospital discharge; neurologic outcomes at discharge T: from inception to March, 2017		increase (OR = 17.59; 95%CI = 0.87–356.81; p = 0.06). For survival to admission, bretylium showed a significant benefit compared to placebo (OR = 4.04; 95%CI = 1.22–13.43; p = 0.02; Figure 3) For survival to admission, nifekalant showed a significant increase compared to lidocaine (OR = 2.91; 95%CI = 1.44–5.87; I2 = 34%; p = 0.003). On sensitivity analysis, both amiodarone and lidocaine had a significant increase in survival to admission, with no effect on survival to discharge.	

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
McLeod SL et al. Comparative effectiveness of antiarrhythmics for out-of-hospital cardiac arrest: A systematic review and network meta-analysis. Resuscitation 2017:121:90-97	Systematic review and network meta-analysis (Medline, Embase, and Cochrane Library)	P: adult patients experiencing out-of-hospital cardiac arrest (OHCA). I: 5 antiarrhythmic drugs C: other antiarrhythmic drugs or placebo O: ROSC; survival to hospital admission; survival to hospital discharge; neurologically intact survival T: from inception to March, 2017	8 RCTs (n=4,464)	For ROSC, lidocaine was associated with a significant increase in ROSC compared to placebo (1.15; 95% CI: 1.03-1.28), and was also superior to bretylium (1.61; 95% CI: 1.00-2.60). For survival to hospital admission, both amiodarone (1.18; 95% CI: 1.08-1.30) and lidocaine (1.18; 95% CI: 1.07-1.30) were associated with a significant increase compared to placebo. For survival to hospital discharge or neurologically intact survival, no antiarrhythmic was more effective than placebo.	Amiodarone and lidocaine were the only agents associated with improved survival to hospital admission. For the outcomes most important to patients, survival to hospital discharge and neurologically intact survival, no antiarrhythmic was convincingly superior to any other or to placebo.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				For any outcome, no antiarrhythmic was convincingly superior to any other.	
Sato S, et al. Meta-analysis of the efficacies of amiodarone and nifekalant in shock-resistant ventricular fibrillation and pulseless ventricular tachycardia. Sci Rep 2017;7:12683.	Systematic review and meta-analysis (PubMed, Cochrane Central Register of Controlled Trials, and Igaku Chuo Zasshi)	P: adult patients with OHCA/IHCA and had VF or pVT) I: amiodarone or nifekalant C: lidocaine, placebo, or a non-treatment antiarrhythmic drug O: short-term survival (defibrillation success, VF/pVT termination, return to spontaneous circulation, survival until admission to the hospital/intensive care unit, and three-hour survival) and long-term survival (30-day survival, 1-year survival, and survival until discharge	33 studies (7 RCTs; 6 observational studies; 20 retrospective studies)	For both short-term (OR: 1.25, 95% CI: 0.91–1.71) and long-term survival (OR: 1.00, 95% CI: 0.63–1.57), amiodarone showed no significant benefit compared to control treatments. For both short-term (OR: 3.23, 95% CI: 2.21–4.72)and long-term survival (OR: 1.88, 95% CI: 1.36–2.59), nifekalant showed a significant benefit compared to control treatments. There was no significant difference in short-term (OR:	Nifekalant may be more beneficial than amiodarone for both short-term and long-term survival in these conditions. However, the efficacy of amiodarone in either outcome remains unclear.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
		from hospital) T: from inception to December 2016		0.85, 95% CI: 0.63–1.15) or long-term survival (OR: 1.25, 95% CI: 0.67–2.31) between amiodarone- and nifekalant-treated patients.	
Khan SU, et al. Amiodarone, lidocaine, magnesium or placebo in shock refractory ventricular arrhythmia: A Bayesian network meta-analysis. Heart Lung 2017;46:417-424	Systematic review and Bayesian network meta-analysis (PubMed/MEDLINE, EMBASE and Cochrane Central Register of Controlled Clinical Trials)	P: adult patients with OHCA/IHCA and had VF or VT) I: amiodarone, lidocaine, and magnesium C: , placebo O: survival to hospital discharge, survival to hospital admission/24 h and ROSC T: from 1981 to February 2017	11 studies (7 RCTs; 2 prospective observational studies; 2 retrospective observational studies)	For survival to hospital discharge, lidocaine was significantly better than 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). For survival to hospital admission/24 h, lidocaine was significantly superior to placebo (OR, 1.68; 95% CI, 1.03–2.75; P-value = 0.04; I2 = 0). For achievement of ROSC,	We conclude that lidocaine may be the most effective anti-arrhythmic agent for survival to hospital discharge in patients with pulseless VT or VF.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				lidocaine showed a significant benefit 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 MgSO4 (OR, 1.51; 95% Cr.I. 0.86–2.88). A sensitivity analysis was conducted on the included RCTs for OHCA due to ventricular arrhythmia, 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.	
Bretylium					
AHA Part III: Adult Advanced	1992 AHA Guideline	• Bretylium	• 10 references	• Bretylium	• Bretylium is useful in treating both VF

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Cardiac Life Support JAMA 1992;286:2199-2241				tosylate is a quaternary ammonium compound used in the treatment of resistant VT and VF unresponsive to defibrillation, epinephrine, and lidocaine. Its cardiovascular actions are complex and include a release of catecholamines initially on injection, followed by a postganglionic adrenergic blocking action that frequently induces hypotension. • There are data documenting the primary antifibrillatory effect of bretylium in animals, although this concept has recently been challenged.	and VT but no better than lidocaine in direct comparisons. • Bretylium should not be used as a first-line antiarrhythmic agent. This simplifies selection of a therapy and precludes potential adverse hemodynamic effects.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
AHA Part 6: Advanced cardiovascular life support; Section 5: Pharmacology I: Agents for Arrhythmias. Circulation 2000;102:I-112-28.	AHA Guideline	• Bretylium	• 6 references cited	• AHA has dropped reference to bretylium because of tis limited utility and availability. • In 1999 bretylium was unavailable from the manufacturer.	• After 1999 bretylium was been removed from ACLS treatment algorithms and guidelines because of a high occurrence of side effects, the availability of safer agents at least as efficacious and the limited supply and availability of the drug.
Beta Blockers					
Miraglia D et al. Esmolol in the management of prehospital refractory ventricular fibrillation: A systematic review and meta-analysis Am J Emerg Med 2020;38:1921-34	Systematic review and meta-analysis	• Esmolol	• 3253 unique records, of which 2 observational studies were found to be in accordance with the research purpose, totaling 66 patients, of whom 33.3% (n=22) received esmolol • We considered for inclusion any controlled clinical study design (randomized controlled	Esmolol was likely associated with: • An increased rate of survival to discharge (RR 2.82, 95% CI 1.01–7.93, p = 0.05) (GRADE: Very low). There was no statistical significance at the individual study level but there was modest statistical significance at the meta-analysis level • Survival with favorable neurological outcome (RR 3.44, 95% CI 1.11–10.67, p =	• Effectiveness of esmolol for refractory VF/pVT remains unclear; evidence is inconclusive. • We are uncertain of the effects of esmolol on any of the reported outcomes as a result of this assessment; additionally, the optimal information size was not achieved for the meta-analysis, and sequential testing on an accumulated number of participants did not surpass trial sequential monitoring boundaries. Therefore, the conclusion should be that the intervention might be beneficial, but larger sample sizes are needed as the estimates are still inconclusive • At this time, there is inadequate evidence

