C1. Automated External Defibrillator Versus Manual Defibrillator (ALS 495: EvUp)

Worksheet author(s): Mark Link
Council: AHA
Date Submitted:

PICO / Research Question: Automatic Versus Manual Modes for Multimodal Defibrillators

Among adults who are in cardiac arrest in any setting (P), does AED or a multifunctional defibrillator in automatic mode use (I), compared with standard resuscitation (using a manual defibrillator) (C), change outcomes (O)?

Current evidence indicates that the benefit of using a multimodal defibrillator in manual instead of automatic mode during cardiac arrest is uncertain (Class IIb, LOE C).

Outcomes: Any clinical outcome
Type (intervention, diagnosis, prognosis):

Additional Evidence Reviewer(s):
Conflicts of Interest (financial/intellectual, specific to this question):

Year of last full review: 2010 / 2015 / New question: 2010

Last ILCOR Consensus on Science and Treatment Recommendation:

2010/2015 Search Strategy:

((((manual[Title/Abstract]) OR automatic[Title/Abstract])) AND ((defibrillation, electric[MeSH Terms]) NOT defibrillator, implantable[MeSH Terms])) AND ((((((((((life support care[MeSH Terms]) OR "life support"[Title/Abstract]) OR cardiopulmonary resuscitation[MeSH Terms]) OR "cardiopulmonary resuscitation"[Title/Abstract]) OR "CPR"[Title/Abstract]) OR "return of spontaneous circulation"[Title/Abstract]) OR "ROSC"[Title/Abstract]) OR heart arrest[MeSH Terms]) OR "cardiac arrest"[Title/Abstract])) NOT ((animals[MH] NOT humans[MH])))

2019 Search Strategy: **((((manual[Title/Abstract]) OR automatic[Title/Abstract])) AND ((defibrillation, electric[MeSH Terms]) NOT defibrillator, implantable[MeSH Terms])) AND ((((((((((life support care[MeSH Terms]) OR "life support"[Title/Abstract]) OR cardiopulmonary resuscitation[MeSH Terms]) OR "cardiopulmonary resuscitation"[Title/Abstract]) OR "CPR"[Title/Abstract]) OR "return of spontaneous circulation"[Title/Abstract]) OR "ROSC"[Title/Abstract]) OR heart arrest[MeSH Terms]) OR "cardiac arrest"[Title/Abstract])) NOT ((animals[MH] NOT humans[MH])))**

Database searched:Pubmed
Date Search Completed:
Search Results (Number of articles identified / number identified as relevant):
Inclusion/Exclusion Criteria:
Link to Article Titles and Abstracts (if available on PubMed):

https://www.ncbi.nlm.nih.gov/myncbi/collections/59068204/

Summary of Evidence Update:
Evidence Update Process for topics not covered by ILCOR Task Forces

1. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

Organisation (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)**
	Study Type:	**Inclusion Criteria:**	**1° endpoint:**	
Nehme Z, et al. Manual Versus Semiautomatic Rhythm Analysis and	Retrospective: observational	All shockable cardiac arrests from 2005 to 2015	Although the proportion of patients shocked within 2 minutes of arrival increased during the	Semiautomated rhythm analysis was no better than manual rhythm analysis, and may be associated with worsened survival

Defibrillation for Out-of-Hospital Cardiac Arrest PMID: 28698191			SAED protocol for initial shockable rhythms (from 58.9% to 69.2%; P<0.001), there was no difference in unadjusted rate of successful cardioversion after first shock (from 12.3% to 13.8%; P=0.13). the SAED protocol was associated with a reduction in survival to hospital discharge (AOR, 0.71; 95% CI, 0.55-0.92; P=0.009), event survival (AOR, 0.74; 95% CI, 0.62-0.88; P=0.001), and prehospital return of spontaneous circulation (AOR, 0.81; 95% CI, 0.68-0.96; P=0.01) when compared with the manual protocol.	
Zijlstra JA Automated external defibrillator and operator performance in out-of-hospital cardiac arrest. PMID: 28526495	Retrospective	AEDs used between January 2012 and December 2014.	1114 AED recordings with 3310 analysis periods (1091 shock advices; 2219 no-shock advices). Sensitivity for coarse ventricular fibrillation was 99% and specificity for non-shockable rhythm detection 98%. The AED gave an incorrect shock advice in 4% (44/1091) of all shock advices, due to device-related (n=15) and operator-related errors (n=28)	AEDs are reasonably accurate, but not perfect.
Loma-Osorio P The Girona Territori Cardioprotegit Project: Performance	Retrospective	AED in a public defibrillation program from June 2011 to June 2015	231 AED activations. The specificity of the device in identifying a shockable rhythm was 100%, but there were 8	AEDs with excellent specificity, but not excellent sensitivity (it missed 17% of the shockable rhythms)

Evaluation of Public Defibrillators. PMID: 28522305			false negatives (sensitivity 83%).	
Cheskes S The association between manual mode defibrillation, pre-shock pause duration and appropriate shock delivery when employed by basic life support paramedics during out-of-hospital cardiac arrest. PMID: 25737080	Retrospective	2012 AED use	Among 2019 treated OHCA, 335 (20%) presented in a shockable rhythm. Manual defibrillation was performed in 155 (46%) of these cases (196 shocks by ALS, 143 shocks by BLS). There were no differences in the proportion of shocks delivered with pre-shock pause duration <20s (ALS 82.8% vs. BLS 84.8%, p=.65) nor pre-shock pause duration (s) (median, Q1, Q3); ALS: 12.0 (7.0,17.0) vs. BLS: 11.0 (5.0,17.0), p=.13 while BLS had a significantly shorter peri-shock pause duration(s) (median, Q1, Q3); ALS: 17.0 (12.0, 23.0) vs. BLS: 15.0 (9.0, 22.0), p=.05. There were no differences in the rate of inappropriate shocks (ALS 1.0% vs. BLS 0.7%), p=1.0 between levels of paramedics	Manual mode defibrillation no better than automated
Israelsson J Sensitivity and specificity of two different automated external defibrillators. PMID: 28923243	Retrospective	2938 rhythm analyses performed by AEDs in 240 consecutive patients	Among 194 shockable rhythms, 17 (8.8%) were not recognized by AED A, while AED B recognized 100% (n=135) of shockable episodes (sensitivity 91.2 vs 100%, p<0.01). In AED A, 8 (47.1%) of these	Not all AED algorhythms are accurate

			episodes were judged to be algorithm errors while 9 (52.9%) were caused by external artifacts. Among 1039 non-shockable rhythms, AED A recommended shock in 11 (1.0%), while AED B recommended shock in 63 (4.1%) of 1523 episodes (specificity 98.9 vs 95.9, p<0.001). In AED A, 2 (18.2%) of these episodes were judged to be algorithm errors (AED B, n=40, 63.5%), while 9 (81.8%) were caused by external artifacts (AED B, n=23, 36.5%).	

Reviewer Comments (including whether meet criteria for formal review):

Of the studies identified, only two directly compared AED to manual defibrillator use. Limited evidence suggests no definite benefit of one approach over the other. There is insufficient evidence to warrant an updated systematic review.

	Approval Date
Evidence Update coordinator	
ILCOR board	

***Once approval has been made by Evidence Update coordinator, worksheet will go to ILCOR Board for acknowledgement.**

Reference list

Nehme Z, Andrew E, Nair R, Bernard S, Smith K Manual Versus Semiautomatic Rhythm Analysis and Defibrillation for Out-of-Hospital Cardiac Arrest. Circ Cardiovasc Qual Outcomes. 2017 Jul;10(7). pii: e003577. doi: 10.1161/CIRCOUTCOMES.116.003577.

Zijlstra JA, Bekkers LE, Hulleman M, Beesems SG, Koster RW. Automated external defibrillator and operator performance in out-of-hospital cardiac arrest. Resuscitation. 2017 Sep;118:140-146. doi: 10.1016/j.resuscitation.2017.05.017.
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Loma-Osorio P, Nuñez M, Aboal J, Bosch D, Batlle P, Ruiz de Morales E, Ramos R, Brugada J, Onaga H, Morales A, Olivet J, Brugada R. The Girona Territori Cardioprotegit Project: Performance Evaluation of Public Defibrillators. Rev Esp Cardiol (Engl Ed). 2018 Feb;71(2):79-85. doi: 10.1016/j.rec.2017.04.011. Epub 2017 May 16.

Cheskes S, Hillier M, Byers A, Verbeek PR, Drennan IR, Zhan C, Morrison LJ.
The association between manual mode defibrillation, pre-shock pause duration and appropriate shock delivery when employed by basic life support paramedics during out-of-hospital cardiac arrest. Resuscitation. 2015 May;90:61-6. doi: 10.1016/j.resuscitation.2015.02.022. Epub 2015 Feb 28.

Israelsson J(1), Wangenheim BV(2), Årestedt K(3), Semark B(4), Schildmeijer K(5), Carlsson J(6). Sensitivity and specificity of two different automated external defibrillators.
Resuscitation. 2017 Nov;120:108-112. doi: 10.1016/j.resuscitation.2017.09.009.
Epub 2017 Sep 18.

C2a. Waveform Analysis for Predicting Successful Defibrillation (ALS 601: EvUp)

Worksheet author(s): Cindy Hsu
Council: AHA
Date Submitted:

PICO / Research Question: ALS 601: Waveform analysis for predicting successful defibrillation

Among adults who are in cardiac arrest in any setting (P), does a technique for prediction of the likelihood of success of defibrillation (analysis of VF, etc) (I), compared with standard resuscitation (without such prediction) (C), improved outcomes (O) (eg, termination of rhythm, ROSC)?

Outcomes: ROSC, sustained ROSC, defibrillation success, return to organized rhythm, survival to hospital admission, survival to hospital discharge, neurologically intact survival

Type (intervention, diagnosis, prognosis): Intervention
Additional Evidence Reviewer(s):
Conflicts of Interest (financial/intellectual, specific to this question): None

Year of last full review: 2010 / 2015 / New question: 2010

Last ILCOR Consensus on Science and Treatment Recommendation:

2010 CoSTR: There is insufficient evidence to support routine use of VF waveform analysis to guide defibrillation management in adult cardiac arrest in- or out-of-hospital [Jacobs 2010 s325].

AHA: The value of VF waveform analysis to guide management of defibrillation in adults with in-hospital and out-of-hospital cardiac arrest is uncertain. (Class IIb, LOE C) (2010 Part 8)

2010/2015 Search Strategy: 2019

2019 Search Strategy:

(((defibrillator[MeSH Terms]) OR defibrillation, electric[MeSH Terms])) AND waveform[Title/Abstract]

Database searched: 1/15/2020
Date Search Completed: 1/15/2020
Search Results (Number of articles identified / number identified as relevant): 129/19
Inclusion/Exclusion Criteria:
Inclusion: Randomized trials, non-randomized controlled trials, and observational studies (cohort studies and case-control studies) comparing the outcome of prediction of the likelihood of success of defibrillation (analysis of VF, etc) with standard resuscitation in cardiac arrest.
Exclusion: Ecological studies, animal studies, case series, case reports, reviews, abstracts, editorials, comments, letters to the editor and unpublished studies were not included.

Link to Article Titles and Abstracts (if available on PubMed):
https://www.ncbi.nlm.nih.gov/sites/myncbi/1PgE4WBCzHi505/collections/59128879/public/

Summary of Evidence Update:
Evidence Update Process for topics not covered by ILCOR Task Forces

1. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

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

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
Freese et al 2013 (NCT00535106; PMID: 23979627)	**Study Aim:** To determine whether a waveform analysis algorithm could be used to identify VF unlikely to respond to immediate defibrillation, allowing selective initial treatment with CPR in an effort to improve overall survival. **Study Type:** Multicenter, double-blind, randomized study	**Inclusion Criteria:** OHCA patients in in 2 urban EMS systems who were treated with AEDs (n=987). The VF waveform analysis used a predefined threshold value below which ROSC was unlikely with immediate defibrillation, allowing selective treatment with a 2-minute interval of CPR before initial defibrillation.	**Intervention:** VF waveform analysis algorithm **Comparison:** Standard shock-first protocol	**1° endpoint:** Survival to hospital discharge **2° endpoint:** ROSC, sustained ROSC, and survival to hospital admission Of 6738 patients enrolled, 987 patients with VF of primary cardiac origin were included in the primary analysis. No immediate or long-term survival benefit was noted for either treatment algorithm (ROSC, 42.5% vs. 41.2%, P=0.70; sustained ROSC, 32.4% vs. 33.4%,	**Conclusion:** Use of a waveform analysis algorithm to guide the initial treatment of OHCA patients presenting in VF did not improve overall survival compared with a standard shock-first protocol. **Study Limitations:** No standardization of post-resuscitation inpatient care at either site. Only 1 waveform analysis parameter was studied. No ability to measure CPR performance during the study.

				P=0.79; survival to admission, 34.1% vs. 36.4%, P=0.46; survival to hospital discharge, 15.6% versus 17.2%, P=0.55, respectively).	

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)**
Balderston et al; 2018 (PMID: 29910058)	**Study Type:** Retrospective observational study (n=80)	**Inclusion Criteria:** 80 adult non-traumatic OHCA patients with a presenting VF rhythm and defibrillator data available with at least one defibrillation attempt between 10/1/2014 and 9/31/2016. Maximum amplitude during 3-second ECG tracings prior to each defibrillation attempt and the amplitude immediately prior to defibrillation were analyzed.	**1° endpoint:** Defibrillation success; ROSC; Survival to hospital discharge (SHD) **Results:** Both the amplitude just prior to defibrillation and the highest amplitude within 3 seconds of the defibrillation were significantly higher in successful vs unsuccessful defibrillations (0.21 vs 0.11 mV, P = 0.0001 and 0.51 vs 0.36 mV, P =< 0.0001). Amplitude immediately prior to defibrillation and maximal amplitude within 3 seconds of defibrillation were also higher in defibrillations with ROSC vs. defibrillations without ROSC (0.23 vs. 0.12 mV, P < .0001; and 0.52 vs. 0.38 mV, P < .0001). In defibrillations that resulted in SHD, immediate pre-defibrillation amplitude and maximum amplitude were also significantly larger (0.20 vs. 0.11 mV, P <.0001; and 0.52 vs. 0.35 mV, P <.0001). Binary logistic regression including both measures showed that only immediate pre-defibrillation amplitude remained	Amplitude of the VF waveform at the moment of defibrillation has a strong association with successful defibrillation, ROSC, and SHD.

			significantly associated with ROSC while maximal amplitude did not (P = .006 and P = .135).	
Agerskov et al 2017 (PMID: 28901546)	**<u>Study Type:</u>** Retrospective observational study (n=196)	**<u>Inclusion criteria:</u>** Adult OHCA occurring between 2011 and 2014 in the Capital Region of Denmark where an AED was applied prior to ambulance arrival (n=196).	**<u>1° endpoint:</u>** ROSC at hospital arrival; Converting rates among patients with initial shockable rhythm **<u>Results:</u>** 62/196 (32%) of AED-applied OHCA provided audio visual (AV) feedback while no feedback was provided in 134 (68%). There was no difference in ROSC at hospital arrival according to AV-feedback; 34 (55%, 95% CI [13-67]) vs. 72 (54%, 95% CI [45-62]), P = 1 (odds ratio (OR) 1.1, 95% CI [0.6-1.9]) or 30-day survival; 24 (39%, 95% CI [28-51]) vs. 53 (40%, 95% CI [32-49]), P = 0.88 (OR 1.1 (95% CI [0.6-2.0])). There was no difference in converting rates among patients with initial shockable rhythm receiving one or more shocks according to AED energy waveform and energy level.	In OHCA patients with an AED applied prior to ambulance arrival, there was no difference in survival according to AV-feedback. In addition, there was no difference in converting rate in patients with initial shockable rhythm according to waveform and energy level.
Coult et al 2018 (PMID: 28893389)	**<u>Study Type:</u>** Retrospective cohort study (n=692)	**<u>Inclusion criteria:</u>** adult OHCA patients presenting with an initial VF in King County, WA, from 2005 to 2014 who required at least 2 shocks with defibrillator data. Amplitude Spectrum Area (AMSA) and Median Slope (MS) were calculated from 5-second pre-shock segments with and without CPR, and compared to logistic models combining each measure with	**<u>1° endpoint:</u>** Shock success during CPR **<u>Results:</u>** VF segments from 692 patients were analyzed during CPR before 1372 shocks and without CPR before 1283 shocks. Combining waveform measures with prior ROR increased areas under receiver operating characteristic curves for AMSA/MS with CPR (0.66/0.68 to 0.73/0.74, $p < 0.001$) and without CPR (0.71/0.72 to 0.76/0.76, $p < 0.001$).	Prior ROR improves prediction of shock success during CPR, and may enable waveform measure calculation without chest compression pauses.

		prior return of organized rhythm (ROR).		
Hulleman et al 2017 (PMID: 28844935)	**Study type:** Retrospective observational study (n=716)	**Inclusion criteria:** OHCA patients from cardiac causes between July 2005 and December 2011 with ECG VF recordings AED or manual defibrillator from the from the ARREST registry in the Netherlands. Multivariate logistic regression with log-transformed AMSA of first artifact-free VF segment was used to assess the association between AMSA and survival, according to presence of STEMI or previous MI, adjusting for resuscitation characteristics, medication use and comorbidities.	**1° endpoint:** Survival; STEMI **Results:** Of 716 VF-patients, 328 (46%) had STEMI as cause of OHCA. Previous MI was present in 186 (26%) patients. Survival was 66%; neither previous MI (P=0.11) nor STEMI (P=0.78) altered survival. AMSA was a predictor of survival (ORadj: 1.52, 95%-CI: 1.28-1.82). STEMI was associated with lower AMSA (8.4mV-Hz [3.7-16.5] vs. 12.3mV-Hz [5.6-23.0]; P<0.001), but previous MI was not (9.5mV-Hz [3.9-18.0] vs 10.6mV-Hz [4.6-19.3]; P=0.27). When predicting survival, there was no interaction between previous MI and AMSA (P=0.14). STEMI and AMSA had a significant interaction (P=0.002), whereby AMSA was no longer a predictor of survival (ORadj: 1.03, 95%-CI: 0.77-1.37) in STEMI-patients. In patients without STEMI, higher AMSA was associated with higher survival rates (ORadj: 1.80, 95%-CI: 1.39-2.35).	The prognostic value of AMSA is altered by the presence of STEMI: while AMSA has strong predictive value in patients without STEMI, AMSA is not a predictor of survival in STEMI-patients.
Nakagawa et al 2017 (PMID: 28104427)	**Study type:** Retrospective observational study (n=285)	**Inclusion criteria:** 285 VF patients given prehospital electric shocks by EMS. ΔAMSA was calculated by subtracting AMSA1 from last AMSA immediately before the last prehospital electric shock. Multivariate logistic regression analysis was performed	**1° endpoint:** ROSC **Results:** AMSA1 (odds ratio (OR) 1.151, 95% confidence interval (CI) 1.086-1.220) and ΔAMSA (OR 1.289, 95% CI 1.156-1.438) were independent factors influencing ROSC induction by electric shock. Area under the curve (AUC) for predicting ROSC was 0.851 for AMSA1-only and 0.891 for AMSA1+ΔAMSA.	Post-shock ROSC was accurately predicted by adding ΔAMSA to AMSA1. AMSA-based ROSC prediction enables application of electric shock to only those patients with high probability of ROSC, instead of interrupting chest compressions and delivering unnecessary shocks to patients with low probability of ROSC.