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
			trials [RCTs] and controlled non-randomized trials [CnRTs]), and observational studies (cohort studies and case control studies) with a control group (i.e. patients not receiving esmolol) published in English as full-text articles in indexed journals between January 2000 and December 2019 that reported survival rates and neurological outcome in adults (≥18 years) resuscitated from prehospital	0.03) (GRADE: Very low). • Return of spontaneous circulation (ROSC) (RR 2.63, 95% CI 1.37–5.07, p = 0.004) (GRADE: Very low) • Survival to intensive care unit (ICU)/hospital admission (RR 2.63, 95% CI 1.37–5.07, p = 0.004) (GRADE: Very low). • The GRADE quality of evidence was graded as very low for each outcome and as having a high risk of confounding. • The overall risk of bias within individual studies was judged as serious for both studies, with confounding bias, selection of participants, and measurement of outcomes being	to either support the use of esmolol during refractory cardiac arrest or the routine use of a β-blocker after cardiac arrest.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
			cardiac arrest on-scene or in the emergency department (ED). • 1° outcomes of the study were survival to discharge and survival with favorable neurological outcome. • 2° outcomes included sustained ROSC, survival to intensive care unit (ICU)/hospital admission, survival at 30 days and one year, and survival with favorable neurological outcome at 30 days and one year	the primary sources. • The overall risk of bias within both studies was judged as serious because they included at least one category with serious risk of bias. • Both studies were at moderate risk of selection bias. • Both studies were at overall low risk of bias for classification of interventions and deviations from Intended interventions. • One study was at moderate risk of bias for missing data. The other study was at low risk of bias for missing data. • Both studies were at moderate risk of bias for measurement of outcomes and low risk of bias	

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				for selection of reported results • The body of evidence was initially classified as very low quality evidence (i.e. permitting low confidence in the estimated effect).	
King C et al. Esmolol – a novel adjunct to ACLS algorithm? Emerg Med J 2020;37:650-51	Systematic review – synopsis of Miraglia D et al. The Evolving Role of Esmolol in Management of Pre-Hospital Refractory Ventricular Fibrillation; a Scoping Review. Arch Academ Emerg Med 2020;8:e15	• Esmolol • Medline 1946—March 2020 using the OVID interface	• 114 papers were found of which 83 were irrelevant, 6 removed as they were case studies or case reports, 1 was a letter to the editor, 19were based on animal models or experiments and 3 were literature reviews; 2 papers represented small retrospective observational series studies (6	• Driver study (2014; 6 esmolol vs 19 standard ACLS) showed no differences in ROSC, survival to admission or to discharge • Lee study (2016) showed improved ROSC and survival to hospital admission (56% vs 16% p=0.007 for each) but NSD in 30 day, 3 month or 6 month survival	• Currently, there is insufficient evidence in the existing literature to support the regular use of esmolol in resistant cardiac arrest; additional research is warranted to evaluate the effects of esmolol against the best current standard of care

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
			esmolol vs 19 standard ACLS and 16 esmolol vs 25 std ACLS patients in refractory VF		
Miraglia D et al. The Evolving Role of Esmolol in Management of Pre-Hospital Refractory Ventricular Fibrillation; a Scoping Review. Arch Academ Emerg Med 2020;8:e15	Scoping review	• Esmolol in out-of-hospital refractory VF vs conventional ACLS • Failed ≥ 3 defib attempts, 3 mg epi, 300 mg amiodarone • Most patients had witnessed arrest, bystander CPR • Esmolol administered in ED upon arrival in ongoing arrest	• Search restricted to English-written publications Jan 2000-July2019 • 2817 records → 2 peer-reviewed observational studies totalling 66 patients (22 esmolol recipients) • Driver 2014 (n=15 → 6 esmolol) • Lee 2016 (n=41 → 16 esmolol)	• Driver study: "improved" but NSD sustained ROSC and survival to ICU admission (same endpoints (66.7% vs 31.6%, p= NSD); NSD survival to discharge (50% vs 15.8%) or CPC ≤ 2 (50% vs 10.5%) • Lee study: improved sustained ROSC and survival to ICU admission 56.3% vs 16% (p=0.007) for each; NSD survival to discharge and CPC ≤ 2 at 30, 90, 180 days (18.8% in esmolol group vs 8% control for each of these endpoints) • This scoping review	• Current research shows promising results on the use of esmolol as feasible adjuvant therapy for refractory VF/pVT out-of- hospital cardiac arrest. • However, there is a paucity of research and a lack of literature to support this therapy.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				erroneously states that sustained ROSC was significantly more common in esmolol recipients than control in both studies; review of actual studies indicates this was only true in the Lee study	
Long DA et al. Does B-Blockade for treatment of refractory ventricular fibrillation improve outcomes? Ann Emerg Med 2020;76:42-45	Clinical synopsis of: Gottlieb M, Dyer S, Peksa A. Betablockade for the treatment of cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia: a systematic review and meta-analysis. Resuscitation. 2020;146:118-25	• Beta blockade in refractory VF/pulseless VT • Refractory VF/VT defined as refractory to ≥ 3 shocks, or electrical storm (≥ 4 episodes/hr or ≥20 episodes VF/VT qd) • Esmolol, propranolol, left stellate ganglion block evaluated	• 3 studies (n=115): 2 performed in ED and 1 unspecified location; 1 study prospective and observational; 2 retrospective observational • Esmolol, propranolol, left stellate ganglion block as interventions • None of studies assessed adverse events	• Based on GRADE certainty of evidence low to very low Pooled data meta-analysis results: • Temporary ROSC (n=66) 86.5% (BB) vs 31.8% (OR 14.46 95% CI (3.63,57.57)) • Sustained ROSC (n=66) 59.1% vs 22.7% (OR 5.76 95% CI (1.79,18.52)) • Admission survival (n=66) 59.1% vs 22.7% (OR 5.76 95% CI (1.79,18.52))	• Results of this meta-analysis suggest that b-blockade in patients with cardiac arrest caused by refractory ventricular fibrillation or pulseless ventricular tachycardia may lead to increased rates of return of spontaneous circulation, survival to discharge, and survival with a favorable neurologic outcome • Given the paucity of studies found and included through screening of the literature in this meta-analysis and the low confidence of the results, further high-quality clinical investigations are necessary to evaluate the efficacy

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				• Survival to discharge (n=115) 53.1% vs 10.6% (OR 7.92 95% CI (1.85,33.89)) • Survival with favorable neuro outcome (n=66) 27.3% vs 9.1% (OR 4.42 95% CI (1.05,18.56))	of b-blockade in refractory ventricular fibrillation and pulseless ventricular tachycardia before routine ED use.
Gottlieb M, Dyer S, Peksa A. Betablockade for the treatment of cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia: a systematic review and meta-analysis. Resuscitation. 2020;146:118-25	Systematic review and meta-analysis	• Beta blockade in refractory VF/pulseless VT • Refractory VF/VT defined as refractory to ≥ 3 shocks, or electrical storm (≥ 4 episodes/hr or ≥20 episodes VF/VT qd) • Esmolol, propranolol, left stellate ganglion block evaluated	• 3 studies (n=115) • 2 studies performed in ED and 1 unspecified • 1 study prospective and observational; 2 retrospective observational • Esmolol, propranolol, left stellate ganglion block as interventions • None of studies assessed	Beta-blockade was associated with: • Increased rate of temporary ROSC (OR 14.46; 95% CI 3.63,57.57) • Sustained ROSC (OR 5.76; 95% CI 1.79,18.52) • Survival-to-admission (OR 5.76; 95% CI 1.79, 18.52), • Survival-to-discharge (OR 7.92; 95% CI 1.85, 33.89) • Survival with a favorable neurologic outcome (OR 4.42; 95% CI 1.05, 18.56).	• Beta-blockade may be associated with improved outcomes ranging from ROSC to survival with a favorable neurologic outcome. • Future randomized controlled trials are needed to further evaluate this intervention in refractory VF/VT.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
			adverse events	• Overall risk of bias ranged from moderate-to-severe, which was primarily influenced by selection of participants and potential confounding	
Miraglia D et al. The evolving role of novel treatment techniques in the management of patients with refractory VF/pVT out-of-hospital cardiac arrest Am J Emerg Med 2020;38:648-54	Comprehensive literature search (systematic review) of observational studies	• Outcomes of extracorporeal membrane oxygenation, esmolol, double sequential defibrillation and stellate ganglion block • This assessment limited to esmolol findings (2 observational studies)	• 2 observational studies on esmolol	Esmolol: • Driver (2014) - n=6 esmolol recipients – 66.7% temporary ROSC, 66.7% sustained ROSC and admission to ICU, 50% survival, 50% survival with CPC ≤2 • Lee (2016) n=16 esmolol recipients – 66.7% temporary ROSC, 56.3% sustained ROSC and ICU admission, 18.8% survival; 18.8% survival with CPC ≤2	• Insufficient evidence to support effects of evaluated techniques (and in particular esmolol) in treatment of refractory VF/pVT OHCA
Other Antiarrhythmics					
Sharma A et al. Analysis of the 2018 American	Analysis of 2018 AHA	• Antiarrhythmic drugs in	• Review of articles cited	• Nifekalant vs lidocaine – NSD	• Amiodarone or lidocaine may be useful

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Heart Association Focused Update on Advanced Cardiovascular Life Support Use of Antiarrhythmic Drugs During and Immediately After Cardiac Arrest. J Cardiothoracic Vasc Anesth 2020;34:537-44	Focused update	cardiac arrest: amiodarone, lidocaine, nifekalant, bretylium, Mg, sotalol	in 2018 AHA focused update	in survival to discharge • Bretylium vs lidocaine – NSD in ROSC or survival to discharge • Sotalol vs lidocaine – NSD in ROC, survival to discharge or neurologically favorable survival • Amiodarone vs lidocaine – NSD in survival to discharge or neurologically favorable outcome in ALPS • Subsequent systematic review/meta-analysis showed improved survival to hospital admission with either lidocaine or amiodarone without improved survival discharge with either drug; no	for VF/pVT unresponsive to defibrillation • Mg may be useful for polymorphic VT due to torsade • Role of beta blockers uncertain • No proven benefit of nifekalant, sotalol or bretylium compared to existing agents

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				differences in outcome between amiodarone and lidocaine for any outcome • Nifekalant vs amiodarone – no difference in hospital mortality • Insufficient evidence to support or refute beta blockers • Mg – no benefit in ROSC or survival to discharge; limited evidence in torsade based on only 2 observational studies	
Dyer S et al. Electrical storm: A focused review for the emergency physician Am J Emerg Med 2020;38:1481-87	Descriptive review of electrical storm defined as ≥3 episodes VF/VT/ICD shocks over 24 hrs	• Antiarrhythmic drugs (amiodarone, procainamide), beta blockers (esmolol, propranolol, metoprolol), isoproterenol	• 84 referenced articles	• Descriptive only	• Mainly a narrative review suggesting use of antiarrhythmic agent and beta blocker as treatment agents without further formal analyses

RCTs:

Study Acronym; Author; Year Published	**Aim of Study; Study Type; Study Size (N)**	**Patient Population**	**Study Intervention (# patients) / Study Comparator (# patients)**	**Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)**	**Relevant 2° Endpoint (if any); Study Limitations; Adverse Events**
	Study Aim: **Study Type:**	**Inclusion Criteria:**	**Intervention:** **Comparison:**	**1° endpoint:**	**Study Limitations:**
Rahimi M et Al. Crit Care Med. 2023 Jul 1;51(7):903-912. The Effect of Time to Treatment With Antiarrhythmic Drugs on Survival and Neurological Outcomes in Shock Refractory Out-of-Hospital Cardiac Arrest	• Association of time to treatment (drug or placebo) with survival to hospital discharge and neurological outcome. • Post-hoc analysis of Resuscitation Outcomes Consortium Amiodarone, Lidocaine, Placebo (ROC-ALPS) RCT • n = 2994 patients	Adults with non-traumatic OHCA and an initial rhythm of VF or pVT refractory to at least one defibrillation attempt	Randomly assigned to receive amiodarone, lidocaine or placebo	• 1° outcome: survival to hospital discharge and favourable neurological status at discharge (modified Rankin ≤3). • Proportion of patients who survived to hospital discharge decreased as time to drug administration increased, in amiodarone (odds ratio [OR], 0.91; 95% CI, 0.90–0.93 per min), lidocaine (OR, 0.93; 95% CI, 0.91–0.96), and placebo (OR, 0.91; 95% CI, 0.90–0.93). • Improved survival times	This is a post-hoc analysis of a previous RCT, only uses proportion of original study number.