		using post-shock ROSC as a dependent variable.	Compared with the AMSA1-only equation, the AMSA1+ΔAMSA equation had significantly better goodness-of-fit (likelihood ratio test P<0.001) and showed good fit in the bootstrap method.	
Jin et al 2017 (PMID 27951401)	**Study Type:** Retrospective observational study (n=554)	**Inclusion criteria:** A total of 554 shocks from 257 OHCA patients with VF as initial rhythm were analyzed. Post-shock rhythms were analyzed every 5s up to 120s and annotated as VF, asystole (AS) and organized rhythm (OR) at serial time intervals.	**1° endpoint:** Three shock/CPR success definitions were used to evaluate the predictability of AMSA: (1) termination of VF (ToVF); (2) return of organized electrical activity (ROEA); (3) return of potentially perfusing rhythm (RPPR). **Results:** Rhythm changes occurred after 54.5% (N=302) of shocks and 85.8% (N=259) of them occurred within 60s after shock delivery. The observed post-shock rhythm changes were (1) from AS to VF (24.9%), (2) from OR to VF (16.1%), and (3) from AS to OR (12.1%). The area under the receiver operating characteristic curve (AUC) for AMSA as a predictor of shock/CPR success reached its maximum 60s post-shock. The AUC was 0.646 for ToVF, 0.782 for ROEA, and 0.835 for RPPR (p<0.001) respectively.	Post-shock rhythm is unstable in the first minute after the shock. The predictability of AMSA varies depending on the definition of shock/CPR success and performs best with the return of potentially perfusing rhythm endpoint for OHCA.
Hidano et al 2016 (PMID: 27784613)	**Study Type:** Retrospective observational study (n=430)	**Inclusion criteria:** Adults treated by EMS for OHCA VF between January 1, 2006-December 31, 2014. Etiology was classified using hospital information into three exclusive groups: ACS with STEMI, ACS with non-STEMI, or non-ischemic arrest. Waveform	**1° endpoint:** Etiology of OHCA VF **Results:** Of the 430 patients, 35% (n=150) were classified as STEMI, 29% (n=123) as non-STEMI, and 37% (n=157) with non-ischemic arrest. We did not observe differences by etiology in any of the waveform measures prior to shock 1 (Kruskal-Wallis Test) (p=0.28 for AMSA, p=0.07 for CF, p=0.63 for MF, and	Waveform measures may not be useful in distinguishing cardiac arrest etiology.

		measures included amplitude spectrum area (AMSA), centroid frequency (CF), mean frequency (MF), and median slope (MS) assessed during CPR-free epochs immediately prior to the initial and second shock. Waveform measures prior to the initial shock and the changes between first and second shock were compared by etiology group.	p=0.39 for MS). We also did not observe differences for change in waveform between shock 1 and 2, or when the two acute ischemia groups (STEMI and non-STEMI) were combined and compared to the non-ischemic group.	
Coult et al 2016 (PMID 27702580)	**<u>Study Type:</u>** Retrospective observational study (n=442)	**<u>Inclusion criteria:</u>** CPR-free ECG prior to first shock among OHCA VF patients in a large metropolitan region (n=442). Amplitude Spectrum Area (AMSA) and Median Slope (MS) were calculated using ECG epochs ranging from 5s to 0.2s. The relative ability of the measures to predict return of organized rhythm (ROR) and neurologically-intact survival was evaluated at different epoch lengths by calculating the area under the receiver operating characteristic curve (AUC) using the 5-s epoch as the referent group.	**<u>1° endpoint:</u>** return of organized rhythm (ROR) and neurologically-intact survival **<u>Results:</u>** Compared to the 5-s epoch, AMSA performance declined significantly only after reducing epoch length to 0.2s for ROR (AUC 0.77-0.74, p=0.03) and with epochs of ≤0.6s for neurologically-intact survival (AUC 0.72-0.70, p=0.04). MS performance declined significantly with epochs of ≤0.8s for ROR (AUC 0.78-0.77, p=0.04) and with epochs ≤1.6s for neurologically-intact survival (AUC 0.72-0.71, p=0.04).	Waveform measures predict defibrillation outcome using very brief ECG epochs, a quality that may enable their use in current resuscitation algorithms designed to limit CPR interruption.
He et al 2016 (PMID 26863222)	**<u>Study Type:</u>** Retrospective observational study (n=199)	**<u>Inclusion criteria:</u>** A total of 528 defibrillation shocks from 199 OHCA	**<u>1° endpoint:</u>** Defibrillation outcome **<u>Results:</u>**	In this retrospective study, combining AMSA with previous shock information using neural networks greatly improves prediction

		patients were analyzed. VF waveform was quantified using amplitude spectrum area (AMSA) from defibrillator's ECG recordings prior to each shock. Combinations of AMSA with previous shock index (PSI) or/and change of AMSA (ΔAMSA) between successive shocks were exercised through a training dataset including 255 shocks from 99 patients with neural networks. Performance of the combination methods were compared with AMSA based single feature prediction through a validation dataset of 273 shocks from 100 patients.	A total of 61 (61.0%) patients required subsequent shocks (N = 173) in the validation dataset. Combining AMSA with PSI and ΔAMSA obtained highest AUC (0.904 vs. 0.819, p<0.001) among different combination approaches for subsequent shocks. Sensitivity (76.5% vs. 35.3%, p<0.001), NPV (90.2% vs. 76.9%, p = 0.007) and PA (86.1% vs. 74.0%, p = 0.005) were greatly improved compared with AMSA based single feature prediction with a threshold of 90% specificity.	performance of defibrillation outcome for subsequent shocks.
Indik et al 2014 (PMID: 25257639)	**<u>Study Type:</u>** Retrospective observational study (n=89)	**<u>Inclusion criteria:</u>** Adults with witnessed OHCA and an initial rhythm of VF from an Utstein style database were studied (Saving Hearts in Arizona Registry and Education program). AMSA was measured prior to each shock and averaged for each subject (AMSA-avg). Factors such as age, sex, number of shocks, time from dispatch to monitor/ defibrillator	**<u>1° endpoint:</u>** Pre-hospital ROSC, survival to hospital admission, and hospital discharge **<u>Results:</u>** 89 subjects (mean age 62 ± 15 years) with a total of 286 shocks were analyzed. AMSA-avg was associated with pre-hospital ROSC (p = 0.003); a threshold of 20.9 mV-Hz had a 95% sensitivity and a 43.4% specificity. Additionally, AMSA-avg was associated with hospital admission (p < 0.001); a threshold of 21 mV-Hz had a 95% sensitivity and a 54% specificity and with hospital discharge (p < 0.001); a threshold of 25.6 mV-Hz	AMSA is highly associated with pre-hospital ROSC, survival to hospital admission, and hospital discharge in witnessed VF OHCA. Future studies are needed to determine whether AMSA computed during resuscitation can identify patients for whom continuing current resuscitation efforts would likely be futile.

		application, first shock AMSA, and AMSA-avg that could predict pre-hospital ROSC, hospital admission, and hospital discharge were analyzed by logistic regression.	had a 95% sensitivity and a 53% specificity. First-shock AMSA was also predictive of pre-hospital ROSC, hospital admission, and discharge. Time from dispatch to monitor/ defibrillator application was associated with hospital admission (p = 0.034) but not pre-hospital ROSC or hospital discharge.	
Howe et al 2014 (PMID: 24291591)	**<u>Study Type:</u>** Retrospective observational study (n=41)	**<u>Inclusion criteria:</u>** OHCA VF patients in the greater Belfast area treated with a Heartsine defibrillator during 2007 and 2011. Frequency-domain (AMSA, dominant frequency and median frequency) and time-domain (slope and RMS amplitude) VF waveform metrics were calculated in a 4.1Y window prior to defibrillation. Conventional prediction test validity of each waveform parameter was conducted and used AUC>0.6 as the criterion for inclusion as a corroborative attribute processed by the SVM classification model.	**<u>1° endpoint:</u>** Termination of VF **<u>Results:</u>** A total of 41 patients had 115 defibrillation instances. AMSA, slope and RMS waveform metrics performed test validation with AUC>0.6 for predicting termination of VF and return-to-organized rhythm. Predictive accuracy of the optimized SVM design for termination of VF was 81.9% (± 1.24 SD); positive and negative predictivity were respectively 84.3% (± 1.98 SD) and 77.4% (± 1.24 SD); sensitivity and specificity were 87.6% (± 2.69 SD) and 71.6% (± 9.38 SD) respectively.	AMSA, slope and RMS were the best VF waveform frequency-time parameters predictors of termination of VF according to test validity assessment. This a priori can be used for a simplified SVM optimized design that combines the predictive attributes of these VF waveform metrics for improved prediction accuracy and generalization performance without requiring the definition of any threshold value on waveform metrics.
Wu et al 2013 (PMID: 23969193)	**<u>Study Type:</u>** Retrospective observational study (n=350)	**<u>Inclusion criteria:</u>** ECG recordings of 350 OHCA patients were obtained from the AED and analyzed by the method of signal integral. Successful defibrillation was defined as	**<u>1° endpoint:</u>** Successful defibrillation **<u>Results:</u>** Signal integral was significantly greater in successful defibrillation than unsuccessful defibrillation (81.76±32.3mV vs. 34.9±15.33mV, p<0.001). The intersection of the	Signal integral predicted successful electrical shocks on patients with ventricular fibrillation and have potential to optimize the timing of defibrillation and reduce the number of electrical shocks.

		organized rhythm with heart rate ≥40 bpm commencing within one min of post-shock period and persisting for a minimum of 30s.	sensitivity and specificity curve provided a threshold value of 51mV. The corresponding values of sensitivity, specificity, positive predictive and negative predictive values for successful defibrillation were 90%, 86%, 80% and 93%, respectively. The receiver operator curve further revealed that signal integral predicted the likelihood of successful defibrillation (AUC=0.949).	
Nakagawa et al 2012 (PMID: 22488555)	**Study Type:** Retrospective observational study (n=83)	**Inclusion criteria:** A total of 83 OHCA VF victims were classified into 4 groups according to type of cardiac rhythm after shock: ROSC, VF, PEA, and asystole. AMSA and PSA were calculated from ECG prior to shock and compared between groups.	**1° endpoint:** ROSC **Results:** The mean AMSA (4.0-48 Hz) in the ROSC group was 24.2 ± 8.5 mV-Hz, which was significantly higher than that in the VF and asystole groups.	It is possible by analyzing the AMSA of VF to predict cases where electrical defibrillation is more likely to return cardiac rhythm. Furthermore, unnecessary electrical shocks with a low possibility of ROSC can be avoided, and chest compression should be continued to prevent myocardial damage and consequently improve prognosis.
Hall et al 2011 (PMID: 21463200)	**Study Type:** Retrospective case–control study (n=206)	**Inclusion criteria:** Adult OHCA treated by EMS in King County, WA (excluding Seattle), between January 1, 2005, and December 31, 2008. Subjects were eligible if they had a CA before EMS arrival, were treated with an AED, had a complete electronic AED recording of the resuscitation, and manifested VF either upon initial EMS evaluation (primary) or later during the course of resuscitation (secondary). We identified each qualifying	**1° endpoint:** Survival **Results:** Survival was 42% in the primary group and 0% in the secondary group. There was a trend toward more favorable waveform values in the primary compared with the secondary group (9.48 versus 9.29, p = 0.10 for AMSA; 13.75 versus 14.12, p = 0.003 for COP; and 0.36 versus 0.44, p = 0.09 for DFA). The restricted, matched primary group experienced a survival of 37%, compared with 0% for the secondary group.	The electrophysiologic status of the heart may be suitable for resuscitation in at least some secondary ventricular fibrillation cases and that other pathophysiology may contribute substantially to the poor prognosis. Alternately, waveform measures may not predict clinical outcomes in secondary ventricular fibrillation.

		secondary VF case and a convenience sample of controls with primary ventricular fibrillation. Compared waveform measures of amplitude spectrum area (AMSA), cardioversion output predictor (COP), and detrended fluctuation analysis (DFA) prior to initial shock between the primary (n = 178) and secondary (n = 28) groups.		
Endoh et al 2011 (PMID: 21113633)	**<u>Study Type:</u>** Retrospective observational study (n=152)	**<u>Inclusion criteria:</u>** OHCA VF ECG waveforms stored in ambulance-located defibrillators were collected. Pre-defibrillation waveforms were divided into 1.0- or 5.12-s VF waveforms. Indices in frequency domain or nonlinear analysis were calculated on the 5.12-s waveform. Simultaneously, CWT was performed on the 1.0-s waveform, and total low-band (1-3 Hz), mid-band (3-10 Hz), and high-band (10-32 Hz) energy were calculated.	**<u>1° endpoint:</u>** Successful defibrillation **<u>Results:</u>** In 152 OHCA patients, a total of 233 ECG pre-defibrillation recordings, consisting of 164 unsuccessful and 69 successful episodes, were analyzed. Indices of frequency domain analysis (peak frequency, centroid frequency, and amplitude spectral area), nonlinear analysis (approximate entropy and Hurst exponent, detrended fluctuation analysis), and CWT analysis (mid-band and high-band energy) were significantly different between unsuccessful and successful episodes ($P < 0.01$ for all). However, logistic regression analysis showed that centroid frequency and total mid-band energy were effective predictors ($P < 0.01$ for both).	Energy spectrum analysis based on CWT as short as a 1.0-s VF ECG waveform enables prompt and reliable prediction of successful defibrillation.
Foomany et al 2010 (PMID: 21097215)	**<u>Study Type:</u>** Retrospective observational study (n=29)	**<u>Inclusion criteria:</u>** A database of 29 human VF tracings was extracted from	**<u>1° endpoint:</u>** Defibrillation success **<u>Results:</u>**	The results indicate that the proposed wavelet based waveform markers perform well in discriminating between

		the defibrillator recordings collected by the EMS and was used to validate the waveform markers.	The results obtained by the comparison of the wavelet based features with other spectral, and correlation-based features indicates that the proposed wavelet features perform well with an overall accuracy of 79.3% in predicting the shock outcomes and hence demonstrate potential to provide near real-time feedback to EMS personnel in optimizing resuscitation outcomes. We also performed comparative analysis of 5 existing techniques (spectral and correlation based approaches) against the proposed wavelet markers.	the successful and unsuccessful cases with an overall accuracy of 79.3%. Future work involves verfying the robustness of the proposed SDW feature and its variant in larger human VF database.
Lin et al 2010 (PMID: 20071067)	**Study Type:** Retrospective observational study (n=155)	**Inclusion criteria:** ECG recordings of VF signals from AEDs were obtained for subjects with OHCA in Taipei city. To examine the time effect on DFA, study also analysed VF signals in subjects who experienced sudden cardiac death during Holter study from PhysioNet, a publicly accessible database. Waveform parameters including root-mean-squared (RMS) amplitude, mean amplitude, amplitude spectrum analysis (AMSA), frequency analysis as well as fractal measurements including scaling exponent (SE) and DFA were calculated. A	**1° endpoint:** first-shock success **Results:** 155 OHCA subjects (37 successful and 118 unsuccessful defibrillations) with VF were included for analysis. Among the VF waveform parameters, only AMSA (7.61+/-3.30 vs. 6.30+/-3.13, P=0.028) and DFAalpha2 (0.38+/-0.24 vs. 0.49+/-0.24, P=0.013) showed significant difference between subjects with successful and unsuccessful defibrillation. The area under the curves (AUCs) for AMSA and DFAalpha2 was 0.63 (95% confidence interval (CI)=0.52-0.73) and 0.65 (95% CI=0.54-0.75), respectively. Among the waveform parameters, only DFAalpha2, SE and dominant frequency showed significant time effect.	The VF waveform analysis based on DFA could help predict first-shock defibrillation success in patients with OHCA. The clinical utility of the approach deserves further investigation.

		defibrillation was regarded as successful when VF was converted to an organised rhythm within 5s after each defibrillation.		
Li et al 2008 (PMID: 18090359	**<u>Study Type:</u>** Retrospective cohort study (n=229)	**<u>Inclusion criteria:</u>** ECGs were recorded in conjunction with AEDs during CPR in human victims. A shockable rhythm was defined as disorganized rhythm with an amplitude > 0.1 mV or, if organized, at a rate of > or = 180 beats/min. Wavelet-based transformation and shape-based morphology detection were used for rhythm classification. Morphologic consistencies of waveform representing QRS components were analyzed to differentiate between disorganized and organized rhythms. For disorganized rhythms, the amplitude spectrum area was computed in the frequency domain to distinguish between shockable VF and nonshockable asystole. For organized rhythms, in victims in whom the absence of a heartbeat was independently confirmed, the heart rate was estimated	**<u>1° endpoint:</u>** Identification of shockable and nonshockable rhythm **<u>Results:</u>** To derive the algorithm, we used 29 recordings on 29 patients from the Creighton University ventricular tachyarrhythmia database. For validation, the algorithm was tested on an independent population of 229 victims, including recordings of both ECG and depth of chest compressions obtained during suspected OHCA. The recordings included 111 instances in which the ECG was corrupted during chest compressions. A shockable rhythm was identified with a sensitivity of 93% and a specificity of 89%, yielding a positive predictive value of 91%. A nonshockable rhythm was identified with a sensitivity of 89%, a specificity of 93%, and a positive predictive value of 91% during uninterrupted chest compression.	The algorithm fulfilled the potential lifesaving advantages of allowing for uninterrupted chest compression, avoiding pauses for automated rhythm analyses before prompting delivery of an electrical shock.

		for further classification.		

Reviewer Comments (including whether meet criteria for formal review):
One randomized controlled study and 18 retrospective observational studies were identified in this search. The waveform analyses and outcomes studied were highly heterogeneous. As such, it may be difficult to perform meaningful meta-analyses that would impact ILCOR's recommendation. However, given that 1 RCT and over 15 observational studies have been published since ILCOR's last formal review in 2010, another formal systematic review on this topic is recommended.