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
				administering amiodarone at any point compared to placebo (OR, 1.32; 95% CI, 1.05–1.65). Lidocaine only improved survival at later time points compared with placebo (p = 0.048).	
Lupton JR et al. Survival by time-to-administration of amiodarone, lidocaine, or placebo in shock-refractory out-of-hospital cardiac arrest. Acad Emerg Med. 2023 Mar 4	• Evaluate effect of time between EMS arrival to drug administration on efficacy of amiodarone and lidocaine compared to placebo. • Post-hoc analysis of 10-site, 55-EMS-agency double-blind RCT for amiodarone, lidocaine, or placebo in OHCA (ALPS) n = 2802 patients	Initial shockable rhythm (VF, pVT) who received amiodarone, lidocaine or placebo before achieving ROSC	ALPS RCT examined effects of amiodarone, lidocaine and placebo.	• Patients receiving amiodarone (compared to placebo) had increased survival to admission (62% v 48.5% p = 0.001, OR 1.76 95% CI 1.24-2.5), survival to discharge (37.1% v 28% p = 0.021, OR 1.56 95% CI 1.07-2.29) and functional survival (31.6% v 2.23% p = 0.029, OR 1.55 95% CI 1.04-2.32) • No significant difference between	This is a post-hoc analysis of a previous RCT, only uses proportion of original study number.

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
				lidocaine <8min and placebo (p>0.05) Amiodarone or lidocaine ≥8 min had no significant difference in outcome compared to placebo (p>0.05)	
Lane DJ et al. Bayesian analysis of amiodarone or lidocaine versus placebo for out-of-hospital cardiac arrest Heart. 2022 Oct 28;108(22):1777-1783.	• To assess the probability of improved survival or improved neurological outcome. • Post-hoc Bayesian analysis of ALPS RCT n = 3026 adult patients enrolled in RCT	Adult patients with OHCA with refractory VF or pVT (all patients enrolled to ALPS RCT)	Randomly assigned to receive amiodarone, lidocaine or placebo	• Improved survival with amiodarone ranged from 83% (strong prior) to 95% (weak prior) compared with placebo and from 78% (strong) to 90% (weak) for lidocaine. • Probability of improved neurological outcome from amiodarone ranged from 96% (weak) to 99% (strong) compared with placebo and from 88% (weak) to 96%	This is a post-hoc analysis of a previous RCT.

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
				(strong) for lidocaine. In conclusion, amiodarone had high probabilities of improved survival and neurological outcome whereas treatment with lidocaine had a more modest benefit.	
Rahimi M et al. Effect of Time to Treatment With Antiarrhythmic Drugs on Return of Spontaneous Circulation in Shock-Refractory Out-of-Hospital Cardiac Arrest J Am Heart Assoc. 2022 Mar 15;11(6):e023958	• Evaluate effect of time to treatment (drug/placebo administration) with ROSC at hospital arrival. • Post-hoc analysis of ROC ALPS RCT n = 1112 patients achieved ROSC at hospital arrival (total 3026 enrolled in RCT)	Adults with non-traumatic OHCA and an initial rhythm of VF or pVT refractory to at least one defibrillation attempt	Randomly assigned to receive amiodarone, lidocaine or placebo	• 36.7% patients achieved ROSC at hospital arrival (350 amiodarone, 396 lidocaine, 366 placebo) • Proportion of patients with ROSC decreased as time to medication increased: amiodarone (OR 0.92 95%CI 0.9-0.94), lidocaine (OR 0.95 95% CI 0.93-0.96) and placebo (OR 0.95 95% CI 0.93-0.96) With shorter times to drug administration, the proportion with ROSC was higher in	This is a post-hoc analysis of a previous RCT, only uses proportion of original study number.

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
				amiodarone versus placebo recipients.	
Salcido DD, et al. Effects of intra-resuscitation antiarrhythmic administration on rearrest occurrence and intra-resuscitation ECG characteristics in the ROC ALPS trial. Resuscitation 2018:129:6-12	To investigate the relationship between rearrest and intra-resuscitation antiarrhythmic drugs in the context of the Resuscitation Outcomes Consortium (ROC) amiodarone, lidocaine, and placebo (ALPS) trial. Pospective, randomized, controlled, double-blind trial conducted from February 2013 to January 2017 n=1,144	Patients 18 years or older with nontraumatic OHCA, documented persistent, or recurring VF/VT after ≥1 shock	I: lidocaine (n=420), amiodarone (n=363) C: placebo (n=361) O: rearrest, survival to hospital discharge, good neurologic function at hospital discharge (MRS <=3), quantitative ECG measures at first analyzable VF, immediately prior to ROSC, and at onset of first rearrest.	Rearrest rate was 44.0% overall; 42.9% for placebo, 45.7% for lidocaine, and 43.0% for amiodarone.	Rearrest rates did not differ between antiarrhythmic and placebo treatment groups. ECG waveform characteristics were correlated with treatment group and rearrest. Rearrest was inversely associated with survival and neurologic outcomes.
Kudenchuk PJ, et al. Antiarrhythmic Drugs for Nonshockable-Turned-Shockable Out-of-Hospital Cardiac Arrest: The ALPS Study (Amiodarone,	To evaluate the effectiveness of amiodarone and lidocaine for OHCA due to shock-resistant VF/VT (The Amiodarone, Lidocaine or Placebo Study (ALPS)).	Patients 18 years of age or older with atraumatic out-of-hospital cardiac arrest, established intravenous or intraosseous vascular access, and persistent (nonterminating)	I: lidocaine (n=420), amiodarone (n=363) C: placebo (n=361) O: The primary outcome of the trial was survival to hospital discharge.	Active-drug recipients in this cohort required fewer shocks, supplemental doses of their assigned drug, and ancillary antiarrhythmic drugs than recipients of a placebo (P<0.05).	Although not statistically significant, point estimates for survival were greater after amiodarone or lidocaine than placebo, without increased risk of adverse effects or

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Lidocaine, or Placebo). Circulation 2017;136:2119-2131	Prospective, randomized, double-blind, placebo-controlled multicenter trial n=4,089	or recurrent (restarting after successful termination) VF/VT after one or more shocks.	Secondary outcome were survival to discharge with favorable neurological functional status, defined on the modified Rankin scale as 3 or less, and adverse drug-related effects.	In all, 16 (4.1%) amiodarone, 11 (3.1%) lidocaine, and 6 (1.9%) placebo-treated patients survived to hospital discharge (P=0.24). No significant interaction between treatment assignment and discharge survival occurred with the initiating OHCA rhythm (asystole, pulseless electric activity, or VF/VT). Survival in each of these categories was consistently higher with active drugs, although the trends were not statistically significant. Adjusted absolute differences (95% confidence interval) in survival from nonshockable-turned-shockable arrhythmias with amiodarone versus	disability and consistent with previously observed favorable trends from treatment of initial shock-refractory VF/VT with these drugs.

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
				placebo were 2.3% (-0.3, 4.8), P=0.08, and for lidocaine versus placebo 1.2% (-1.1, 3.6), P=0.30.	