	Approval Date
Evidence Update coordinator	
ILCOR board	

***Once approval has been made by Evidence Update coordinator, worksheet will go to ILCOR Board for acknowledgement.**

C2b. Waveform Analysis for Predicting Successful Defibrillation (ALS 601: EvUp)

Worksheet author(s): Justin L. Benoit, MD, MS, FAEMS
Council: AHA
Date Submitted: 12/19/2019

PICO / Research Question:
Among adults who are in cardiac arrest in any setting (P), does a technique for prediction of the likelihood of success of defibrillation (analysis of VF, etc) (I), compared with standard resuscitation (without such prediction) (C), improved outcomes (O) (eg, termination of rhythm, ROSC)?

Outcomes: ROSC, termination of VF, survival
Type (intervention, diagnosis, prognosis):

Additional Evidence Reviewer(s):
Conflicts of Interest (financial/intellectual, specific to this question):

Year of last full review: 2010 / 2015 / New question: 2010

Last ILCOR Consensus on Science and Treatment Recommendation:

2010/2015 Search Strategy:

("waveform analysis") AND ventricular fibrillation[MeSH Terms]

2019 Search Strategy:
Database searched:Pubmed
Date Search Completed: December 2019
Search Results (Number of articles identified / number identified as relevant):17/8
Inclusion/Exclusion Criteria:
Link to Article Titles and Abstracts (if available on PubMed):

https://www.ncbi.nlm.nih.gov/sites/myncbi/1PgE4WBCzHi505/collections/59068929/public/

Summary of Evidence Update:
Evidence Update Process for topics not covered by ILCOR Task Forces

1. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

Organisation (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
Freese JP Circulation. 2013 Aug 27;128(9):995-1002. doi: 10.1161/CIRCULATIONAHA.113.003273.	Multicenter, double-blind, randomized study Assess the efficacy of guided initial resuscitative management using a waveform analysis algorithm compared with a standard shock-first protocol for the management of out-of-hospital cardiac arrest presenting in VF. N=987	EMS systems in New York, NY, and London, UK Out-of-hospital cardiac arrests presenting in VF. Study inclusion required that the patient's arrest was of cardiac origin as described by the rescuers in accordance with the Utstein style,13 that the initial defibrillator used during the resuscitation was a study device, and that the subject presented in VF as determined by the initial rhythm assessment of the automated external	After the arrival of certified first responders or emergency medical technicians/paramedics, CPR was initiated only until an AED was applied. All AED CPR intervals were set to 2 minutes. The study device (FR2+, Philips Healthcare, Seattle, WA) used an impedance-compensating biphasic truncated exponential waveform and fixed 150-J energies. No other interventions (advanced airway management, vascular access,	The primary outcome for this study was survival to hospital discharge. For the overall study population, no differences were noted between the 2 arms for any outcome end point: Survival to hospital discharge (15.6% versus 17.2%; P=0.55) were similar between the waveform analysis algorithm and the standard shock-first protocol, respectively.	Secondary outcomes included ROSC, sustained ROSC defined as ROSC maintained until hospital arrival, and survival to hospital admission, each defined in accordance with the Utstein template. ROSC (42.5% versus 41.2%; P=0.70), sustained ROSC (32.4% versus 33.4%; P=0.79), survival to hospital admission (34.1% versus 36.4%; P=0.46),

		defibrillator (AED). Pediatric patients (age <18 years) and those for whom resuscitative care was terminated as a result of a “do not resuscitate” order were excluded, as were patients for whom data from the study device were not able to be obtained or for whom the initial AED analysis was incomplete.	pharmaceutical administration) were performed during this initial treatment phase. AEDs were randomized to either a standard shock-first protocol or VF waveform analysis algorithm. The AED recommended an immediate defibrillatory shock for all VF in the standard shock-first arm. In the waveform analysis arm, the initial rhythm analysis used a proprietary algorithm (Philips Healthcare) to analyze the VF waveform and to assign a resulting numeric VF score. N=487 (VF Waveform Analysis N=500 (Shock-First Protocol)		

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value;	Summary/Conclusion Comment(s)

			OR or RR; & 95% CI)	
Coult J Circ Arrhythm Electrophysiol. 2019 Jan;12(1):e006924. doi: 10.1161/CIRCEP.118.006924.	Retrospective Cohort Study In the current investigation, we evaluate a comprehensive set of waveform measures with and without chest compressions to determine if comparable prognostic performance can be achieved during ongoing compressions and, in turn, if waveform measures have potential to serve as a dynamic guide to resuscitation during high-performance CPR. N=1151	Patients who suffered out-of-hospital VF cardiac arrests in greater King County, WA, from 2005 to 2015. Patients were eligible if they presented to EMS with an initial arrest rhythm of VF and received at least 1 shock from an MRx, Forerunner 3 (Philips Healthcare, Bothell, WA), Lifepak 12, or Lifepak 15 (Physio-Control, Redmond, WA) defibrillator, as these defibrillator models are the predominant models used in the EMS jurisdiction and record transthoracic chest impedance in conjunction with the ECG. Patients were a priori ineligible if they received public access or police defibrillation before EMS arrival. Eligible patients were excluded if the defibrillator recording did not include at least one 5-s VF ECG segment with a concurrent impedance signal before a shock. Patients were also	The primary outcome was functionally-intact survival, defined as survival to hospital discharge with a Cerebral Performance Category score of 1 or 2. Intermediate outcomes were return-of-circulation, defined as a pulse with measurable blood pressure at end of EMS care, and return-of-rhythm after shock, defined as at least 2 QRS complexes within any 5-s period during the first 2 minutes following a defibrillation attempt. Without chest compressions, AUCs for prediction of functionally-intact survival ranged from 0.56 to 0.75 for the 27 measures, with a median of 0.73. During chest compressions, AUCs for prediction of functionally-intact survival ranged from 0.53 to 0.75, with a median of 0.69 For prediction of the primary outcome of	VF waveform measures predict functionally-intact survival when calculated during chest compressions, but prognostic performance is generally reduced compared with compression-free analysis. However, support vector machine models exhibited similar performance with and without compressions while also achieving the highest area under the receiver operating characteristic curve. Such machine learning models may, therefore, offer means to guide resuscitation during uninterrupted cardiopulmonary resuscitation.

		excluded if they had a paced rhythm because pacer artifact may interfere with VF waveform analysis.	functionally-intact survival, the measure with the highest AUC was the support vector machine combination measure (Table 2). AUC values were similar without chest compressions (AUC, 0.75; 95% CI, 0.73–0.78) versus with chest compressions (AUC, 0.75; 95% CI, 0.72–0.78; P=0.75 for difference). Without chest compressions, survival ranged from 12% in the lowest quintile to 71% in the highest quintile. With chest compressions, survival ranged from 13% in the lowest quintile to 69% in the highest quintile (Figure 5).	
Aiello S J Am Heart Assoc. 2017 Nov 4;6(11). pii: e006749. doi: 10.1161/JAHA.117.006749.	Prospective animal cohort study We therefore hypothesized that real-time monitoring of AMSA during ventilation pauses of CPR could more effectively guide the decision about when to deliver an electrical shock and thereby improve resuscitation outcomes. We tested this hypothesis in a swine model of	Animal study Three groups of 12 pigs each (total, n=36 pigs) were block-randomized to 1 of 3 defibrillation protocols. The duration of untreated VF was stratified into 6, 9, and 12 minutes to model variable downtime yielding 9 unique combinations of untreated VF durations and	Successful resuscitation was defined as achieving ROSC lasting >5 minutes; and survival as remaining hemodynamically viable at 240 minutes postresuscitation. Kaplan–Meier curves were analyzed from the time VF was induced in all 36 animals (Figure 3A)	The AD protocol improved the time precision for shock delivery, resulting in less shock burden and less postresuscitation myocardial dysfunction, potentially improving survival compared with time-fixed, guidelines-driven, shock delivery protocols.

	electrically induced VF and resuscitation by conventional CPR using a basic life support protocol and compared 3 defibrillation protocols: (1) an AMSA-Driven (AD) protocol, (2) a Guidelines-Driven (GD) protocol, and (3) a Guidelines-Driven/AMSA-Enabled (GDAE) protocol that allowed earlier shock delivery upon exceeding an AMSA threshold. N=36	defibrillation protocols per block.	and from the time ROSC occurred in 27 animals (Figure 3B). In both instances, survival was higher in the AD group attaining overall statistical significance and pairwise statistical significance between AD and GDAE. Likewise, the survival time from VF induction was the longest (minutes) in the AD group (198±104) followed by GD (158±109) and by GDAE (82±102), attaining overall statistical significance (P=0.032) and pairwise statistical significance between AD and GDAE (P=0.030).	
Nakagawa Y Resuscitation. 2017 Apr;113:8-12. doi: 10.1016/j.resuscitation.2016.12.025.	Retrospective cohort study Here, with the aim of predicting post-shock ROSC, we developed a novel equation by adding a change in AMSA (ΔAMSA) to the prehospital AMSA1 and compared the equation with the conventional AMSA-only equation to evaluate the validity of the proposed equation. N=285	Subjects were 285 patients (228 men and 57 women; mean age, 63.8 ± 17.0 years) who were given prehospital electric shocks (mean number of electric shocks, 2.0 ± 1.2 times; range, 1–7 times) by paramedics after VF was verified	ROSC was defined as detection of pulse in the radial artery or noticeable body movement. The AUC was 0.803 (95% CI = 0.743–0.863) in the base model, 0.851 (95% CI = 0.797–0.906) in model 1, and 0.891 (95% CI = 0.842–0.937) in model 2.	This study showed that an equation containing not only AMSA1 calculated from VF waveform, but also the difference between the first and last AMSA, predicted ROSC well in patients undergoing out-of-hospital VF.

He M PLoS One. 2016 Feb 10;11(2):e0149115. doi: 10.1371/journal.pone.0149115.	Retrospective cohort study. The purpose of the present study was to investigate whether combing VF waveform feature amplitude spectrum area (AMSA)with previous shock information using neural networks could improve the performance of defibrillation prediction in OHCA patients. N=199	ECG were recorded for victims experienced OHCA and CPR by defibrillator through two adhesive adult defibrillation/pacing pads. The electronic data did not contain any patient's identifiable information.	Defibrillation outcome was regarded as successful or return of a potentially perfusing rhythm if an organized rhythm was present within 60 seconds after the shock, and had a rate of 40 beats/min or greater. For first shocks, AUC was unchanged (0.770) when different combination approaches were applied. For subsequent shocks, AUC was significantly increased when combinations C1 (0.883 vs. 0.819, p = 0.005) and C3 (0.904 vs. 0.819, p<0.001) were employed, but no statistical difference was observed between C2 and AMSA (0.825 vs. 0.819, p = 0.818). The prediction performances of different combination approaches and AMSA for subsequent shocks in validation set by the BP neural network method were listed in Table 1. Compared with	Combining AMSA with previous shock information using neural networks greatly improves prediction performance of defibrillation outcome for subsequent shocks.

			AMSA based single feature prediction, C1 and C3 remarkably improved the sensitivity (C1: 68.6% vs. 35.5%, p<0.001; C3: 76.5% vs. 35.3%, p<0.001), NPV (C1: 87.4% vs. 76.9%, p = 0.026; C3: 90.2% vs. 76.9%, p = 0.007) and PA (C1: 84.4% vs. 74.0%, p = 0.017; C3: 86.1% vs. 74.0%, p = 0.005)with a threshold of 90% specificity. However, no statistical differences were observed in prediction power whenC2 was employed.	
Shandilya S BMC Med Inform Decis Mak. 2012 Oct 15;12:116. doi: 10.1186/1472-6947-12-116.	Retrospective Cohort Study We developed a unique approach of computational VF waveform analysis, with and without addition of the signal of end-tidal carbon dioxide (PetCO2), using advanced machine learning algorithms. We compare these results with those obtained using the Amplitude Spectral Area (AMSA) technique. N=57	Out-of-hospital cardiac arrest (OHCA) subjects was provided by the Richmond Ambulance Authority (RAA) using the E-Series monitor/defibrillator (Zoll Medical Corporation, Chelmsford, MA) which provides standard biphasic defibrillation.	Successful defibrillation was defined as a period of greater than 15 seconds with narrow QRS complexes under 150 beats per minute with confirmatory evidence from the medical record or ECG that a return of spontaneous circulation (ROSC) has occurred. Classification using our machine-learning approach with 6–10 features yielded an ROC AUC of 85% and	We have developed a novel algorithm for predicting successful defibrillation of VF. The model is built upon knowledge extracted with multiple signal-processing and machine-learning methods.

			accuracy of 82.2%, for the model built with ECG data only. ROC AUC for AMSA was 60.9%.	
Nakagawa Y Tokai J Exp Clin Med. 2012 Apr 20;37(1):1-5. PMID: 22488555	Retrospective Cohort Study We examine whether outcome after electrical defibrillation can be predicted by the use of AMSA and PSA values in out-of-hospital VF patients in Japan who received shock treatment by paramedics at the site of onset. N=83	Subjects comprised 83 out-of-hospital cardiac arrest victims who had previously received CPR by paramedics of fire stations in four cities located in western Kanagawa prefecture in Japan between 2006 and 2008.	Outcome: ROSC The mean AMSA value (1.3-48 Hz) in the ROSC group was 40.2 ± 20.0, while that in the VF, PEA, and asystole groups was 28.4 ± 14.0, 26.9 ± 12.8, and 26.1 ± 10.8, respectively. Similarly, the mean AMSA value (1.3-48 Hz) was significantly higher in the ROSC group than in the VF (p = 0.0067) and asystole (p = 0.0476) groups, but not significant higher than in the PEA group (p = 0.1327) (Fig. 2). The mean PSA value (4.0-48 Hz) in the ROSC group was 21.9 ± 21.7, while that in the VF, PEA, and asystole groups was 8.4 ± 7.3, 8.3 ± 9.2, and 10.2 ± 13.1, respectively. Multiple comparison results confirmed no statistically significant difference in mean	In conclusion, this study demonstrated that by analyzing AMSA values of VF waveforms it is possible to predict cases wherein electrical defibrillation is more likely to restore a cardiac rhythm.

			PSA (4.0-48 Hz) values among the four patient groups (Fig. 3). The mean PSA value (1.3-48 Hz) in the ROSC group was 92.6 ± 128.3, while that in the VF, PEA, and asystole groups was 54.2 ± 103.0, 27.7 ± 23.2, and 28.3 ± 25.0, respectively. No statistically significant difference was confirmed for mean PSA values (1.3-48 Hz) among the four patient groups (Fig. 4).	
Lin LY Resuscitation. 2010 Mar;81(3):297-301. doi: 10.1016/j.resuscitation.2009.12.003.	Retrospective Cohort Study We examined whether the DFA analysis of the VF waveform recorded by automated external defibrillators (AEDs) predicted the success of defibrillation and outcome in a series of patients with OOHCA. N=155	We collected all OOHCA cases with AED usage from January 2001 to the end of December 2006 in Taipei city. Data from adult patients (>18 years old) with non-traumatic cardiac arrest with an initial rhythm of VF were collected.	Among the VF waveform parameters, only AMSA (7.61 ± 3.30 vs. 6.30 ± 3.13, P = 0.028) and DFAα2 (0.38 ± 0.24 vs. 0.49 ± 0.24, P = 0.013) were significantly different between subjects with successful and unsuccessful defibrillation. The AUCs for AMSA and DFAα2 were 0.63 (95% CI = 0.52–0.73) and 0.65 (95% CI = 0.54–0.75), respectively.	In conclusion, our results showed that the VF waveform analysis based on amplitude-independent DFA analysis could help predict first-shock defibrillation success in patients with OOHCA.

Reviewer Comments (including whether meet criteria for formal review):

Freese 2013 was an RCT of VF waveform analysis to guide shocks versus traditional guideline based shocks but showed no difference in outcomes. Multiple other observational studies were identified. Consideration of an updated SysRev is warranted.

C3. Confirmation of Correct Tracheal Tube Placement (ALS 469: EvUp)

Worksheet author(s): Bryan Fischberg [BLF]
Council: AHA
Date Submitted:

PICO / Research Question: ALS 469 Confirmation of Correct Tracheal Tube Placement
Among adults who are in cardiac arrest, needing/with an advanced airway during CPR in any setting (P), does use of devices (eg, waveform capnography, CO2 detection device, esophageal detector device, or tracheal ultrasound) (I), compared with compared with not using devices (C), change placement of the ET tube between the vocal cords and the carina, success of intubation (O)?

Type (intervention, diagnosis, prognosis): Intervention
Additional Evidence Reviewer(s):
Conflicts of Interest (financial/intellectual, specific to this question): BLF has none.

Year of last full review: 2010 / 2015 / New question: 2015
Search Completed: April 14, 2014

Last ILCOR Consensus on Science and Treatment Recommendation:

Consensus on Science:

Waveform Capnography For the important outcome of detection of correct placement of a tracheal tube during CPR, we identified very-low-quality evidence (downgraded for risk of bias and indirectness) from 1 observational study(Silvestri 2005, 497) showing that the use of waveform capnography compared with no waveform capnography in 153 critically ill patients (51 with cardiac arrest) decreased the occurrence of unrecognized esophageal intubation on hospital arrival from 23% to 0% (OR, 29; 95% CI, 4–122). For the important outcome of detection of correct placement of a tracheal tube during CPR, we identified low-quality evidence (downgraded for serious risk of bias and imprecision) from 3 observational studies(Tanigawa 2000, 1432; Grmec 2002, 701; Takeda 2003, 153) with 401 patients and 1 randomized study(Tanigawa 2001, 375) including 48 patients that showed that the specificity for waveform capnography to detect correct tracheal placement was 100% (95% CI, 87%–100%). The sensitivity was 100% in 1 study(Grmec 2002, 701; Takeda 2003, 153) when waveform capnography was used in the prehospital setting immediately after intubation, and esophageal intubation was less common than the average (1.5%). The sensitivity was between 65% and 68% in the other 3 studies(Tanigawa 2000, 1432; Tanigawa 2001, 375; Takeda 2003, 153) when the device was used in OHCA patients after intubation in the emergency department (ED). The difference may be related to prolonged resuscitation with compromised or nonexistent pulmonary blood flow. Based on the pooled sensitivity/specificity from these studies and assumed esophageal intubation prevalence of 4.5%, the false-positive rate (FPR) of waveform capnography was 0% (95% CI, 0%–0.6%). Colorimetric CO2 Detection Devices For the important outcome of detection of correct placement of a tracheal tube during CPR, we identified very-low-quality evidence (downgraded for risk of bias and indirectness) from 7 observational studies(Anton 1991, 271; MacLeod 1991, 267; Ornato 1992, 518; Sanders 1994, 771; Hayden 1995, 499; Bozeman 1996, 595; Grmec 2002, 701) including 1119 patients that evaluated the diagnostic accuracy of colorimetric CO2 devices. The specificity was 97% (95% CI, 84%–99%), the sensitivity was 87% (95% CI, 85%–89%), and the FPR was 0.3% (95% CI, 0%–1%). Esophageal Detection Devices For the important outcome of detection of correct placement of a tracheal tube during CPR, we identified very-low-quality evidence (downgraded for risk of bias, indirectness, inconsistency, and a strong suspicion of publication bias) from 4 observational studies(Oberly 1992, 317; Bozeman 1996, 595; Tanigawa 2000, 1432; Takeda 2003, 153) including 228 patients, low-quality evidence (downgraded for risk of bias and indirectness) from 1 randomized study(Tanigawa 2001, 375) including 48 patients, and very-low-quality evidence (downgraded for risk of bias, indirectness, inconsistency, and a strong suspicion of publication bias) from 1 observational study(Pelucio 1997, 563) including 168 patients that evaluated esophageal detection devices. The pooled specificity was 92% (95% CI, 84%–96%), the pooled sensitivity was 88% (95% CI, 84%–192%), and the FPR was 0.2% (95% CI, 0%–0.6%). Low-quality evidence (downgraded for risk of bias and suspected publication bias) from 1 observational study(Tanigawa 2001, 375) showed no statistically significant difference between the performance of a bulb (sensitivity 71%, specificity 100%)- and a syringe (sensitivity 73%, specificity 100%)-type esophageal detection devices in the detection of tracheal placement of a tracheal tube. Ultrasound for Tracheal Tube Detection For the important outcome of detection of correct placement of a tracheal tube during CPR, we identified low-quality evidence (downgraded for suspicion of publication bias and indirectness) from 3 observational studies(Chou 2011, 1279; Chou 2013, 1708; Zadel 2015, 1) including 254 patients in cardiac arrest that evaluated the use of ultrasound to detect tracheal tube placement. The pooled specificity was 90% (95% CI, 68%–98%), the sensitivity was 100% (95% CI, 98%–100%), and the FPR was 0.8% (95% CI, 0.2%–2.6%).