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	Study Type:	**Inclusion Criteria:**	**1° endpoint:**	
Amiodarone and/or Lidocaine				
Perry E et al. The impact of time to amiodarone administration on survival from out-of-hospital cardiac arrest. Resusc Plus. 2023 Jun 7;14:100405	• Retrospective cohort study of adult patients with shock refractory VF/pVT using Ambulance Registry Data • n = 2,026 adults with VF/pVT OHCA • Time-dependent propensity score matching	• n= 2,026 adults with shock refractory VF/pVT treated by EMS between January 2010-Decmber 2019 1,393 (68.8%) received amiodarone during the shock-refractory VF/pVT episode, all after 3 defibrillations had been administered (as	• 1° outcome was survival to hospital discharge • 2° outcomes: pre-hospital ROSC, event survival (a pulse on arrival at hospital) • Amiodarone administration within 28 minutes of the emergency call was associated with a higher likelihood of ROSC (≤18 minutes: RR = 1.031 (95% CI 1.018–1.043) and event survival (≤18 minutes: RR = 1.046 (95% CI 1.025–1.067) Amiodarone administration within 23 minutes of the emergency call was	• Administration of amiodarone within 28 minutes associated with improved ROSC and event survival outcomes and increased survival to hospital discharge • No documentation of neurological outcome of patients who survived to discharge • Excluded patients with initial defibrillation by first responder/public, who were a higher-survival cohort

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
		per EMS guidelines)	associated with increased likelihood of survival to hospital discharge (≤18 minutes: RR = 1.166 (95% CI 1.092–1.244)	
Kishihara Y et al. Comparison of the effects of lidocaine and amiodarone for out-of-hospital cardiac arrest patients with shockable rhythms: a retrospective observational study from a multicenter registry. BMC Cardiovasc Disord. 2022 Nov 5;22(1):466	• Retrospective observational propensity-matched record-review study using OHCA registry. n = 1970 adult patients with VF/pVT who were administered amiodarone or lidocaine	• Adult cardiogenic OHCA with VF/pVT treated by EMS who received either amiodarone or lidocaine during resuscitation n = 105 administered lidocaine, 1865 amiodarone	• 1° outcome was 30-day survival • 2° outcome: good neurological outcome at 30 days (CPC score 1-2) • Amiodarone used as reference • 30-day survival following lidocaine: OR 1.44 (95% CI 0.58-3.61) 30-day good neurological outcome following lidocaine: OR 1.77 (95% CI 0.59-5.29)	• No significant differences in both 30-day survival or good neurological outcomes between amiodarone and lidocaine • Only 5.3% patients received lidocaine, whereas 94.7% were administered amiodarone • Only OHCA with cardiogenic cause included
Wissa J et al. Time to amiodarone administration and survival outcomes in refractory ventricular fibrillation Emerg Med Australas. 2021 Dec;33(6):1088-1094	• Retrospective observational record review of ambulance service database for adult OHCA with refractory VF n = 502 patients	Adult OHCA of medical aetiology with refractory VF treated by ambulance service & received amiodarone	• 1° outcome: survived event, discharged alive, 30 day survival • Time to amiodarone negatively associated with survival (OR 0.93 for event survival; 95% CI 0.89–0.97) Optimal time window for amiodarone administration is within 23 min after arrest.	• Patients receiving amiodarone within the optimal time had significantly better survival (survived event 38.3% vs 20.6%, p< 0.001; discharge survival 25.5% vs 9.7%, p< 0.001; 30-day survival 25.1% vs 9.7%, p< 0.001) No data on neurological outcomes
Wagner D et al. Comparative Effectiveness of Amiodarone and	• Retrospective cohort study of adult patients with	• Adult in-hospital cardiac arrest with	• 1° outcome: ROSC • 2° outcomes: 24h survival, survival to hospital discharge and	Compared with amiodarone, lidocaine is associated with statistically significant higher rates of ROSC, 24h survival,

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Lidocaine for the Treatment of In-Hospital Cardiac Arrest Chest. 2023 May;163(5):1109-1119	in-hospital cardiac arrest with refractory VF/pVT. n = 14,630 patients	refractory VF/pVT receiving amiodarone or lidocaine. • January 2000 – December 2014 • 68.7% (n= 10,058) treated with amiodarone 31.3% (n=4572) treated with lidocaine	favourable neurologic outcome When compared with amiodarone, lidocaine associated with statistically significant increased rates of: ROSC (OR 1.15, p=0.01), 24h survival (OR 1.16, p=0.004) survival to discharge (OR 1.19, p <0.001) and favourable neurologic outcome (OR 1.18, p<0.001)	survival to hospital discharge and favourable neurologic outcome, in patients with in-hospital cardiac arrest with refractory pVT/VF.
Lee DK et al. Impact of early intravenous amiodarone administration on neurological outcome in refractory ventricular fibrillation: Retrospective analysis of prospectively collected prehospital data. Scan J Trauma Resus Emerg Med 2019; 27: 109-117	• Retrospective analysis of prospectively collected prehospital data • n=134 adults presenting with VF and nonresponsive to ≥3 shocks • Patients divided into 2 groups based on CPC 1-2 vs not at hospital discharge	• Adult OHCA due to initial VF • Persistent VF despite 3 shocks → 300 mg IV amiodarone + 150 mg if required	• 1°: Good neurological outcome at hospital discharge based on elapsed time from call-to-amiodarone (CPC 1-2) • 2°: Prehospital ROSC, total ROSC, survival to admission, survival to discharge based on call-to-amiodarone administration time • In univariate logistic regression, probability of good neurological outcome at hospital discharge decreased as the call-to amiodarone administration interval increased (OR 0.89 [95% CI = 0.80–0.99]) • In multivariate logistic regression TTM (OR 5.86 (1.27,27.09) & call-to-amio ≤ 20 min (OR 10.12 (1.37, 74.92) independently	• Early amiodarone administration (call-to-amiodarone administration interval ≤ 20 min) was an independent factor associated with good CPC at discharge in OHCA patients with initial VF and subsequent refr VF • Notably only 15 of 134 (11%) of patients were discharged with CPR 1-2 • Other system efficiencies could also account for benefit from earlier treatment (i.e. everything done sooner and more responsive substrate to any intervention)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			associated with better neurological outcome • Age, sex, public place, witnessed arrest, bystander CPR, targeted temperature management (TTM), the call-to-epinephrine administration interval, and the call-to-amiodarone administration interval were included in the multivariable logistic regression analysis	
Daya MR et al. Survival after IV versus IO amiodarone, lidocaine or placebo in out-of-hospital shock-refractory cardiac arrest. Circulation 2020;141:188-198	• Prespecified observational analysis of a randomized placebo-controlled clinical trial • n=3019 adults with nontraumatic OHCA due to VF randomized to amiodarone, lidocaine or placebo	• n=3019 adults with nontraumatic OHCA due to VF randomized to amiodarone, lidocaine or placebo • 2358 received assigned drugs IV; 661 IO	• 1° survival to hospital discharge • 2° survival to hospital admission, favorable neurological survival (modified Rankin scale 0-3). • Unadjusted and adjusted analyses were similar • Adjusted analysis for IV administration – amiodarone vs placebo 1.26 (1.06,1.50), lidocaine vs placebo 1.21 (1.02,1.45); for IO NSD • Statistically significant interaction between route of vascular access and survival not evident (p=0.32) • Adjusted analysis for survival to hospital admission, survival with mRS ≤ 3 all showed significant benefit	• Effects of amiodarone and lidocaine were significantly greater for IV than IO route across all outcomes and beneficial only for the IV route • Study underpowered to statistically significant interactions