Treatment Recommendations

We recommend using waveform capnography to confirm and continuously monitor the position of a tracheal tube during CPR in addition to clinical assessment (strong recommendation, low-quality evidence).

We recommend that if waveform capnography is not available, a nonwaveform CO2 detector, esophageal detector device, or ultrasound in addition to clinical assessment is an alternative (strong recommendation, low-quality evidence).

2010/2015 Search Strategy: 2015

((((((((((endotracheal tube) OR "Intubation, intratracheal"[MH] OR "tracheal intubation"[TI] OR "endotracheal intubation"[TI] OR "ETT"[TI] OR "advanced airway management"[TI] OR "intubation"[TI] OR "intubation/methods"[MH]) OR "advanced airway management"[TI])))) AND ((((((((((((Heart Arrest[MeSH Major Topic]) OR Cardiopulmonary resuscitation[MeSH Major Topic]) OR Ventricular Fibrillation[MeSH Major Topic]) OR heart Massage[MeSH Major Topic]) OR asystole[Title/Abstract]) OR (cardiac arrest[Title/Abstract]) OR Cardiac compression[Title/Abstract]) OR cardiac massage[Title/Abstract]) OR Cardiac compression[Title/Abstract]) OR cardiac massage[Title/Abstract) OR chest compression*[Title/Abstract]) OR CPR[Title/Abstract]) OR heart compression[Title/Abstract])))) AND (((((((capnography) OR Waveform[Title/Abstract]) OR CO2 Detection Device) OR Carbon dioxide device) OR Esophageal detector device) OR edd) OR instrumentation[MeSH Subheading]))) NOT (((animals[mh] NOT humans[mh]))) NOT (("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or Case Reports[ptyp])))

2019 Search Strategy:

((((((((((endotracheal tube) OR "Intubation, intratracheal"[MH] OR "tracheal intubation"[TI] OR "endotracheal intubation"[TI] OR "ETT"[TI] OR "advanced airway management"[TI] OR "intubation"[TI] OR "intubation/methods"[MH]) OR "advanced airway management"[TI])))) AND ((((((((((((Heart Arrest[MeSH Major Topic]) OR Cardiopulmonary resuscitation[MeSH Major Topic]) OR Ventricular Fibrillation[MeSH Major Topic]) OR heart Massage[MeSH Major Topic]) OR asystole[Title/Abstract]) OR (cardiac arrest[Title/Abstract]) OR Cardiac compression[Title/Abstract]) OR cardiac massage[Title/Abstract]) OR Cardiac compression[Title/Abstract]) OR cardiac massage[Title/Abstract) OR chest compression*[Title/Abstract]) OR CPR[Title/Abstract]) OR heart compression[Title/Abstract])))) AND (((((((capnography) OR Waveform[Title/Abstract]) OR CO2 Detection Device) OR Carbon dioxide device) OR Esophageal detector device) OR edd) OR instrumentation[MeSH Subheading]))) NOT (((animals[mh] NOT humans[mh]))) NOT (("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or Case Reports[ptyp])))

Database searched: PubMed

Date Search Completed: November 2019
Search Results (Number of articles identified / number identified as relevant): 128 provided, by title 17 were identified as relevant, 5 were entered in tables, 1 outside reference was added to the table
Inclusion/Exclusion Criteria: (See above.)
Link to Article Titles and Abstracts (if available on PubMed):
https://www.ncbi.nlm.nih.gov/sites/myncbi/1PgE4WBCzHi505/collections/58987508/public/

Summary of Evidence Update:
Evidence Update Process for topics not covered by ILCOR Task Forces

1. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

Organisation (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
ACEP; 2016	*Policy Statement (Not in the originally provided citation list.)*	Verification of Endotracheal Tube Placement	0	Direct visualization is primary; EtCO2, esophageal detector, U/S, bronchoscopy are secondary confirmation.	Aligned with current CoSTR, but secondary imaging includes bronchoscopy.
Sandroni; 2018	Review	Capnography during cardiac arrest	6 in subsection related to ET placement	Nothing new. Positive $EtCO_2$ informs respiratory placement, but does not reliably distinguish endobronchial position; negative is unreliable in arrest.	Nothing new. Reinforced ERC guidelines.

RCT:

Study Acronym; Author;	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) /	Endpoint Results (Absolute Event Rates, P value;	Relevant 2° Endpoint (if any);

Year Published			Study Comparator (# patients)	OR or RR; & 95% CI)	Study Limitations; Adverse Events
Umesh G; 2013	Study Aim: to evaluate the utility of the Umesh's intubation detector (UID) device for rapid and reliable differentiation of tracheal from oesophageal intubation by novice users Study Type: Prospective, double blind and randomized (N=100)	Inclusion Criteria: Patients aged 18–65 years scheduled to undergo general endotracheal anaesthesia	Intervention: UID randomly connected to two identical ET placed in trachea and esophagus in all patients. Comparison: Novice observer indicated if UID bag inflation suggested tracheal vs esophageal placement during two chest compressions.	1° endpoint: Out of the 100 tracheal intubations, 96 were accurately Identified, 4 were opined as indeterminate. Out of the 100 oesophageal intubations, 99 were accurately identified, 1 was misinterpretation as tracheal intubation. Conclusion: UID device can be used by novices for rapid and reliable differentiation of tracheal from oesophageal intubation in healthy adult patients.	Study Limitations: The depth of chest compressions was limited to approximately one inch (2.5 cm) in order to minimise the risk of complications related to chest compression. The number of compressions was limited to only two in order to observe if the device can help rapidly distinguish tracheal from oesophageal intubation. Adverse Events: None

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)
Hunt KA; 2019	Study Type: Observational (N=64)	Inclusion Criteria: Premature newly borns in delivery suite	1° endpoint: Time following intubation for $EtCO_2$ levels to be initially detected and to reach 4 mm Hg (5.4 cm H_2O) and 15 mm Hg (20.4 cm H_2O). (both P<0.001)	*Done in infants*, but concluded time is variable, and capnography is likely to detect $EtCO_2$ faster than colorimetric devices. Speaks to comparison among techniques.
Langhan ML; 2018	Study Type: Multicenter retrospective cohort study (N=9,639)	Inclusion Criteria: Primary tracheal intubation in children younger than 18 yr 2011-2015 in	1° endpoint: Profiled EtCO2 use and adverse events. Among conclusions, the rate of esophageal intubation with delayed recognition was similar with waveform capnography	*Neither during cardiac arrest nor in adults; but compares methods*. Discussion notes that "given that the rate of esophageal intubation with delayed recognition

		NEAR4KIDS registry	versus colorimetry (0.39% vs. 0.46%; p = 0.62)	was significantly higher in children with [tracheal intubation]-associated cardiac arrests (defined as cardiac arrest ≤ 20 minutes of induction/intubation), and that all of these cases utilized colorimetric $EtCO_2$ detector, consideration should be made to utilize waveform capnography in children with high risk for [tracheal intubation]-associated cardiac arrests identified in [a] previous study.
Silvestri S; 2018	Study Type: Controlled cadaveric experiment (N=2 cadavers, 195 ventilations)	Inclusion Criteria: Ventilations via tracheal tube provided to two cadavers.	1° endpoint: Quantitative waveform capnography with all ventilations. Compared intratracheal, hypopharyngeal, esophageal positions.	*Cadaveric, not during cardiac arrest*. A binary classification test showed no false negatives or false positives, indicating 100% sensitivity (NPV 1.0, 95%CI 0.98–1.00) and 100% specificity (PPV 1.0, 95%CI 0.93–1.00). Conclusion: Though current guidelines question the reliability of waveform capnography for verifying endotracheal tube location during low-perfusion states such as cardiac arrest, our findings suggest that it is highly sensitive and specific.
Bullock A.; 2017	Study Type: Retrospective chart review (N=292)	Inclusion Criteria: Children ≤ 21 years intubated or received CPR in 2 academic children's hospital pediatric EDs between 2009-2012	1° endpoint: Profile of EtCO2 monitoring use, length of CPR, ROSC, and adverse events. Intubation occurred in 95% of cases and CPR in 30% of cases. Capnography was documented in only 38% of intubated patients and 13% of patients requiring CPR. There was an overall decrease in capnography use after publication of the 2010 AHA recommendations	*Mostly in pediatric patients, but enrolled up to age 21.* Discussion notes: "9 subjects (3%) had a misplaced ETT identified by colorimetry; however, there was no documented detection of ETT dislodgement with waveform capnography. When esophageal intubations or dislodgement of the ETT is unrecognized, death can result; lack of capnography monitoring is frequently cited as a key factor in these events"

			(P = 0.05). Capnography use was associated with a longer duration of CPR and return of spontaneous circulation	
Karacabey S; 2016	Study Type: Prospective, single-center, observational study (N=115)	Inclusion Criteria: Adult patients emergently intubated for respiratory failure, cardiac arrest or severe trauma excluding patients with severe neck trauma, neck tumors, history of neck operation or tracheotomy.	1° endpoint: 30 were cardiac arrest patients other 85 patients were non-cardiac arrest patients intubated with rapid sequence intubation. Overall accuracy of the ultrasonography was 97.18% (95% CI, 90.19-99.66%), and the value of kappa was 0.869 (95% CI, 0.77-0.96), indicating a high degree of agreement between the ultrasonography and capnography. Ultrasonography took significantly less time than capnography in total.	*Not all patients were in cardiac arrest.* "In our study, we had a high rate of esophageal intubation (38%) because the intubations were performed by inexperienced first-year emergency medicine residents. Thus, we found that ultrasonography provides a faster diagnosis of false intubations. Based on the results of study, we learned that the combination of tracheal [ultrasonography] and lung sliding is superior to capnography. In addition, in cardiac arrest patients, this combination is better than capnography because [ultrasonography] is not affected by low pulmonary flow. Furthermore, we demonstrated the considerable time advantage of ultrasound over capnography in confirming proper endotracheal intubation. However, [ultrasonography] was also affected by CPR, and the success rates in these patients were decreased compared with the success rates of those undergoing RSI"
Wojtczak JA; 2014	Study Type: Controlled phantom, porcine, cadaver experiment (N=1/ea.)	Inclusion Criteria: Images of LMA and ETT with cuffs filled with air, saline, and saline+contrast.	Results/discussion: Tracheal US does not interrupt chest compressions and is not affected by low pulmonary flow or airway obstruction, but is limited by US scattering and artifacts generated in air-tissue interfaces. This study	*Not in adult patients being resuscitated. Demonstrates concept only.* Similar improvement in visualization was obtained in cadavers after filling of the cuffs with saline. Therefore, it is likely that saline-filled cuffs may be detected in patients after endotracheal

			demonstrates that the replacement of air with saline in ETT or LMA cuffs enables their detection and the visualization of the surrounding structures or tissues and markedly limits US artifacts.	intubation or placement of the supraglottic airway.
Chou HC; 2013	Study Type: Prospective observational study (N=89)	Inclusion Criteria: Patients undergoing emergency intubation during CPR	1° endpoint: Accuracy of tracheal ultrasonography in assessing endotracheal tube position during CPR. (Referenced against the combination of clinical auscultation and quantitative waveform capnography.) Results: 7 (7.8%) had esophageal intubations. The sensitivity, specificity, positive predictive value, and negative predictive value of tracheal ultrasonography were 100% (95% confidence interval [CI]: 94.4-100%), 85.7% (95% CI: 42.0-99.2%), 98.8% (95% CI: 92.5-99.0%) and 100% (95% CI: 54.7-100%), respectively. Positive and negative likelihood ratios were 7.0 (95% CI: 1.1-43.0) and 0.0, respectively.	Real-time tracheal ultrasonography is an accurate method for identifying endotracheal tube position during CPR without the need for interruption of chest compression. Tracheal ultrasonography in resuscitation management may serve as a powerful adjunct in trained hands.

Reviewer Comments (including whether meet criteria for formal review): Evidence since 2015 does not seem sufficient to warrant an updated systematic review.

Reference list

1: Sandroni C, De Santis P, D'Arrigo S. Capnography during cardiac arrest. Resuscitation. 2018 Nov;132:73-77. doi: 10.1016/j.resuscitation.2018.08.018. Epub 2018 Aug 22. Review. PubMed PMID: 30142399.
<<Noted in table(s) above.>>

2: Hunt KA, Yamada Y, Murthy V, Srihari Bhat P, Campbell M, Fox GF, Milner AD, Greenough A. Detection of exhaled carbon dioxide following intubation during resuscitation at delivery. Arch Dis Child Fetal Neonatal Ed. 2019 Mar;104(2):F187-F191. doi: 10.1136/archdischild-2017-313982. Epub 2018 Mar 17. PubMed PMID: 29550769.
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3: Langhan ML, Emerson BL, Nett S, Pinto M, Harwayne-Gidansky I, Rehder KJ, Krawiec C, Meyer K, Giuliano JS Jr, Owen EB, Tarquinio KM, Sanders RC Jr, Shepherd M, Bysani GK, Shenoi AN, Napolitano N, Gangadharan S, Parsons SJ, Simon DW, Nadkarni VM, Nishisaki A; for Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) and National Emergency Airway Registry for Children (NEAR4KIDS) Investigators. End-Tidal Carbon Dioxide Use for Tracheal Intubation: Analysis From the National Emergency Airway Registry for Children (NEAR4KIDS) Registry. Pediatr Crit Care Med. 2018 Feb;19(2):98-105. doi: 10.1097/PCC.0000000000001372. PubMed PMID: 29140968.
<<*Noted in table(s) above.*>>

4: Ducharme S, Kramer B, Gelbart D, Colleran C, Risavi B, Carlson JN. A pilot, prospective, randomized trial of video versus direct laryngoscopy for paramedic endotracheal intubation. Resuscitation. 2017 May;114:121-126. doi: 10.1016/j.resuscitation.2017.03.022. Epub 2017 Mar 20. PubMed PMID: 28336412.
<<*Non-contributory to this PICO.*>>

5: Silvestri S, Ladde JG, Brown JF, Roa JV, Hunter C, Ralls GA, Papa L. Endotracheal tube placement confirmation: 100% sensitivity and specificity with sustained four-phase capnographic waveforms in a cadaveric experimental model. Resuscitation. 2017 Jun;115:192-198. doi: 10.1016/j.resuscitation.2017.01.002. Epub 2017 Jan 19. PubMed PMID: 28111195.
<<*Noted in table(s) above.*>>

6: Truszewski Z, Krajewski P, Fudalej M, Smereka J, Frass M, Robak O, Nguyen B, Ruetzler K, Szarpak L. A comparison of a traditional endotracheal tube versus ETView SL in endotracheal intubation during different emergency conditions: A randomized, crossover cadaver trial. Medicine (Baltimore). 2016 Nov;95(44):e5170. PubMed PMID: 27858851; PubMed Central PMCID: PMC5591099.
<<*Not directly contributory to this PICO, but highlighted that videoscope laryngoscopy is rapid and effective. If revisualizing with a secondary imaging method is considered confirmation, this could support that approach.*>>

7: Bullock A, Dodington JM, Donoghue AJ, Langhan ML. Capnography Use During Intubation and Cardiopulmonary Resuscitation in the Pediatric Emergency Department. Pediatr Emerg Care. 2017 Jul;33(7):457-461. doi: 10.1097/PEC.0000000000000813. PubMed PMID: 27455341; PubMed Central PMCID: PMC5259553.
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8: Richardson M, Moulton K, Rabb D, Kindopp S, Pishe T, Yan C, Akpinar I, Tsoi B, Chuck A. Capnography for Monitoring End-Tidal CO2 in Hospital and Pre-hospital Settings: A Health Technology Assessment [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 Mar. Available from http://www.ncbi.nlm.nih.gov/books/NBK362374/
PubMed PMID: 27227208.
<<*Research question #3 of this systematic review dealt with monitoring EtCO2 in adults receiving CPR, but did not address ETT placement or adjustment.*>>

9: Karacabey S, Sanrı E, Gencer EG, Guneysel O. Tracheal ultrasonography and ultrasonographic lung sliding for confirming endotracheal tube placement: Speed and Reliability. Am J Emerg Med. 2016 Jun;34(6):953-6. doi: 10.1016/j.ajem.2016.01.027. Epub 2016 Jan 26. PubMed PMID: 26994679.
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10: Wojtczak JA, Cattano D. Laryngo-tracheal ultrasonography to confirm correct endotracheal tube and laryngeal mask airway placement. J Ultrason. 2014 Dec;14(59):362-6. doi: 10.15557/JoU.2014.0037. Epub 2014 Dec 30. PubMed PMID: 26672974; PubMed Central PMCID: PMC4579715.
<<*Noted in table(s) above.*>>

11: Komasawa N, Cho T, Mihara R, Minami T. Utility of gum-elastic bougie for tracheal intubation during chest compressions in a manikin: a randomized crossover trial. Am J Emerg Med. 2016 Jan;34(1):54-6. doi: 10.1016/j.ajem.2015.09.016. Epub 2015 Sep 21. PubMed PMID: 26456492.
<<*This manikin trial only used the GEB as a primary introducer for ET intubation, not as a secondary or confirmatory device.*>>