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			amiodarone vs placebo; lidocaine vs placebo; NSD for IO	
Benz P et al. Frequency of advanced cardiac life support medication use and association with survival during in-hospital cardiac arrest. ClinTher2020;42: 121-129	• Retrospective single-center medical record review • n=181 in hospital cardiac arrest events	• Adults with in-hospital cardiac arrest between Jan 2017-March 2018	• 1° = frequency and quantity of medications used during resuscitation • 2° = median time to defibrillation, frequency of bicarbonate use • Use of meds: epinephrine 86.7% mean 4.2 mg; sodium bicarbonate 63.5% mean 9 grams (1.9 amps); amiodarone 30.9% mean 311.8 mg (70% of resuscitations with shockable initial rhythms). Lidocaine use surprisingly infrequent (<5% overall; 10% in shockable rhythms) • Amiodarone ROSC 0.63 (0.29,1.4); survival to discharge 0.94 (0.41, 2.16)	• Inconclusive for benefit of amiodarone on ROSC or survival to hospital discharge
Wang CH et al. Outcomes associated with amiodarone and lidocaine for the treatment of adult in hospital cardiac arrest with shock-refractory pulseless ventricular tachyarrhythmia. J Formosan Med Assoc 2020;119:327-34	• Retrospective study single medical center of patients with in-hospital cardiac arrest with VF/pVT • n = 130 Multivariate logistic regression analysis included all available independent variables were considered in the regression model, regardless of	• In-hospital adult nontraumatic cardiac arrest 2006-2015 from VF/pVT requiring > 1 shock • n= 113 who received amiodarone or lidocaine during resuscitation • 86.9% received amiodarone as first AA Rx (median 300 mg)	• 1° outcome termination of VF/pVT within three shocks. Termination of VF/pVT was defined as its displacement to a nonshockable rhythm (organised or asystole). • 2° outcomes included sustained ROSC, survival for 24 h, survival to hospital discharge, and a favourable neurological outcome at hospital discharge. A favorable neurological status was defined as a score of 1 or	• Amiodarone-first strategy seemed to be associated with the termination of VF/pVT using fewer shocks • Other outcomes inconclusive due to small study size • Study flawed in that amiodarone or lidocaine were administered after the 3rd shock – whereas primary outcome was termination within 3 shocks.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	whether they were scored as significant in the univariate analyses.	; 17 received lidocaine first (median 100 mg)	2 on the Cerebral Performance Category (CPC) scale Multivariate logistic regression analyses: • Amiodarone-first group experienced a higher likelihood of terminating the VF/pVT within three shocks (odds ratio: 11.61, (95% CI 1.34,100.84); p-value = 0.03), as compared with the lidocaine-first group • No significant differences between the amiodarone- and lidocaine-first groups in sustained return of spontaneous circulation (1.03 (0.29,3.71), survival for 24 h (0.66 (0.10,4.37), survival to discharge (0.12 (0.01, 1.47), or favourable neurological outcomes at hospital discharge (0.28 (0.02, 3.42).	
Lee BK. Effect of Prophylactic Amiodarone Infusion on the Recurrence of Ventricular Arrhythmias in Out-of-Hospital Cardiac Arrest Survivors: A Propensity-Matched Analysis. J Clin	• Retrospective, observational propensity-matched record review study from 4 tertiary care hospital prospective databases • n= 295 hospitalized OHCA from shockable arrhythmias + 149	• n= 295 hospitalized OHCA from shockable arrhythmias + 149 with nonshockable-turned-shockable arrhythmias undergoing TTM • 124 propensity-matched patients received	• 1° VT recurrence • 2° survival to discharge, neurological outcome (CPC 1-2) … • 50/444 patients (11.3%) had VT recurrence most commonly during TTM induction • Recurrence of ventricular arrhythmia significantly higher in prophylactic amiodarone group than in non-prophylactic amiodarone	• Prophylactic amiodarone after successful resuscitation from cardiac arrest with initial shockable or subsequently occurring shockable rhythm was not associated with the prevention of recurrent ventricular arrhythmias during TTM, improving survival or neurological outcome • Likely highly biased amiodarone treatment group owed to multiple risk factors,

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Med 2019;8:244-53	with nonshockable-turned-shockable arrhythmias undergoing TTM • Assess effectiveness of prophylactic IV amiodarone in preventing ventricular arrhythmia recurrences during TTM (33 and 36°)	prophylactic IV amiodarone vs 320 did not	group in multivariate (nonpropensity) analysis (16.9% vs. 9.1%, p = 0.02); no difference in survival to discharge or neurological outcome • 93 patients in each group were propensity matched… with NSD in VT recurrence, survival or favorable neurological outcome	resulting in a higher VT recurrence rate in adjusted analyses that resolved when propensity-adjusted.
Bellut H. Early recurrent arrhythmias after out-of-hospital cardiac arrest associated with obstructive coronary artery disease: Analysis of the PROCAT registry. Resuscitation. 2019 Aug;141:81-87.	Retrospective single centre study, Paris, France, cardiac arrest centre - between January 2007 and December 2016 in the 24-bed medical ICU at Cochin University Hospital (Paris, France).	256 patients with primary OHCA with VF/VT and coronary angiogram and admitted to ICU. 29 major arrhythmia vs. 227 without major arrhythmia. 36 (14%) patients received a prophylactic AA treatment at admission in the ICU (which was amiodarone in all cases), with no significant difference between the 2 groups (4/29 in the major arrhythmia group	In multivariate analysis, treatment with prophylactic anti-arrhythmic in the ICU was not associated with a change in the risk of recurrence (OR 0.85 [0.21–3.65], p = 0.82).	Early recurrence of major arrhythmia was observed in more than 10% of post-cardiac arrest patients. These events happened mostly within the first 24 h. Too few patients to state whether prophylaxis was helpful.