12: Turle S, Sherren PB, Nicholson S, Callaghan T, Shepherd SJ. Availability and use of capnography for in-hospital cardiac arrests in the United Kingdom. Resuscitation. 2015 Sep;94:80-4. doi: 10.1016/j.resuscitation.2015.06.025. Epub 2015 Jul 13. PubMed PMID: 26184656.
<<*This study was a telephone survey about EtCO2 use practices. No specifics about discriminating ET position.*>>

13: Kodali BS, Urman RD. Capnography during cardiopulmonary resuscitation: Current evidence and future directions. J Emerg Trauma Shock. 2014 Oct;7(4):332-40. doi: 10.4103/0974-2700.142778. Review. PubMed PMID: 25400399; PubMed Central PMCID: PMC4231274.
<<*This is a broad review article with no specificity to discriminating ET position per the PICO. It's literature review of 1960-2014 largely precedes this evidence update's time frame.*>>

14: Chou HC, Chong KM, Sim SS, Ma MH, Liu SH, Chen NC, Wu MC, Fu CM, Wang CH, Lee CC, Lien WC, Chen SC. Real-time tracheal ultrasonography for confirmation of endotracheal tube placement during cardiopulmonary resuscitation. Resuscitation. 2013 Dec;84(12):1708-12. doi: 10.1016/j.resuscitation.2013.06.018. Epub 2013 Jul 9. PubMed PMID: 23851048.
<<*Noted in table(s) above. This article predates the 4/14/2014 end of the last search period.*>>

15: Umesh G, Tim TJ, Prabhu M, Prasad KN, Jasvinder K. Umesh's intubation

detector (UID) for rapid and reliable identification of tracheal intubation by
novices in anaesthetised, paralysed adult patients. J Clin Monit Comput. 2013
Oct;27(5):517-20. doi: 10.1007/s10877-013-9455-4. Epub 2013 Mar 20. PubMed PMID:
23512256.
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16: Heines SJ, Strauch U, Roekaerts PM, Winkens B, Bergmans DC. Accuracy of
end-tidal CO2 capnometers in post-cardiac surgery patients during controlled
mechanical ventilation. J Emerg Med. 2013 Jul;45(1):130-5. doi:
10.1016/j.jemermed.2012.11.019. Epub 2013 Jan 30. PubMed PMID: 23375221.
<<*This study examined the accuracy of* CO_2 *levels, not discriminating ET position. This article predates the 4/14/2014 end of the last search period.*>>

17: Phelan MP, Ornato JP, Peberdy MA, Hustey FM; American Heart Association's Get
With The Guidelines-Resuscitation Investigators. Appropriate documentation of
confirmation of endotracheal tube position and relationship to patient outcome
from in-hospital cardiac arrest. Resuscitation. 2013 Jan;84(1):31-6. doi:
10.1016/j.resuscitation.2012.08.329. Epub 2012 Sep 1. PubMed PMID: 22947260.
<<*This study simply examined the compliance of documenting ET position assessment and confirmation. This article predates the 4/14/2014 end of the last search period.*>>

C4. Oxygen Dose During CPR (ALS 889: EvUp)

Worksheet author(s): **Jasmeet Soar**
Council: **ERC**
Date Submitted: **2 Dec 2019**

PICO / Research Question:
(P) In adults with cardiac arrest in any setting,
(I) Does administering a maximal oxygen concentration (e.g. 100% by face mask or closed circuit),
(C) compared with no supplemental oxygen (e.g. 21%) or a reduced oxygen concentration (e.g. 40-50%),
(O) change: Survival with favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days and/or 1 year, Survival only at discharge, 30 days, 60 days, 180 days and/or 1 year, ROSC?

Conflicts of Interest (financial/intellectual, specific to this question): No relevant COI

Year of last full review: 2015 ALS CosTR [Soar 2015 e71, Callaway 2015 s84]
Last ILCOR Treatment Recommendation in 2015:

We suggest the use of the highest possible inspired oxygen concentration during CPR (weak recommendation, very-low-quality evidence).

2015 Search Strategy:

PubMed: (Search Completed: October 30, 2014) ("Oxygen"[Mesh] OR “oxygen concentration”[TIAB] OR “supplemental oxygen”[TIAB] OR “oxygen therapy”[TIAB] OR “titrated oxygen”[TIAB] OR “inspired oxygen”[TIAB] OR paO2[TIAB] OR “100% oxygen”[TIAB] OR “high flow oxygen”[TIAB] OR "Hyperoxia"[Mesh] OR "Oxidative Stress"[Mesh] OR ((Hyperoxi*[TIAB] OR Hypoxi*[TIAB] OR Normoxi*[TIAB]) AND (Ventilat*[TIAB] OR "Oxygen Inhalation Therapy"[Mesh:NoExp] OR "Respiration, Artificial"[Mesh: NoExp]))) AND ("Heart Arrest"[Mesh] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR asystole*[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR "cardio-pulmonary arrest"[TIAB] OR "cardio-pulmonary arrests"[TIAB] OR "Out-of-Hospital Cardiac Arrest"[Mesh]) AND ("resuscitation"[Mesh] OR resuscitat* OR CPR OR prehospital OR pre-hospital OR “out-of-hospital”[TIAB] OR “out of hospital”[TIAB] OR "Emergency Medical Services"[Mesh]) NOT (neonat*OR newborn*) NOT ("letter"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] or Case Reports[Publication Type])

443 results

2019 Search Strategy:
PubMed: (Search Completed: December 2, 2019) ("Oxygen"[Mesh] OR “oxygen concentration”[TIAB] OR “supplemental oxygen”[TIAB] OR “oxygen therapy”[TIAB] OR “titrated oxygen”[TIAB] OR “inspired oxygen”[TIAB] OR paO2[TIAB] OR “100% oxygen”[TIAB] OR “high flow oxygen”[TIAB] OR "Hyperoxia"[Mesh] OR "Oxidative Stress"[Mesh] OR ((Hyperoxi*[TIAB] OR Hypoxi*[TIAB] OR Normoxi*[TIAB]) AND (Ventilat*[TIAB] OR "Oxygen Inhalation

Therapy"[Mesh:NoExp] OR "Respiration, Artificial"[Mesh: NoExp]))) AND ("Heart Arrest"[Mesh] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR asystole*[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR "cardio-pulmonary arrest"[TIAB] OR "cardio-pulmonary arrests"[TIAB] OR "Out-of-Hospital Cardiac Arrest"[Mesh]) AND ("resuscitation"[Mesh] OR resuscitat* OR CPR OR prehospital OR pre-hospital OR “out-of-hospital”[TIAB] OR “out of hospital”[TIAB] OR "Emergency Medical Services"[Mesh]) NOT (neonat*OR newborn*) NOT ("letter"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] or Case Reports[Publication Type])

Database searched: PubMed

Date Search Completed: search run 30 Oct 2013 to 2 Dec 2019

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

205 new articles identified since 2015 Search

Inclusion/Exclusion Criteria: Human and manikin studies included. Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) are eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols) are excluded.

7 studies reviewed in further detail,

2 relevant (2 observational studies and 1 systematic review).

Link to Article Titles and Abstracts (if available on PubMed):

1. https://www.ncbi.nlm.nih.gov/pubmed/27328890
   [Spindelboeck 2016 24]
   Indirect evidence
   Observational data from PaO2 during CPR and after ROSC suggests higher values associated with ROSC

2. https://www.ncbi.nlm.nih.gov/pubmed/27402395
   Indirect evidence
   [Patel 2018 407]
   Observational data
   Higher intra-arrest Pao_2 is independently associated with higher rates of survival to discharge in adults with IHCA.

3. https://www.ncbi.nlm.nih.gov/pubmed/29653154
   [Patel 2018 83]
   Systematic review and meta-analysis identified 2 studies that showed an association between intra-arrest hyperoxia and decreased mortality. Did not identify any new studies on this subject.

4 excluded after further review:

1 study of abdominal CPR [Sha 2017 1117]: https://www.ncbi.nlm.nih.gov/pubmed/29216947

3 animal studies [Nelskyla 2017 1; Kin 105 941; Kjaergaard 106 doi: 10.1186/s13049-016-0262-z]
https://www.ncbi.nlm.nih.gov/pubmed/28438718
https://www.ncbi.nlm.nih.gov/pubmed/25936476
https://www.ncbi.nlm.nih.gov/pubmed/27165087

Summary of Evidence Update:

Evidence Update Process for topics not covered by ILCOR Task Forces

2. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

Organisation (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
2015	ILCOR CoSTR [Soar 2015 e71, Callaway 2015 s84]	Oxygen during CPR	1 observational study	Higher intra-arrest PaO2 associated with improved ROSC	Give highest feasible inspired oxygen during CPR

RCT: NIL

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 [New 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)

[Spindelboeck 2016 24]	Study Type: Observational Arterial blood gases (ABG) during CPR for OHCA	Inclusion Criteria: Austria, OHCA, G2010 Intubated patients with ABG during CPR.	1° endpoint: Survival to hospital admission (HA) 83 patients with ABG during CPR. Increased PaO2 associated with higher rates of HA	Indirect evidence. Did not look at FiO2. Patients wither higher intra-arrest PaO2 have improved survival
[Patel 2018 407]	Study Type: IHCA, USA, 235 patients	Inclusion Criteria: IHCA + blood gas during CPR	1° endpoint: intra-arrest PaO2 levels with rates of ROSC and survival to hospital discharge in adults with IHCA. Patients with higher intra-arrest PaO2 levels had progressively higher rates of ROSC (58% vs 71% vs 72% vs 79% vs 100%, P ¼ .021) and survival to discharge (16% vs 23% vs 30% vs 33% vs 56%, P ¼ .031). In multivariate analysis, PaO2 300 mm Hg was independently associated with higher survival to discharge (odds ratio 60.68; 95% confidence interval: 3.04-1210.28; P ¼ .007; referent PaO2 < 60 mm Hg).	Indirect evidence. Did not look at FiO2. Patients wither higher intra-arrest PaO2 have improved survival

Reviewer Comments (including whether meet criteria for formal review):

This topic was last reviewed in 2015. There remain no adult human studies that directly compare one inspired oxygen concentration with a different inspired oxygen concentration during CPR.

Indirect evidence from studies that measure blood oxygen levels during CPR show an association between increased oxygen levels and improved outcome. This may be a measure of patient condition and effectiveness of CPR as well as inspired oxygen during CPR

My opinion is that there is insufficient data to justify a systematic review at this time. Reference list [new relevant studies]

Patel JK, Schoenfeld E, Parikh PB, Parnia S. Association of Arterial Oxygen Tension During In-Hospital Cardiac Arrest With Return of Spontaneous Circulation and Survival. J Intensive Care Med. 2018 Jul;33(7):407-414.

Spindelboeck W, Gemes G, Strasser C, Toescher K, Kores B, Metnitz P, Haas J, Prause G. Arterial blood gases during and their dynamic changes after cardiopulmonary resuscitation: A prospective clinical study. Resuscitation. 2016 Sep;106:24-9.

C5. Automatic Ventilators Versus Manual Ventilation During CPR (ALS 490: EvUp)

Worksheet author(s): **Gustavo Flores**
Council: **AHA**
Date Submitted:

PICO / Research Question:
Automatic Transport Ventilators

Population: Adult and pediatric patients in cardiac arrest in any setting (in-hospital or out-of-hospital) and who have advanced airways in place

Intervention: The use of automatic ventilators

Comparator: Use of manual ventilation

Outcomes: Ventilation, oxygenation, hands-off time, continuous compressions, survival

Type (intervention, diagnosis, prognosis):

Additional Evidence Reviewer(s):
Conflicts of Interest (financial/intellectual, specific to this question):

Year of last full review: 2010 / 2015 / New question: 2010

Last ILCOR Consensus on Science and Treatment Recommendation:

Consensus on science

One pseudorandomised study suggested that the use of an auto- matic transport ventilator with intubated patients may enable the EMS team to perform more tasks while subjectively providing ventilation similar to that provided by hand with a resuscitation bag (LOE 2).[186] One study suggested that the use of an automatic transport ventilator with intubated patients provides oxygenation and ventilation similar to that achieved with a bag-valve device but with no difference in survival (LOE 2).[187]

Treatment recommendation

There is insufficient evidence to support or refute the use of an automatic transport ventilator over manual ventilation during resuscitation of the cardiac arrest victim with an advanced airway.

2010/2015 Search Strategy:

(Ventilators, Mechanical) AND ((((((((((life support care[MeSH Terms]) OR "life support"[Title/Abstract]) OR cardiopulmonary resuscitation[MeSH Terms]) OR "cardiopulmonary resuscitation"[Title/Abstract]) OR "CPR"[Title/Abstract]) OR "return of spontaneous circulation"[Title/Abstract]) OR "ROSC"[Title/Abstract]) OR heart arrest[MeSH Terms]) OR "cardiac arrest"[Title/Abstract])) NOT ((animals[MH] NOT humans[MH])))

2019 Search Strategy:

(Ventilators, Mechanical) AND ((((((((((life support care[MeSH Terms]) OR "life support"[Title/Abstract]) OR cardiopulmonary resuscitation[MeSH Terms]) OR "cardiopulmonary resuscitation"[Title/Abstract]) OR "CPR"[Title/Abstract]) OR "return of spontaneous circulation"[Title/Abstract]) OR "ROSC"[Title/Abstract]) OR heart arrest[MeSH Terms]) OR "cardiac arrest"[Title/Abstract])) NOT ((animals[MH] NOT humans[MH])))

Database searched:

Pubmed

Date Search Completed:

7 Decembere 2019

Search Results (Number of articles identified / number identified as relevant):
54 articles, 3 relevant

Inclusion/Exclusion Criteria:
Link to Article Titles and Abstracts (if available on PubMed):

https://www.ncbi.nlm.nih.gov/sites/myncbi/1PgE4WBCzHi505/collections/59068177/public/

Summary of Evidence Update:
Evidence Update Process for topics not covered by ILCOR Task Forces

1. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

Organisation (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
Allen S; et al; 2017; PMID 28807986	Study Aim: To determine if a small, turbine-driven ventilator would allow rescuers to adhere more closely to advanced cardiac life support (ACLS) guidelines. Study Type: Randomized controlled trial N = 24	24 ACLS-trained healthcare providers	2 rounds of CPR were performed with a self-inflating bag, and 2 rounds were with the ventilator	When compared with a ventilator, volunteers ventilated with a self-inflating bag within ACLS guidelines. However, volunteers ventilated with increased variation, at higher VT levels, and at higher peak pressures with the self-inflating bag. Hands-off time was also significantly lower with the ventilator.	

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)
	<u>Study Type:</u>	<u>Inclusion Criteria:</u>	<u>1° endpoint:</u>	

El Sayed M, et al; 2019; PMID 30681557	**Study Aim:** Describe the impact of prehospital mechanical ventilation on prehospital time intervals and on mortality. **Study Type:** Obsevational Retrospective matched-cohort study N = 5740	Four consecutive public releases of the US National Emergency Medical Services Information System dataset (2011-2014) EMS activations with recorded ventilator use were randomly matched with activations without ventilator use (1 to 1) on age (range ± 2 years), gender, provider's primary impression, urbanicity, and level of service.	Both total on-scene time and total prehospital time intervals increased with reported ventilator use (4.10 minutes (95% confidence interval [CI]: 2.71-5.49) and 3.59 minutes (95% CI: 3.04-4.14), respectively). Mortality was higher at hospital discharge (29.0% vs 21.1%, P = .01) but not at emergency department (ED) discharge (8.4% vs 7.4%, P = .19) with prehospital ventilator use.	Ventilator use by EMS agencies in 911 calls in the US is associated with higher prehospital time intervals without observed impact on survival to ED discharge.

El Sayed M, et al; 2018; PMID 29032875	**Study Aim:** Describe trends of ventilator use by EMS agencies during 911 calls in the United States and identifies factors associated with this use. **Study Type:** Observational retrospective N = 260,663	**Inclusion Criteria:** Four consecutive releases of the US National Emergency Medical Services Information System (NEMSIS) public research dataset (2011-2014) to describe scene EMS activations (911 calls) with and without reported ventilator use.	Patients with ventilator use were older (mean age 67±18years), nearly half were males (49.2%), mostly in urban areas (80.2%) and cared for by advanced life support (ALS) EMS services (89.5%). CPAP mode of ventilation was most common (71.6%). "Breathing problem" was the most common dispatch complaint for EMS activations with ventilator use (63.9%). Common provider impression categories included "respiratory distress" (72.5%), "cardiac rhythm disturbance" (4.6%), "altered level of consciousness" (4.3%) and "cardiac arrest"(4.0%). Ventilator use was consistently higher at the Specialty Care Transport (SCT) and Air Medical Transport (AMT) service levels and increased over the study period for both suburban and rural EMS activations. Significant factors for ventilator use included demographic characteristics, EMS agency type, specific complaints, provider's primary impressions and condition codes.	Providers at different EMS levels use ventilators during 911 scene calls in the US. Training of prehospital providers on ventilation technology is needed.

Rognås, et al; 2013; PMID 24308781	**Study Aim:** Evaluate whether the development and implementation of an SOP for controlled ventilation during transport could change pre-hospital critical care anaesthesiologists 'behaviour and thereby increase the use of automated ventilators during transport of patients ventilated via an endotracheal tube or a supraglottic airway device (SAD). **Study Type:** Prospective quality control study N = 515	**Inclusion Criteria:** Consecutive transported patients of all ages treated with pre-hospital endotracheal intubation or insertion of an SAD. **Exclusion Criteria:** Inter-hospital transfers.	1. The overall percentage of included patients ventilated on an automated ventilator. The SOP increased the overall prevalence of automated ventilator use from 0.40 (0.34-0.47) to 0.74 (0.69-0.80) with a prevalence ratio of 1.85 (1.57-2.19). This difference is statistically significant (p = 0.00). 2. The percentage of included TBI patients ventilated on an automated ventilator. The SOP increased the prevalence of automated ventilator use from 0.44 (0.26-0.62) to 0.85 (0.62-0.97) with a prevalence ratio of 1.94 (1.26-3.0). This difference is statistically significant (p = 0.0039). 3. The percentage of included post-ROSC patients ventilated on an automated ventilator. The SOP increased the prevalence of automated ventilator use from 0.39 (0.26-0.48) to 0.69 (0.58-0.78) with a prevalence ratio of 1.79 (1.36-2.35). This difference is statistically significant (p = 0.00).	The introduction of the SOP could significantly increase both the overall prevalence of ventilator use and the prevalence of ventilator use in transported TBI patients and patients who had achieved ROSC after pre-hospital CA.

Reviewer Comments (including whether meet criteria for formal review):

There is insufficient data to warrant an updated systematic review.

C6. Steroids During CPR (ALS 433: EvUp)

Worksheet author(s): Tonia Nicholson, Mike Parr
Council: ANZCOR
Date Submitted: Dec 2019

PICO / Research Question: Among adults who are in cardiac arrest in any setting (P), does the administration of corticosteroids during CPR (I) compared with not using corticosteroids (C), improve outcome (O) (eg. Survival)?

Outcomes: Survival with Favourable neurological outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year;
Survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year;
ROSC.

Type (intervention, diagnosis, prognosis): Intervention

Additional Evidence Reviewer(s): N/A

Conflicts of Interest (financial/intellectual, specific to this question): N/A

Year of last full review: 2015

Last ILCOR Consensus on Science and Treatment Recommendation:

Consensus on Science:
In-hospital cardiac arrest. For the critical outcome of **survival to discharge with favorable neurological outcome**, there was low-quality evidence (downgraded for indirectness and for imprecision from 1 RCT in 268 patients with IHCA that showed improved outcome with methylprednisolone, vasopressin and epinephrine during cardiac arrest, and hydrocortisone in those with post-ROSC shock compared with only epinephrine nad placebo (18/130 [13.9%] versus 7/138 [5.1%];RR,2.94;95% CI, 1.16-6.50, which translates to 98 more /1000 surviving with good neurological outcome [95% CI , from 8 to 279 more/1000 surviving with good neurologic outcome]).
For the critical outcome of **survival to discharge**, there was low-quality evidence (downgraded for indirectness and for imprecision) from 1 RCT or 100 patients with IHCA that showed improved outcome with the combination of methylprednisolone, vasopressin and epinephrine during cardiac arrest and hydrocortisone after ROSC for those with shock, compared with the used of only epinephrine and placebo (9/48 [19%] versus 2/52 [4%]; RR,4.87; 95% CI, 1.17-13.79, which translates to 149 more /1000 surviving to discharge [95% CI,7-492 more /1000 surviving to discharge]).
For the important outcome of **ROSC,** there was low-quality evidence (downgraded for indirectness and imprecision) from 2 RCTs involving 368 patients with IHCA showing improved outcome with the use of methylprednisolone and vasopressin in addition to epinephrine, compared with the use of placebo and epinephrine alone (combined RR,1.34; 95% CI,1.21-1.43, which translates to 130-267 more achieving ROSC with the combination of methylprednisolone ,vasopressin and epinephrine during cardiac arrest, compared with the use of only epinephrine and placebo [95% CI, 130-267 more achieving ROSC]).

Out-of-hospital cardiac arrest. For the critical outcome of **survival to discharge,** there was very-low-quality evidence (downgraded for risk of bias, indirectness and imprecision) from 1 RCT and 1 observational study showing no association with benefit with the use of steroids. Paris had no long-term survivors and Tsai showed survival to discharge in 8% (3/36) receiving hydrocortisone compared with 10% (6/61) receiving placebo (p = 0.805).
For the important outcome of **ROSC,** we found very-low-quality evidence from 1 RCT and 1 observational study with a combined total of 183 patients. The RCT showed no improvement in ROSC (and ICU admission) with dexamethasone given during cardiac arrest compared with placebo (5.4% [2/37] versus 8.7% [4/46]), but observational study showed an association with improved ROSC with hydrocortisone compared with no hydrocortisone (58% versus 38%; p=0.049).

Treatment Recommendation
For IHCA, the task force was unable to reach a consensus recommendation for or against the use of steroids in cardiac arrest. We suggest against the routine use of steroids during CPE for OHCA (weak recommendation, very-low-quality evidence).

2015 Search Strategy:

The search performed for the 2015 ILCOR CoSTR used the following terms:

Corticosteroid terms: corticosteroid'/exp; corticosteroid*:ti,ab; mineralocorticoids:ti,ab; 'steroid'/exp; steroids:ti,ab; prednisone:ti,ab; prednisolone:ti,ab; methylprednisolone:ti,ab; dexamethasone:ti,ab; fludrocortisone:ti,ab

Cardiac arrest terms: heart arrest'/exp; "cardiac arrest":ti,ab; "cardiac arrests":ti,ab; "cardiovascular arrest":ti,ab; "cardiovascular arrests":ti,ab; "heart arrest":ti,ab; "heart arrests":ti,ab; "asystole":ti,ab; "pulseless electrical activity":ti,ab; "cardiopulmonary arrest":ti,ab; "cardiopulmonary arrests":ti,ab; CPR:ti,ab; 'resuscitation'/exp; resuscitat*:ti; "chest compression":ti,ab; "chest compressions":ti,ab; 'heart massage'/exp; "heart massage":ti,ab; "cardiac massage":ti,ab; "cardiac compression":ti,ab; "cardiac compressions":ti,ab; "thoracic compression":ti,ab; "thoracic compressions":ti,ab; "basic life support":ti,ab

2019 Search Strategy: Explanation of search strategy approach for updating ALS 433

The search for 2015 PICO on steroids was run on 18 July 2014, so the current search included only studies published since 2014.

#	Search string (developed for the EMBASE.com platform, which includes Medline and Embase databases)	Explanation
#1	'heart arrest'/exp 'heart arrest$':ti,ab 'cardiac arrest$':ti,ab 'cardiovascular arrest$':ti,ab 'cardiopulmonary arrest'/exp 'cardiopulmonary arrest$':ti,ab 'cardio-pulmonary arrest$':ti,ab 'resuscitation'/exp rosc:ti,ab 'post-rosc':ti,ab 'post-resuscitation':ti,ab 'return of spontaneous circulation':ti,ab resuscitat*:ti,ab	**Population – Cardiac arrest** Terms related to cardiac arrest and/or ROSC should be the focus of the article, so these terms must appear in either the title or the abstract, or the article must be tagged with EMTREE terms for cardiac arrest or ROSC. Note, general terms for life support such as 'basic life support' (as used in prior search) or ''advanced cardiac life support' were considered too generic, and terms relating to CPR techniques such as chest compressions and heart massage were considered too specifically focusing on the process of CPR rather than the post-ROSC patient.
#2	#1 NOT ('animal'/exp NOT 'human'/exp OR 'nonhuman'/exp OR 'rodent'/exp OR 'animal experiment'/exp OR 'experimental animal'/exp OR rat:ti,ab OR rats:ti,ab OR mouse:ti,ab OR mice:ti,ab OR dog$:ti,ab OR pig$:ti,ab OR porcine:ti,ab OR swine:ti,ab OR chick$:ti,ab)	**Exclude non-human studies** The search results must include citations from the newborn population string, so a 'non-human studies' filter was applied to it.
#3	#2 NOT ([conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [book]/lim OR 'case report'/de)	**Exclude publication types** Conference abstracts and other ineligible study types were removed here.
#4	#3 AND [2014-2020]/py	**Date limit** The date of the last ILCOR search was 18 July 2014. This search string can be combined with intervention strings or other population strings to produce a final number of records.
#5	'steroid'/de 'corticosteroid'/de 'mineralocorticoid'/de corticosteroid$:ti,ab mineralocorticoid$:ti,ab steroid$:ti,ab prednisone:ti,ab prednisolone:ti,ab methylprednisolone:ti,ab	**Intervention terms – steroids** To identify steroid studies. These terms must appear in the title or abstract, or the article must be tagged with EMTREE terms for steroids. Note, the EMTREE terms were not exploded as that includes a large number of irrelevant interventions. Instead, studies coded directly to the steroid EMTREE term (or the corticosteroid EMTREE term, etc.) were captured, along with studies that include these terms as free text, or include the specific drugs that were included in the search for

#	Search string (developed for the EMBASE.com platform, which includes Medline and Embase databases)	Explanation
	fludrocortisone:ti,ab hydrocortisone:ti,ab dexamethasone:ti,ab	the 2015 ILCOR CoSTR (hydrocortisone was added to this set of specific drugs as it is mentioned in the 2015 Consensus on science).
#6	#4 AND #5	**Population + intervention**
#7	(((after OR post) NEAR/4 (rosc OR spontaneous OR circulation OR resuscitation OR cardiac OR arrest)):ti,ab) OR postarrest:ti,ab OR 'post-arrest':ti,ab OR 'post-rosc':ti,ab OR (surviv* NEAR/3 (cardiac OR arrest OR resuscitation OR ohca OR 'oh ca' OR ihca OR 'ih ca'))	**Post-arrest terms** This string is useful to stratify studies according to whether they include reference to post-ROSC status. However, this string could potentially exclude relevant studies, and should not be relied upon to filter the identified studies.
#8	#6 AND #7	**Population + intervention + post-arrest terms**
#9	#6 NOT #8	**Population + intervention (minus + post-arrest terms)**

Database searched: EMBASE.com platform (includes Medline and EMBASE)/Cochrane Reviews

Date Search Completed: 02 Dec 2019

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

Embase/Medline 702
Cochrane: 99
Trials Registry: 281

Inclusion/Exclusion Criteria:

Inclusion – Adults (>18yrs) with non-traumatic cardiac arrest

Exclusions - Steroids given post-ROSC, paediatric patients, animal studies, letters, commentaries, editorials, case series, poster presentations only, journal club reviews, interim analyses.

Link to Article Titles and Abstracts (if available on PubMed):

Summary of Evidence Update:

Evidence Update Process for topics not covered by ILCOR Task Forces

Although the initial screen of abstracts selected 7 were excluded from further review for the following reasons:

1) Articles were journal club discussions of Mentzelopoulos, 2013:

-Botnaru, T, Altherwi, T and Dankoff, J. (2015). Improved neurologic outcomes after cardiac arrest with combined administration of vasopressin, steroids, and epinephrine compared to epinephrine alone. Canadian Journal of Emergency Medicine. 17(2):202-205.

-Hwang, JY, Arredondo, AF and Paul, TK. (2014). Lung cancer screening, targeted temperature after cardiac arrest, and vasopressin and steroids in cardiac arrest. American Journal of Respiratory and Critical Care Medicine. 189(8):995-996.

2) Studies involved steroids being given post cardiac arrest (not during CPR).

-Donnino, MW, Andersen, LW, Berg, KM, Chase, M, Sherwin, R, Smithline, H, Carney, E, Ngo, L, Patel, PV, Liu, X, Cutlip, D, Zimetbaum, P and Cocchi, MN. (2016). Corticosteroid therapy in refractory shock following cardiac arrest: A randomized, double-blind, placebo-controlled, trial. Critical Care. 20(1).

3) Article was reanalysis of data from studies done in 2009 and 2013:

Mentzelopoulos, SD, Koliantzaki, I, Karvouniaris, M, Vrettou, C, Mongardon, N, Karlis, G, Makris, D, Zakynthinos, E, Sourlas, S, Aloizos, S, Xanthos, T and Zakynthinos, SG. (2018). Exposure to Stress-Dose Steroids and Lethal Septic Shock After In-Hospital

Cardiac Arrest: Individual Patient Data Reanalysis of Two Prior Randomized Clinical Trials that Evaluated the Vasopressin–Steroids–Epinephrine Combination Versus Epinephrine Alone. Cardiovascular Drugs and Therapy. 32(4):339-351.

Relevant Guidelines or Systematic Reviews

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

RCT: None

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**

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) Post-arrest Steroid Use May Improve Outcomes of Cardiac Arrest Survivors. Tsai, MS, Chuang, PY, Huang, CH, Tang, CH, Yu, PH, Chang, WT and Chen, WJ. (2019). Critical care medicine. 47(2):167-175.	**<u>Study Type:</u>** Population-based Retrospective cohort study (Using National Health Insurance Research Database of Taiwan). Propensity scoring estimated using large number of variables (age, gender, PC, co-morbidities, previous steroid use, drugs and DC shocks during CPR, treatment setting, socio-economic status, geographic distribution & year. Steroid and non-steroid groups then matched by PS in ratio 1:3	**<u>Inclusion Criteria:</u>** >18yrs Non-traumatic cardiac arrest. Resuscitation attempted during ED visit (OHCA 2004-2011). No PMHx steroid use. Intervention considered as administration of steroid during CPR. Steroids included were - hydrocortisone, methylprednisolone, triamcinolone, dexamethasone and betamethasone.	**<u>1° endpoint</u>** (for those with no prior steroid exposure): Survival to admission- Before PS matching: With steroids = 37.16% Without = 15.36% Adjusted OR = 2.42% (2.14-2.74) After PS matching: With steroids = 37.19 % Without steroids = 19.00 Adjusted OR = 2.72 (2.35-3.14) **<u>2° endpoints:</u>** Additional end points for Survival to d/c and 1yr survival, with similar results: AOR for 1 yr survival after PSM (and exclusion of those given steroids pre-arrest) = 1.93 (1.48-2.53)	Results suggest an association between use of glucocorticoids during CPR and increased frequency of survival to admission, discharge and 1 yr survival. *<u>Limitations:</u>* Care delivered post-cardiac arrest couldn't be completely adjusted for (though attempts were made with the adjustment for treatment setting & yr of CA). Results applicable to homogeneous Asian population but may not be applicable to other races.

	Study Size: 145,644 patients analyzed, 2912 received intervention. Subsequently, those with prior steroid use removed -> 1393 who were exposed to steroids, matched with 4179 with no exposure.			
2) Hydrocortisone administration was associated with improved survival in Japanese patients with cardiac arrest. Niimura, T, Zamami, Y, Koyama, T, Izawa-Ishizawa, Y, T, Harada, K, et al. Scientific reports. (2017). 7(1):17919.	**Study Type:** Population-based Retrospective cohort study (Using National Health Insurance Research Database of Japan). Propensity scoring used to adjust for baseline characteristics, medical treatment and drug administration. A weighted Cox proportional hazards regression analysis was done to estimate a hazard ratio of survival to d/c **Study Size:** 2233 of whom 2.7% received IV hydrocortisone. With PS matching, cohort of 48 patients matched for use of hydrocortisone vs no hydrocortisone.	**Inclusion Criteria:** >18 and <75yrs with non-traumatic cardiac arrest. Both IH & OHCA.	**1° endpoint** Survival to discharge rate: 21% in hydrocortisone group (13 patients) vs 11% in no-hydrocortisone group (240 patients). OR = 2.2 (95% CI:1.12-3.97, p= 0.015.) A cohort of 48 cases were then matched by propensity score matching. Rate of survival to d/c in hydrocortisone group still tended to be higher, but the difference wasn't statistically significant (OR 2.8, 95% CI:0.88-8.64, p=0.083). A weighted Cox proportional hazards regression analysis was done to estimate a hazard ratio of survival to d/c = 4.6 (95% CI:2.18-9.72, p <0/001). **2° endpoint** ROSC – 25% with hydrocortisone, 8% without (p < 0.001)	**Summary/Conclusion Comment(s)** The results suggest an association between hydrocortisone administration and high rates of survival to discharge. 85% were IHCAs. The ratio of vasoactive medication used in the study was higher in the hydrocortisone group. No information in database on CPC (so assessment of neurological outcome not possible). No detailed description of the timing of drug administration in the database, so administration during and after CPR couldn't be distinguished.

Reviewer Comments (including whether meet criteria for formal review):

Since the 2015 PICO regarding the use of steroids during CPR was addressed, there have been at least 2 large, population-based observational studies done, both of which suggest a possible association between improved survival and the use of corticosteroids during CPR.
The Niiumura study attempts to adjust for the use of vasopressin and other steroids during CPR, to try and isolate the effects of hydrocortisone. It was not able to distinguish whether the drug had been given during or after CPR.
The Tsai study used propensity scoring and cohort matching to assess the effect of several steroids on survival after cardiac arrest. They attempted to exclude patients given steroids post-arrest rather than during arrest, by excluding those given a triage score of >1 on arrival in ED, and those in ED > 6hrs.
Though neither of these studies are RCTs, they are both large and use propensity scoring to try and adjust for multiple confounders.

A formal systematic review adding in these new studies may not result in a body of evidence that is sufficient to modify the current 2015 COST regarding the use of steroids during cardiac arrest, but it may highlight the potential utility of RCTs comparing the addition of administration of corticosteroid during CPR with the administration of placebo, in addition to standard care.

Reference list

1)Bolvardi, E, Seyedi, E, Seyedi, M, Abbasi, AA, Golmakani, R and Ahmadi, K. (2016). Studying the influence of epinephrine mixed with prednisolone on the neurologic side effects after recovery in patients suffering from cardiopulmonary arrest. Biomedical and Pharmacology Journal. 9(1):209-214.

2)Botnaru, T, Altherwi, T and Dankoff, J. (2015). Improved neurologic outcomes after cardiac arrest with combined administration of vasopressin, steroids, and epinephrine compared to epinephrine alone. Canadian Journal of Emergency Medicine. 17(2):202-205.

3)Donnino, MW, Andersen, LW, Berg, KM, Chase, M, Sherwin, R, Smithline, H, Carney, E, Ngo, L, Patel, PV, Liu, X and et al. Corticosteroid therapy in refractory shock following cardiac arrest: a randomized, double-blind, placebo-controlled, trial. Critical care (London, England). 2016; 20(1) (no pagination).

4)Hwang, JY, Arredondo, AF and Paul, TK. (2014). Lung cancer screening, targeted temperature after cardiac arrest, and vasopressin and steroids in cardiac arrest. American Journal of Respiratory and Critical Care Medicine. 189(8):995-996.

5)Mentzelopoulos, SD, Koliantzaki, I, Karvouniaris, M, Vrettou, C, Mongardon, N, Karlis, G, Makris, D, Zakynthinos, E, Sourlas, S, Aloizos, S, Xanthos, T and Zakynthinos, SG. (2018). Exposure to Stress-Dose Steroids and Lethal Septic Shock After In-Hospital Cardiac Arrest: Individual Patient Data Reanalysis of Two Prior Randomized Clinical Trials that Evaluated the Vasopressin–Steroids–Epinephrine Combination Versus Epinephrine Alone. Cardiovascular Drugs and Therapy. 32(4):339-351.

6)Niimura, T, Zamami, Y, Koyama, T, Izawa-Ishizawa, Y, Miyake, M, Koga, T, Harada, K, Ohshima, A, Imai, T, Kondo, Y, Imanishi, M, Takechi, K, Fukushima, K, Horinouchi, Y, Ikeda, Y, Fujino, H, Tsuchiya, K, Tamaki, T, Hinotsu, S, Kano, MR and Ishizawa, K. (2017). Hydrocortisone administration was associated with improved survival in Japanese patients with cardiac arrest. Scientific reports. 7(1):17919.

7)Tsai, MS, Chuang, PY, Huang, CH, Tang, CH, Yu, PH, Chang, WT and Chen, WJ. (2019). Post-arrest Steroid Use May Improve Outcomes of Cardiac Arrest Survivors. Critical care medicine. 47(2):167-175.

C7. Buffering Agents for Cardiac Arrest (ALS 483: EvUp)

Worksheet author(s): Joseph P. Ornato, MD
Council: AHA
Date Submitted: 1/17/20

PICO / Research Question: ALS 483: Buffering agents for cardiac arrest

Among adults who are in cardiac arrest in any setting (P), does buffering agent administration (I), compared with not using buffering agents (C), change (O)?