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		vs 32/227 in controls		
Other Antiarrhythmics or combinations				
Lian R et al. The first case series analysis on efficacy of esmolol injection for in-hospital cardiac arrest patients with refractory shockable rhythms in China Front Pharmacol. 2022 Sep 30;13:930245	• Retrospective case series analysis of adult IHCA with refractory VF/pVT treated with esmolol – no control n = 29	• Adult IHCA with refractory shockable rhythms (VF/pVT) persisting after ≥3 defibrillation attempts, who received esmolol during CA • n = 9, given esmolol ≤5 defibrillation attempts n = 20, given esmolol bolus after 5th defibrillation attempt	• Efficacy assessment: sustained ROSC (≥20 minutes), ≥24h ROSC, ≥72h ROSC, survival to hospital discharge • Sustained ROSC: 79% • ≥24h ROSC: 62% • ≥72h ROSC: 59% • Survival to hospital discharge: 59% No statistically significant difference between those administered esmolol bolus ≤5 defibrillation attempts and those given it after >5 defibrillations, in any measured outcome	• Success rates of sustained ROSC, 24 h ROSC, 72 h ROSC, and survival to hospital discharge were 79%, 62%, 59%, and 59%. • Small study size Less benefit seen in patients with end-stage heart failure
Patrick C et al. Feasibility of prehospital esmolol for refractory ventricular fibrillation J Am Coll Emerg Physicians Open. 2022 Apr 9;3(2):e12700	• Retrospective observational analysis of esmolol for adult out-of-hospital cardiac arrest with refractory VF • n = 63 with cardiac arrest and refractory VF (control) n = 70 with cardiac arrest and RVF	Adult out-of-hospital cardiac arrest with refractory VF who received ≥3 EMS defibrillations between June 2017 and June 2020	• 1° outcome: to assess 'feasibility' defined as >75% of patients meeting RVF criteria receiving prehospital esmolol • 2° outcome: ROSC during EMS encounter, 24h hospital survival, survival to hospital discharge • 38% patients who received esmolol achieved prehospital ROSC compared to 24%	• 87% eligible patients with cardiac arrest and refractory VF received esmolol prehospitally • OR 1.99 (95% CI 0.89-4.47) of ROSC during EMS encounter for those who received esmolol, compared to those who did not. This was not statistically significant. • Small sample size • Lower proportion of patients received antiarrhythmics after the

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	received single bolus 0.5mg/kg esmolol (intervention)		in the control group (p=0.09). 24h survival and survival to discharge were the same in both groups.	addition of esmolol to the protocol
Stupca K et al. Esmolol, vector change, and dose-capped epinephrine for prehospital ventricular fibrillation or pulseless ventricular tachycardia Am J Emerg Med. 2023 Feb;64:46-50.	• Retrospective, multicentre, cohort study of prehospital cardiac arrest with refractory VF/pVT • Patients receiving 'EMS bundle' – esmolol, vector change defibrillation, dose-capped epinephrine of 3mg – compared to standard ACLS care n = 83 patients	• Prehospital cardiac arrest with VF/pVT having received ≥3 defibrillations, ≥3 epinephrine and 300mg amiodarone. • n = 36, standard ACLS care n = 47, 'EMS bundle'	• 1° outcome: sustained ROSC (>20 mins without recurrence of cardiac arrest) • 2° outcome: incidence of ROSC, survival to hospital arrival, survival to hospital discharge and neurologically intact survival at hospital discharge • Those who received standard ACLS care achieved significantly higher rates of sustained ROSC (58.3% vs 17%, p < 0.001), any ROSC (66.7% vs 19.1%, p < 0.001), and survival to hospital arrival (55.6% vs 17%, p < 0.001) Survival to hospital discharge (16.7% vs 6.4%, p=0.17) and neurologically intact survival at hospital discharge (5.9% vs 4.3%, p=1.00) were not significantly different between groups	• Those who received the EMS bundle achieved significantly less likely to achieve sustained ROSC or survive to hospital admission Neurologically intact survival rates were low and similar between groups
Huebinger R Time to Antiarrhythmic and Association with Return of	• Retrospective observational analysis of national EMS database	• Adult non-traumatic cardiac arrests with initial	• Outcomes: time to antiarrhythmic administration, ROSC • Median time to initial amiodarone dose was	Longer time to administration of antiarrhythmic associated with decreased rate of ROSC

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Spontaneous Circulation in the United States Prehosp Emerg Care. 2023;27(2):177-183.	n = 11,939 patients	shockable rhythm and received an antiarrhythmic • n = 9236 received amiodarone n = 1327 received lidocaine	19.9 minutes (IQR 15.8-25.6) • Median time to initial lidocaine dose was 19.5 minutes (IQR 15.2-25.4) • Rate of ROSC higher for lidocaine (30.2%) than amiodarone (24.5%) Increased time to initial antiarrhythmic associated with decreased rates of ROSC for amiodarone (OR 0.9, 95% CI 0.9-0.94) and lidocaine (OR 0.9 95% CI 0.8-0.97)	
Li DL et al. Quinidine in the Management of Recurrent Ventricular Arrhythmias: A Reappraisal JACC Clin Electrophysiol. 2021 Oct;7(10):1254-1263.	• Retrospective analysis of single tertiary centre of patients with in-hospital recurrent sustained ventricular arrhythmias n = 37 patients	Adult inpatients receiving first-time quinidine for recurrent sustained ventricular arrhythmias (VT and VF)	• 1° outcome: first recurrence of VA, ICD shock and repeated VA ablation (and/or other procedures for VA suppression) • 2° outcomes: death, orthotopic heart transplant • Quinidine reduced acute VA from median of 3 episodes (IQR 2-7.5) to 0 (IQR 0-0.5) during median 3 days before and 4 days after initiation ($p < 0.001$) • Decreased from median 10.5 episodes/day (IQR 5-15) to 0.5 (IQR 0-4) in those with electrical storm (p=0.004) Of those discharged on quinidine, 54.2% has VA recurrence, median 138 days.	• Quinidine can be useful as a short-term therapy in patients with recurrent VAs and structural heart disease • 24.3% patients experienced adverse effects that led to drug discontinuation. • Small cohort