Outcomes: ROSC, survival, neuro outcome

Type (intervention, diagnosis, prognosis): Intervention
Additional Evidence Reviewer(s): Joseph P. Ornato, MD
Conflicts of Interest (financial/intellectual, specific to this question): none

Year of last full review: 2010 / 2015 / New question: 2015

Last ILCOR Consensus on Science and Treatment Recommendation:
Consensus on Science
Two studies evaluated buffering agents during CPR. Both had limitations but showed no improvement in outcome. Two retrospective cohort studies also showed no benefit in the use of buffering agents during CPR. Two studies demonstrated increased ROSC, hospital admission, and survival at hospital discharge with bicarbonate use. Four cohort studies reported that bicarbonate use was associated with poor short- and long-term outcome.

Treatment Recommendation
Routine administration of sodium bicarbonate for treatment of in-hospital and out-of-hospital cardiac arrest is not recommended.

2010/2015 Search Strategy: 2019

2019 Search Strategy:

(((((sodium bicarbonate[MeSH Terms]) OR bicarbonate[Title/Abstract]) OR buffers[MeSH Terms]) OR buffer[Title/Abstract])) AND (((((((((life support care[MeSH Terms]) OR "life support"[Title/Abstract]) OR cardiopulmonary resuscitation[MeSH Terms]) OR "cardiopulmonary resuscitation"[Title/Abstract]) OR "CPR"[Title/Abstract]) OR "return of spontaneous circulation"[Title/Abstract]) OR "ROSC"[Title/Abstract]) OR heart arrest[MeSH Terms]) OR "cardiac arrest"[Title/Abstract])) NOT ((animals[MH] NOT humans[MH])))

Database searched: PUBMED, Cochrane
Date Search Completed: 1/17/20
Search Results (Number of articles identified / number identified as relevant): 501/5
Inclusion/Exclusion Criteria: only adult out-of-hospital arrests included

Link to Article Titles and Abstracts (if available on PubMed):

https://www.ncbi.nlm.nih.gov/sites/myncbi/1PgE4WBCzHi505/collections/59128795/public/

Summary of Evidence Update:
Evidence Update Process for topics not covered by ILCOR Task Forces

1. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

Organisation (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
	None in adults (see Raymond TT et al, Resuscitation 2015 89:106-13 for systematic review in children				

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
Ahn S et al. 2018 J Thorac Dis; 10:2295-302	**Study Aim:** To evaluate the efficacy of sodium bicarbonate administration in out-of-hospital cardiac arrest (OHCA)	**Inclusion Criteria:** Adult, non-traumatic out of hospital cardiac arrest **Exclusion Criteria:** DNR before/during CPR (n=41); ROSC within 10 min (n=39); Unavailable	**Intervention:** (n=157) After 10 minutes of ACLS, femoral arterial blood samples were obtained for ABGA from patients who	**1° endpoint:** The primary end point was the change of acidosis, evaluated as the pH and bicarbonate levels. The	**Study Limitations:** Single center, small # of cases.

	patients with severe metabolic acidosis during prolonged CPR **<u>Study Type:</u>** Prospective, double-blind, randomized placebo-controlled pilot trial was conducted between January 2015 and December 2015, at a single center emergency department (ED). N= 157	10-min ABGA (n=17) ;Without severe metabolic acidosis in 10-min ABGA (n=5);Extracorporeal cardiopulmonary resuscitation (n=5)	failed to achieve ROSC. **<u>Comparison:</u>** Patients fulfilling the study inclusion criteria were randomly assigned (1:1) to the study group, receiving sodium bicarbonate 50 mEq/L, or to the control group, receiving normal saline 50 mL injection over 2 minutes, in a double-blinded fashion.	secondary end points were sustained ROSC, defined as the restoration of a palpable pulse ≥20 minutes, survival to hospital admission, and good neurologic survival at 1 and 6 months, defined as cerebral performance category (CPC) 1 or 2. **<u>Results:</u>** Sodium bicarbonate group had significant effect on pH (6.99 vs. 6.90, P=0.038) and bicarbonate levels (21.0 vs. 8.0 mEq/L, P=0.007). However, no significant differences showed between sodium bicarbonate and placebo groups in sustained ROSC (4.0% vs. 16.0%, P=0.349) or good neurologic survival at 1 month (0.0% vs. 4.0%, P=1.000).	

Nonrandomized Trials, Observational Studies

Study Acronym; Author;	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P	Summary/Conclusion Comment(s)

Year Published			**value; OR or RR; & 95% CI)**	
Weng YM et al. Am J Emerg Med 2013; 31:562-5	**<u>Study Type:</u>** **Non-randomized, retrospective cohort study. N= 92**	**<u>Inclusion Criteria:</u>** Adult patients presented to the ED in cardiac arrest IN 2009.	**<u>1° endpoint:</u>** Rate of survival to discharge between pts receiving sodium bicarbonate infusion and those not receiving it based on physician discretion. **<u>Secondary endpoints:</u>** ROSC, sustained ROSC, time to ROSC, vital signs after ROSC.	Patients who received a sodium bicarbonate injection during prolonged CPR had a higher percentage of return of spontaneous circulation, but not statistical significant (ROSC, 40.0% vs. 32.3%; P = .465). Sustained ROSC was achieved by 2 (6.7%) patients in the sodium bicarbonate treatment group, with no survival to discharge. No significant differences in vital signs after ROSC were detected between the 2 groups (heart rate, P = .124; systolic blood pressure, P = .094). Sodium bicarbonate injection during prolonged CPR was not associated with ROSC after adjust for variables by regression analysis (Table 3; P = .615; odds ratio, 1.270; 95% confidence interval: 0.501-3.219) **Conclusions:** The administration of sodium bicarbonate during prolonged CPR did not significantly improve the rate of ROSC in out-of-hospital cardiac arrest.

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)**

Kim J et al. Am J Emerg Med 2016; 34:225-9	**Study Type:** Retrospective matched case-control study. **N= 559**	**Inclusion Criteria:** Adult cardiac arrest ED patients. **Exclusions:** Pts with early termination of ALS w/out any ROSC.	**1° endpoint:** ROSC in ED. **Secondary endpoints:**	Two matched groups, one with ROSC and the other without (both n = 258), were generated. Sodium bicarbonate administration and its total cumulative dose were significantly associated with an increased ROSC, with odds ratios for ROSC of 1.86 (95% confidence interval [CI], 1.09-3.16; P = .022) and 1.18 (per 20 mEq; 95% CI, 1.04-1.33; P = .008), respectively. The positive associations remained unchanged after multivariable adjustment, with odds ratios for ROSC of 2.49 (95% CI, 1.33-4.65; P = .004) and 1.27 (95% CI, 1.11-1.47; P = .001), respectively. **Principal conclusion:** Sodium bicarbonate administration during CPR in emergency department was associated with increased 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)**
Kawano T et al. Resuscitation 2017; 119:63-9	**Study Type:** Retrospective analysis of EMS-treated OHCA pts treated with (n= 5,165) vs without (n= 8,700)sodium bicarbonate	**Inclusion Criteria:** EMS-treated, non-traumatic OHCA pts **Exclusions:**	**1° endpoint:** Survival. **Secondary endpoints:** Neuro outcome (mRs 0-3). **Results:** Of 15 601 OHCA patients, 13,865 were included in this study with 5165	In OHCA patients, prehospital SB administration was associated with worse survival rate and neurological outcomes to hospital discharge.

			(37.3%) managed with SB. In the SB treated group, 118 (2.3%) patients survived and 62 (1.2%) had favorable neurological outcomes to hospital discharge, compared to 1699 (19.8%) and 831 (10.6%) in the non-SB treated group, respectively. In the 1:1 propensity matched cohort including 5638 OHCA patients, SB was associated with decreased probability of outcomes (adjusted OR for survival: 0.64, 95% CI 0.45-0.91, and adjusted OR for favorable neurological outcome: 0.59, 95% CI 0.39-0.88, respectively). The association remained consistent in the multiply imputed cohort (adjusted OR 0.48, 95 CI 0.36-0.64, and adjusted OR 0.54, 95% CI 0.38-0.76, respectively).	
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)**
Chen et al. Am J Emerg Med 2018; 36:1998-2004	**<u>Study Type:</u>** Population-based, retrospective cohort study. Analyzed patients who received sodium bicarbonate during	**<u>Inclusion Criteria:</u>** Adult OHCA including traumatic CA cases. **Exclusions:** Cases where EMS pronounced	**<u>1° endpoint:</u>** Survival to hospital admission. Among 5589 total OHCA patients, 15.1% (844) had survival to hospital admission. For all patients, a positive association was noted	Among patients with OHCA in Taiwan, administration of sodium bicarbonate during ED resuscitation was significantly associated with an increased rate of survival to hospital admission.

	resuscitation in the ED vs those who did not. Total n= 5,589.	dead at scene and didn't transport to hospital.	between sodium bicarbonate administration during resuscitation in the ED and survival to hospital admission (adjusted odds ratio [OR]: 4.47; 95% confidence interval [CI]: 3.82-5.22, p<0.001). In propensity-matched patients, a positive association was also noted (adjusted OR, 4.61; 95% CI: 3.90-5.46, p<0.001).	

Reviewer Comments (including whether meet criteria for formal review):

No well-designed RCTs or systematic reviews. I do not believe a formal review is warranted.

	Approval Date
Evidence Update coordinator	
ILCOR board	

***Once approval has been made by Evidence Update coordinator, worksheet will go to ILCOR Board for acknowledgement.**

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C8. Drugs for Torsades de Pointes (ALS 457: EvUp)

Worksheet author(s): Comilla Sasson, MD, PhD
Council: AHA
Date Submitted: 12/20/19

PICO / Research Question: ALS 457 : Drugs for Torsades de Pointes
Among adults who are in Torsades de Pointes tachycardia in any setting (P), does any drug or combination of drugs (I), compared with not using drugs or alternative drugs (C), change (O)?
Outcomes:

Type (intervention, diagnosis, prognosis): Intervention
Additional Evidence Reviewer(s):
Conflicts of Interest (financial/intellectual, specific to this question): None

Year of last full review: 2010 / 2015 / New question: 2015
n/a

Last ILCOR Consensus on Science and Treatment Recommendation:

2010/2015 Search Strategy: 2019

2019 Search Strategy:

torsades de pointes/dt NOT (((animals[MH] NOT humans[MH])))

Database searched: Pubmed
Date Search Completed: 12/19/19
Search Results (Number of articles identified / number identified as relevant): 44/0
Inclusion/Exclusion Criteria: human studies, observational or RCT design,
Link to Article Titles and Abstracts (if available on PubMed):

https://www.ncbi.nlm.nih.gov/sites/myncbi/1PgE4WBCzHi505/collections/59150641/public/

Summary of Evidence Update:
Evidence Update Process for topics not covered by ILCOR Task Forces

1. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

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

Year Published					

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 (including whether meet criteria for formal review):
There were 44 abstracts and titles which were screened. Two articles, both case reports, were not included. One described the use of phenytoin and the other article for phenytoin + isoproterenol to terminate Torsades de Pointes. There was one animal study on the use of flunarizine and verapamil to terminate TdP. This was conducted in 2010 and did not meet the inclusion criteria. There are no studies which met inclusion criteria for this evidence update.

C9a ETCO2 to Predict Outcome of Cardiac Arrest (ALS 459: EvUp)

Worksheet author(s): Edison Ferreira de Paiva (COI #35) and Brian O'Neil (COI #12)
Council: Interamerican Heart Foundation and American Heart Association
Date Submitted: December 24th 2019

PICO / Research Question: Among adults who are in cardiac arrest in any setting (P), does any $ETCO_2$ level value, when present (I), compared with any $ETCO_2$ level below that value (C), change outcome (O)?
Outcomes: Survival with favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year; Survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year; ROSC
Type (intervention, diagnosis, prognosis): Prognosis

Additional Evidence Reviewer(s): none
Conflicts of Interest (financial/intellectual, specific to this question): not applicable

Year of last full review: 2015
Last ILCOR Consensus on Science and Treatment Recommendation:
<u>2015 Consensus on Science</u>
We did not identify any evidence to address the critical outcome of neurologically intact survival. For the critical outcome of survival at discharge, we have identified low-quality evidence (downgraded for serious risk of bias and serious imprecision) from 1 observational study enrolling 127 patients (Ahrens 2001, 391) showing a correlation with initial $ETCO_2$ 10 mmHg (1.33 kPa) or greater when compared with less than 10 mmHg (OR, 11.4; 95% CI, 1.4-90.2). For the critical outcome of survival at discharge, we have identified low-quality evidence (downgraded for serious risk of bias and serious imprecision) from 1 observational study enrolling 127 patients (Ahrens 2001, 391) showing a correlation with 20 minutes of $ETCO_2$ 20 mmHg (2.67 kPa or greater when compared with less than 20 mmHg (OR, 20.0; 95% CI, 2.0-203.3). For the important outcome of ROSC, we have identified moderate-quality evidence (downgraded for serious risk of bias) from 3 observational studies enrolling 302 patients (Callaham 1990, 358; Cantineau 1996, 791; Ahrens 2001, 391) showing a correlation with initial $ETCO_2$ 10 mmHg or greater when compared with less than 10 mmHg (OR, 10.7; 95% CI, 5.6-20.3). For the important outcome of ROSC, we have identified very-low-quality evidence (downgraded for very serious risk of bias, serious inconsistency, and serious imprecision) from 3 observational studies enrolling 367 patients (Wayne 1995, 762; Levine 1997, 301; Ahrens 2001, 391) showing correlation with 20 minutes $ETCO_2$ 10 mmHg or greater when compared with less than 10 mmHg (OR, 181.6; 95% CI, 40.1-822.6).
<u>2015 Treatment Recommendations</u>

- We recommend against using $ETCO_2$ cutoff values alone as a mortality predictor or on the decision to stop a resuscitation attempt (strong recommendation, low-quality evidence)
- We suggest that an $ETCO_2 \geq$ 10 mmHg measured after tracheal intubation or after 20 minutes of resuscitation, may be a predictor of ROSC (weak recommendation, low-quality evidence)
- We suggest that an $ETCO_2 \geq$ 10 mmHg measured after tracheal intubation, or an $ETCO_2 \geq$ 20 mmHg measured after 20 minutes of resuscitation may be a predictor of survival to discharge (weak recommendation, moderate-quality evidence).

2015 Search Strategy

PubMed: (Search Completed: December 17th, 2013)
136 results
((((((("Heart Arrest"[Mesh] OR "Heart Arrest, Induced"[Mesh] OR "cardiac arrest"[TIAB] OR "cardiovascular arrest"[TIAB] OR "heart arrest"[TIAB] OR "Advanced Cardiac Life Support"[TIAB] OR "ACLS"[TIAB] OR "Ventricular Fibrillation"[Mesh:noexp] OR "Cardiopulmonary Resuscitation"[Mesh] OR "cardiopulmonary resuscitation"[TIAB] OR "CPR"[TIAB] OR "cardiopulmonary arrest"[TIAB]) AND ((((((("Carbon Dioxide"[Mesh] OR "CO_2"[TIAB] OR "Carbon Dioxide"[TIAB]) AND ("Tidal Volume"[Mesh] OR "Tidal volume"[TIAB] OR "End tidal"[TIAB] OR "Endtidal"[TIAB] OR "Expired"[TIAB]))))) OR ("$ETCO_2$"[TIAB] OR $PETCO_2$[TIAB] OR "Capnography"[Mesh]))))))) AND (("Treatment Outcome"[Mesh] OR "Fatal Outcome"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "Prognosis"[Mesh] OR "Survival"[Mesh] OR "Mortality"[Mesh] OR "mortality"[Subheading] OR "Disease-Free Survival"[Mesh] OR "Survival Analysis"[Mesh] OR "Survival Rate"[Mesh] OR “Outcome”[All Fields] OR "outcomes"[All Fields] OR "Predictive Value of Tests"[Mesh] OR "Survivors"[Mesh] OR "return of spontaneous circulation"[TIAB] OR "ROSC"[TIAB])))) NOT ((animals[mh] NOT humans[mh]) NOT ("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or Case Reports[ptyp]))

Embase: (Search Completed: December 17th, 2013)
239 results
'heart arrest'/exp OR 'cardiac arrest':ab, ti OR 'cardiovascular arrest':ab, ti OR 'heart arrest':ab, ti OR 'cardiopulmonary arrest':ab, ti OR 'advanced cardiac life support':ab, ti OR 'acls':ab, ti OR 'heart ventricle fibrillation'/exp OR 'cardiopulmonary resuscitation':ab, ti OR 'cpr':ab, ti AND ('carbon dioxide'/exp OR 'co2':ab, ti OR 'carbon dioxide':ab, ti AND ('tidal volume'/exp OR 'tidal volume':ab, ti OR 'end tidal':ab, ti OR 'endtidal':ab, ti OR 'expired':ab, ti) OR 'etco2':ab, ti OR petco2:ab, ti OR 'capnometry'/de OR 'capnography':ab, ti OR 'end tidal carbon dioxide tension'/exp) AND ('treatment outcome'/exp OR 'fatality'/exp OR 'outcome assessment'/exp OR 'prognosis'/de OR 'survival'/exp OR 'mortality'/exp OR outcome:ab, ti OR outcomes:ab, ti OR 'predictive value'/exp OR 'survivor'/exp OR 'return of spontaneous circulation'/exp OR 'return of spontaneous circulation':ab, ti OR 'rosc':ab, ti) NOT ('animal'/exp NOT 'human'/exp) NOT ([editorial]/lim OR [letter]/lim OR 'case report'/de) AND [embase]/lim