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Funakoshi H Nifekalant versus Amiodarone for Out-Of-Hospital Cardiac Arrest with Refractory Shockable Rhythms; a Post Hoc Analysis Arch Acad Emerg Med. 2022 Jan 1;10(1):e6.	• Post-hoc analysis of nationwide, multi-centre observational study n = 1317	• Adult OHCA with refractory VF/pVT receiving nifekalant or amiodarone after arrival to hospital • June 2014-December 2017 • n = 1275 received amiodarone n = 42 received nifekalant	• 1° outcome: admission after ROSC • 2° outcomes: 30 day survival, 30 day favourable neurological outcome (CPC 1 or 2) For nifekalant (compared to amiodarone): admission after ROSC (-5.9%, 95% CI -7.1 to 22.4, p =0.57), 30 day favorable neurological outcome (0.1%, 95% CI -14 to 13.9, p=0.99, 30 day survival (-3.9%, 95% CI -19.8 to 12, p=0.63)	Nifekalant not associated with improved outcomes re admission after ROSC, 30 day survival or 30 day favourable neurological outcome when compared with amiodarone.
Huebinger R Procainamide for shockable rhythm cardiac arrest in the Resuscitation Outcome Consortium Am J Emerg Med. 2022 May;55:143-146	• Retrospective observational study evaluating procainamide for OHCA from the Resuscitation Outcomes Consortium n = 3087 patients	• Adult OHCA with initial shockable rhythm and received an antiarrhythmic from ROC Epistry 3 • n = 51 procainamide • n = 1776 amiodarone n = 1418 lidocaine	• Prehospital ROSC, ROSC at ED arrival, survival to hospital discharge • Compared to procainamide, amiodarone had similar prehospital ROSC (OR 0.7, 95% CI 0.3–1.8), ED ROSC (OR 0.6, 95% CI 0.3–1.3), and survival (OR 1.0, 95% CI 0.3–3.1). Lidocaine also had a similar prehospital ROSC (OR 0.9, 95% CI 0.4–2.2), ED ROSC (OR 1.2, 95% CI 0.5–2.7), and survival (OR 1.4, 95% CI 0.5–4.0)	While associated with increased prehospital ROSC when compared with amiodarone using multivariable regression, procainamide otherwise had similar prehospital ROSC, ED ROSC, and survival.
Viskin S et al. Quinidine-Responsive Polymorphic Ventricular Tachycardia in Patients With	• Retrospective observational study of patients with polymorphic VT and coronary	• n= 43 adults within days of uncomplicated AMI or coronary revascularization with polymorphic	• 1° outcome termination of polymorphic VT/VF storm • 17 of 23 patients in storm received quinidine (1200-2000 mg qd) responded vs 6 pts who	• The specific form of polymorphic VT described (in context of recent AMI or coronary revascularization) may be responsive to quinidine.

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Coronary Heart Disease. Circulation 2019;139:2304-14.	artery disease – no control • n= 43	VT deteriorating to VF or storm who failed conventional AA Rx including amiodarone, lidocaine and Mg • n=23 had polymorphic VT/VF storm	received non-quinidine therapies (p<0.0001)	• Study non-randomized • Benefit of quinidine may be limited to a specific ischemic patient group
Schupp T, et al. Prognostic impact of beta-blocker compared to combined amiodarone therapy secondary to ventricular tachyarrhythmias. Int J Cardiol 2019:277:118-124	A large retrospective registry analysis, propensity-score matching (before matching, n=1,354; after matching, n=372)	P: patients surviving at least one episode of ventricular tachyarrhythmias I: beta-blocker (before matching, n=1,144; after matching, n=186) C: beta-blocker with amiodarone (before matching, n=210; after matching, n=186) O: all-cause mortality T: from 2002 until 2016	BB associated with improved long-term survival compared to BB-AMIO (univariable: HR = 0.550; p = 0.001, multivariable: HR = 0.712; statistical trend, p = 0.052). After propensity-score matching, BB therapy was still associated with improved survival compared to BB-AMIO (mortality rate 18% versus 26%; log rank p = 0.042; HR = 0.634; 95% CI = 0.407-0.988; p = 0.044). Prognostic superiority of BB was mainly observed in patients with LVEF>= 35% (HR = 0.463; 95% CI = 0.215-0.997; p = 0.049) and in those without atrial fibrillation (non-AF) (HR = 0.415; 95% CI = 0.202-0.852; p = 0.017).	BB therapy is associated with improved secondary long-term prognosis compared to BB-AMIO in patients surviving index episodes of ventricular tachyarrhythmias.
Huang CH, et al. Acute hospital administration of	Retrospective, observational, and nationwide	P: patients with shockable cardiac arrest	Odds ratios for 1-year survival via multiple regression analysis were	In patients with shockable cardiac arrest, 1-year survival rates were improved with

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amiodarone and/or lidocaine in shockable patients presenting with out-of-hospital cardiac arrest: A nationwide cohort study. Int J Cardiol 2017:227:292-298.	population-based cohort study, Nationwide registry analysis (Taiwan National Health Insurance Research Database (NHIRD))	I: amiodarone (n=6,459), lidocaine (n=1,077), amiodarone with lidocaine (n= 1,487) C: placebo (non-treatment., n=18,440) O: 1-year survival; survival to intensive care unit (ICU) admission; survival to discharge T: from 2004 until 2011	1.84 (95% CI: 1.58-2.13; p<0.0001) for amiodarone, 1.88 (95% CI: 1.40-2.53; p<0.0001) for lidocaine, and 2.18 (95% CI: 1.71-2.77; p<0.0001) for dual agent use. The dual treatment group also surpassed the other groups in terms of survival to ICU admission (34.10%) and survival to discharge (12.25%) administration of anti-arrhythmic agents during resuscitation increased chances of survival to ICU admission and survival to discharge compared with non-treatment, with the highest ORs seen in the dual-agent (amiodarone and lidocaine) group.	association of using amiodarone and/or lidocaine, as opposed to non-treatment. Outcomes of patients given one or both medications did not differ significantly in intergroup comparisons.

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)

Despite the large number of studies, there is no compelling new data that is likely to update our existing treatment recommendations for amiodarone and lidocaine.

There is new data on beta-blockers and procainamide that would benefit from a formal systematic review.

Specifically:

1. Review of interim evidence does not provide new data that would alter previous recommendations regarding use of lidocaine and amiodarone in shock-refractory VF/Pulseless VT.

2. Confidence in effect estimates remain low to support an ALS Task Force recommendation about the use of bretylium, nifekalant, or sotalol in the treatment of adults in cardiac arrest with shock-refractory VF/pVT.

3. Use of beta blockers (esmolol, propranolol, metoprolol) for this indication was not included in the 2018 treatment recommendations and this issue warrants a more detailed systematic review.

4. While bretylium has recently re-entered the market following its discontinuation in 1999, no new evidence has since emerged from earlier studies that would change prior guideline recommendations. Those recommendations previously indicated that bretylium should not be used as a first-line antiarrhythmic agent because of a high occurrence of side effects and the availability of safer agents at least as efficacious. More study of the drug is required. (Thind M. Bretylium, a class III antiarrhythmic, returns to the market. Am J Cardiol 2020;133:77-80.)

5. Three observational studies have specifically addressed the prophylactic use of lidocaine and amiodarone following out-of-hospital cardiac arrest, and do not provide sufficient evidence to alter previous recommendations (those indicated there was insufficient evidence to support any specific recommendations).

6. There are limited data on the use of combination drugs (amiodarone and lidocaine) as compared with amiodarone or lidocaine used singly for the treatment of VF/pVT, and these do not provide sufficient evidence to support any recommendations.

7. Use of drugs such as quinidine for unique ventricular rhythm presentations and associated genetic conditions remains mainly anecdotal or based on limited case series in selected patients with insufficient evidence to support any specific recommendations.

8. Procainamide is used in some EMS systems and was not addressed in our 2018 review – this could be part of a formal systematic review.

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