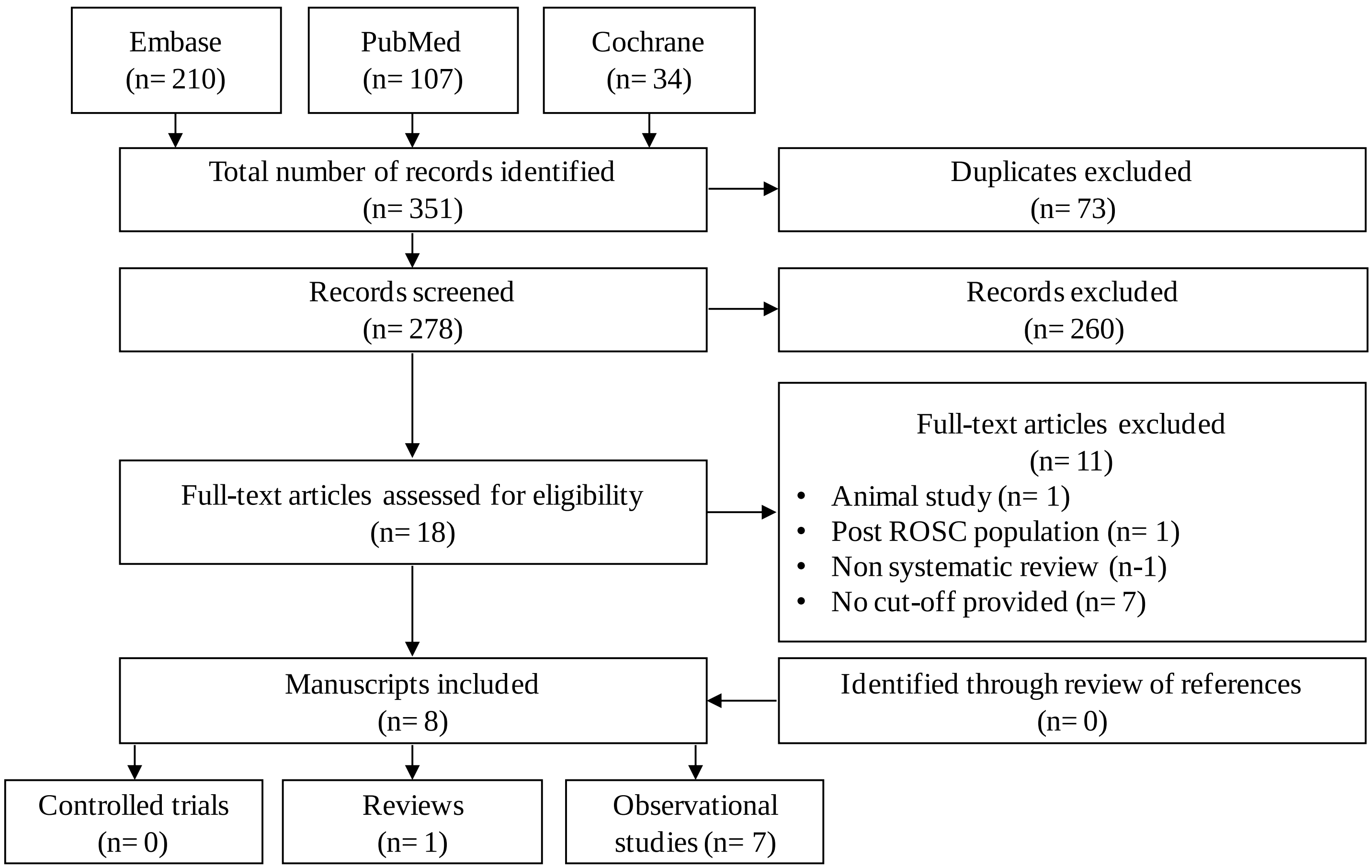
Cochrane: (Search Completed: December 17th, 2013)
17 results
([mh "Heart Arrest"] or [mh "Heart Arrest, Induced"] or "cardiac arrest":ti, ab or "cardiovascular arrest":ti, ab or "heart arrest":ti, ab or "Advanced Cardiac Life Support":ti, ab or "ACLS":ti, ab or [mh ^"Ventricular Fibrillation"] or [mh "Cardiopulmonary Resuscitation"] or "cardiopulmonary resuscitation":ti, ab or "CPR":ti, ab or "cardiopulmonary arrest":ti, ab) and ((([mh "Carbon Dioxide"] or "CO_2":ti, ab or "Carbon Dioxide":ti, ab) and ([mh "Tidal Volume"] or "Tidal volume":ti, ab or "End tidal":ti, ab or "Endtidal":ti, ab or "Expired":ti, ab)) or ("$ETCO_2$":ti, ab or "$PETCO_2$":ti, ab or [mh Capnography])) and ([mh "Treatment Outcome"] or [mh "Fatal Outcome"] or [mh "Outcome Assessment (Health Care)"] or [mh "Outcome and Process Assessment (Health Care)"] or [mh Prognosis] or [mh Survival] or [mh Mortality] or mortality:ti, ab or [mh "Disease-Free Survival"] or [mh "Survival Analysis"] or [mh "Survival Rate"] or Outcome:ti, ab or outcomes:ti, ab or [mh "Predictive Value of Tests"] or [mh Survivors] or "return of spontaneous circulation":ti, ab or ROSC:ti, ab)

2019 Search Strategy: same as in 2015

Database searched: PubMed, Embase and Cochrane

Date Search Completed: November 20th, 2019 (starting from December 17th, 2013)

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



Inclusion/Exclusion Criteria:

Inclusion criteria: Human studies, All kind of clinical trials, Observational studies, Case-control studies, Systematic reviews, Meta-Analysis

Exclusion criteria: Pediatric studies, Animal studies, Case reports, Letters, Studies without specified outcome

Link to Article Titles and Abstracts (if available on PubMed):

https://www.ncbi.nlm.nih.gov/pubmed/29217394[1]
https://www.ncbi.nlm.nih.gov/pubmed/24639823[2]
https://www.ncbi.nlm.nih.gov/pubmed/25939324[3]
https://www.ncbi.nlm.nih.gov/pubmed/26948821[4]
https://www.ncbi.nlm.nih.gov/pubmed/31742569[5]
https://www.ncbi.nlm.nih.gov/pubmed/28847626[6]
https://www.ncbi.nlm.nih.gov/pubmed/27350369[7]
https://www.ncbi.nlm.nih.gov/pubmed/27638460[8]

Summary of Evidence Update:

Evidence Update Process for topics not covered by ILCOR Task Forces

3. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

Author, Year Published, 1st page	**Guideline or systematic review**	**Topic addressed or PICO(S)T**	**Number of articles identified**	**Key findings**	**Treatment recommendations**
Paiva, 2018, 1[2]	Systematic review	PICO (This systematic review was initiated as part of the 2015 International Liaison Committee on Resuscitation Consensus on Science and Treatment Recommendation process)	17 in the qualitative synthesis; 5 in the meta-analysis	Consistent although low-quality evidence that $ETCO_2$ measurements ≥10 mmHg, obtained at various time points during CPR, are substantially related to ROSC; Initial $ETCO_2$ or 20-min $ETCO_2$ > 20 mmHg appears to be a better predictor of ROSC than the 10 mmHg; $ETCO_2$ < 10 mmHg after 20 min of CPR is associated with a 0.5% likelihood of ROSC; Extreme or trending values may be more useful than static mid-range levels	No specific recommendation provided

RCT: None found

Study Acronym; Author, Year Published, 1st page	**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

Author, Year Published, 1st page	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Akinci, 2014, 16	Prospective cohort (80)	OOHCA arriving at ED (22.5% shockable rhythm)	$ETCO_2 \geq 28$ mmHg at 20 min to predict ROSC: SEN 0.87 (95% CI 0.75-0.95) SPE 0.80 (95% CI 0.52-0.96) PPV 0.94 (95% CI 0.85-0.98) NPV 0.63 (95% CI 0.45-0.78) No survival if $ETCO_2$ at 20 min < 14 mmHg	Only 1 hospital; Ambulance, then ED; Small sample size; Time until CPR at the ED 25 min
Pearce, 2015, 77	Retrospective cohort (50)	IHCA (100% PEA)	Initial (within the first 10 min of CPR) $ETCO_2$ to predict ROSC: $ETCO_2$ >10 mmHg: OR 2.49 (95% CI 0.64-9.63, p= 0.186) $ETCO_2$ >20 mmHg: OR 4.77 (95% CI 1.18-19.20, p= 0.028)	Retrospective study; Small sample size; Capnography obtained after ROSC or > 10 min after initiation of CPR was excluded; OR adjusted for age, gender, and arrest location; Not provided and not possible to calculate SEN, SPE, PPV and NPV
Poon, 2016, 80	Prospective cohort (319)	OOHCA arriving at ED (11.4% shockable rhythm)	3-min $ETCO_2$ >10 mmHg to predict ROSC: SEN 0.95 (95% CI 0.89-0.98) SPE 0.27 (95% CI 0.21-0.33) PPV 0.40 (95% CI 0.34-0.46) NPV 0.92 (95% CI 0.82-0.97) Area under ROC curve 0.80 (95% CI 0.71-0.91)	OR adjusted for variables potentially related to outcome; Large number of patients not included due to inadequate documentation of $ETCO_2$
Poppe, 2019, 524	Retrospective cohort (526)	OOHCA (100% PEA)	Initial $ETCO_2$ 20 to 45 vs < 20 mmHg to predict ROSC and 30-day Survival: <u>ROSC</u> SEN 0.59 (95% CI 0.50-0.68) SPE 0.54 (95% CI 0.48-0.59) PPV 0.33 (95% CI 0.29-0.37) NPV 0.77 (95% CI 0.73-0.81) <u>30-day Survival</u> SEN 0.69 (95% CI 0.39-0.91) SPE 0.51 (95% CI 0.46-0.56) PPV 0.04 (95% CI 0.03-0.06) NPV 0.98 (95% CI 0.96-0.99)	Retrospective study; $ETCO_2$ levels too high - maybe patients already with ROSC were included; Discharge < 30 days considered 30-day survival
Singer, 2018, 403	Prospective cohort (100)	OOHCA arriving at ED (14.0% shockable rhythm)	$ETCO_2$ every 1-2 min during CPR > 20 mmHg to predict ROSC: SEN 1.00 (95% CI 0.87-1.00) SPE 0.45 (95% CI 0.33-0.57)	Designed to compare cerebral O_2 saturation and $ETCO_2$ to predict ROSC; Convenience sample; Small sample size;

				$ETCO_2$ levels too high; maybe patients already with ROSC were included
Sutton, 2016, 76	Retrospective cohort (803)	IHCA (rhythm not available)	Any $ETCO_2$ > 10 mmHg during CPR to predict STD and STD with CPC 1 or 2: STD SEN 0.80 (95% CI 0.73-0.86) SPE 0.39 (95% CI 0.35-0.43) PPV 0.24 (95% CI 0.22-0.26) NPV 0.89 (95% CI 0.85-0.92) STD with CPC 1 or 2 SEN 0.51 (95% CI 0.36-0.66) SPE 0.38 (95% CI 0.34-0.42) PPV 0.05 (95% CI 0.04-0.07) NPV 0.92 (95% CI 0.89-0.94)	Retrospective study; Designed to evaluate the association between clinician-reported physiologic monitoring of CPR ($ETCO_2$ and diastolic BP) and ROSC; Survival and neurological outcome were secondary analysis
Wang, 2016, 2367	Retrospective cohort (202)	IHCA (11.9% shockable rhythm)	$ETCO_2$ after intubation and 6 ventilations ≥ 25.5 mmHg to predict ROSC and STD ROSC OR 2.64 (95% CI 1.43-4.88, p= 0.002) STD OR 3.10 (95% CI 1.26-7.60, p= 0.014)	Retrospective study; Large number of patients not included due to inadequate documentation of $ETCO_2$; Not provided and not possible to calculate SEN, SPE, PPV and NPV

OOHCA indicates out of hospital cardiac arrest; ED, emergency department; IHCA, in hospital cardiac arrest; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value; CPR, cardiopulmonary resuscitation; $ETCO_2$, end-tidal CO_2; OR, odds ratio; CI, confidence interval; ROC, receiver operating characteristic; STD, survival to discharge and CPC, cerebral performance category.

Reviewer Comments (including whether meet criteria for formal review):

Eight studies were identified: 1 systematic review (Paiva, 2018, 1) and 7 observational studies - 3 prospective (Akinci, 2014, 16; Poon, 2016, 80; Singer, 2018, 403) and 4 retrospective cohorts (Pearce, 2015, 77; Poppe 2019, 524; Sutton 2016, 76; Wang 2016, 2367). Although no randomized controlled trials have been identified, observational studies are considered adequate to answer the proposed question, as long as they are properly designed and controlled for potential confounders. However, all studies showed great potential for bias, especially due to sample size, time elapsed between arrest and $ETCO_2$ measurement, and lack of information due to inadequate documentation of $ETCO_2$ measurement.

Two of the authors of the systematic review were also authors of the $ETCO_2$ recommendations published by ILCOR in 2015 and used part of the work developed in this process as the basis for their publication. The authors concluded that, although of low quality, evidence consistently indicated that measurements of ECTO2≥ 10 mmHg, obtained at various timing points during resuscitation, were substantially related to ROSC, but values lower than that should not be used as single criteria for withholding the resuscitation attempt. They also suggest that trends or extreme values may be more useful for prognosis than static mid-range levels (Paiva, 2018, 1).

As in 2015, observational cohorts assessed widely varying populations, cutoff values, and timing points. Four studies included out-of-hospital cardiac arrest (OOHCA), 3 of them after the patient's arrival in the ED, and 3 included in-hospital cardiac arrest (IHCA). Two studies, one in and one out of the hospital, included only patients with pulseless electrical activity. Most studies set cutoff points at 10 or 20 mmHg, which were measured immediately after intubation, after 6 ventilations, after 3 minutes, within the first 10 minutes, or every 1 to 2 min. The study with the largest number of patients (n= 803) evaluated the association between the occurrence of any clinician-reported $ETCO_2$ measurement> 10 mmHg during the resuscitation attempt and survival to discharge (STD) or STD with good neurological outcome (Sutton, 2016, 76).

Four studies provided data that allowed the calculation of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPP) for ROSC (Akinci, 2014, 16; Poon, 2016, 80; Poppe, 2019, 524; Singer, 2018 , 403), two for STD (Poppe, 2019, 524; Sutton, 2016, 76) and one for STD with good neurological outcome (Sutton, 2016, 76).

When analyzing the results presented in the table of nonrandomized studies, we observe sensitivity values ranged from 0.59 to 1.00 for ROSC and from 0.69 to 0.80 for STD. However, except for Akinci's study (Akinci, 2014, 16), specificity values were low, ranging from 0.27 to 0.54. PPV values were also much lower than NPV values (0.33 to 0.40 vs. 0.77 to 0.92), indicating that the $ETCO_2$ measurement may be more useful in identifying patients with poor prognosis than those most likely to have ROSC.

In the only study evaluating STD with good neurological outcome, the sensitivity of any $ETCO_2$ measurement> 10 mmHg during the resuscitation attempt was 0.51, with specificity of 0.38, PPV of only 0.05, and NPV of 0.92, also indicating greater utility of $ETCO_2$ in the definition of patients with a worse prognosis than patients more likely to be discharged with good neurological status.

In summary, although since the publication of the Guidelines 2015, and perhaps stimulated by it, several studies on the usefulness of $ETCO_2$ in the definition of prognosis in cardiac arrest have been produced, there is still great variability in the studied populations, cutoff values and timing points for measurement, which make the interpretation of the results difficult. At this time, it is unlikely for a formal Systematic Review to be able to generate significant changes to current recommendations, but the publication of this Evidence Update should contribute to the better design of the future studies.

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C9b ETCO2 to Predict Outcome of Cardiac Arrest (ALS 459: EvUp)

Worksheet author(s): Maureen Chase MD, MPH
Council: SOC
Date Submitted: 1/15/2020

PICO / Research Question: ALS 459 ETCO2 to Predict Outcome of Cardiac Arrest

Among adults who are in cardiac arrest in any setting (P), does any ETCO2 level value, when present (I), compared with compared with any ETCO2 level below that value (C), change Survival with Favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year, Survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year, ROSC (O)?

Outcomes:

9-Critical
Survival with Favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year

8-Critical
Survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year

7-Critical
ROSC

Type (intervention, diagnosis, prognosis): Prognostic

Additional Evidence Reviewer(s):
Conflicts of Interest (financial/intellectual, specific to this question): None

Year of last full review: 2010 / 2015 / New question: 2015
Search Completed: December 17, 2013

Last ILCOR Consensus on Science and Treatment Recommendation:

We recommend against using ETCO2 cutoff values alone as a mortality predictor or on the decision to stop a resuscitation attempt (strong recommendation, low-quality evidence). We suggest that an ETCO2 10 mm Hg or greater measured after tracheal intubation or after 20 minutes of resuscitation, may be a predictor of ROSC (weak recommendation, low-quality evidence). We suggest that an ETCO2 10 mm Hg or greater measured after tracheal intubation, or an ETCO2 20 mm Hg or greater measured after 20 minutes of resuscitation may be a predictor of survival to discharge (weak recommendation, moderate-quality evidence). Values, Preferences, and Task Force Insights In making the strong recommendations against using a specific ETCO2 cutoff value alone as a mortality predictor or on the decision to stop a resuscitation attempt, we have put a higher value on not relying on a single variable (ETCO2) and cutoff value when their usefulness in actual clinical practice, and variability according to the underlying cause of cardiac arrest, has not been established and there are considerable knowledge gaps. The task force was concerned that the etiology (eg, asphyxia, PE) of cardiac arrest could affect ETCO2 values, and that there was a risk of self-fulfilling prophecy if specific threshold values were followed. There was concern about the accuracy of ETCO2 values measured during CPR. During open discussions there were requests that the ILCOR recommendation be far more prescriptive to prevent futile and prolonged resuscitation attempts.

2010/2015 Search Strategy: 2015

((((((("Heart Arrest"[Mesh] OR "Heart Arrest, Induced"[Mesh] OR "cardiac arrest"[TIAB] OR "cardiovascular arrest"[TIAB] OR "heart arrest"[TIAB] OR "Advanced Cardiac Life Support"[TIAB] OR "ACLS"[TIAB] OR "Ventricular Fibrillation"[Mesh:noexp] OR "Cardiopulmonary Resuscitation"[Mesh] OR "cardiopulmonary resuscitation"[TIAB] OR "CPR"[TIAB] OR "cardiopulmonary arrest"[TIAB]) AND ((((((("Carbon Dioxide"[Mesh] OR "CO2"[TIAB] OR "Carbon Dioxide"[TIAB]) AND ("Tidal Volume"[Mesh] OR "Tidal volume"[TIAB] OR "End tidal"[TIAB] OR "Endtidal"[TIAB] OR "Expired"[TIAB]))))) OR ("ETCO2"[TIAB] OR PETCO2[TIAB] OR "Capnography"[Mesh]))))))) AND (("Treatment Outcome"[Mesh] OR "Fatal Outcome"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "Prognosis"[Mesh] OR "Survival"[Mesh] OR "Mortality"[Mesh] OR "mortality"[Subheading] OR "Disease-Free Survival"[Mesh] OR "Survival Analysis"[Mesh] OR "Survival Rate"[Mesh] OR "Outcome"[All Fields] OR "outcomes"[All Fields] OR "Predictive Value of Tests"[Mesh] OR "Survivors"[Mesh] OR "return of spontaneous circulation"[TIAB] OR "ROSC"[TIAB])))) NOT ((animals[mh] NOT humans[mh]) NOT ("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or Case Reports[ptyp]))

2019 Search Strategy: 2015 search strategy
Database searched: PubMed
Date Search Completed: 11/13/2019
Search Results (Number of articles identified / number identified as relevant): 117/ 23
Inclusion/Exclusion Criteria: see 2015 search strategy
Link to Article Titles and Abstracts (if available on PubMed):
https://www.ncbi.nlm.nih.gov/sites/myncbi/1xstxqFKQhvoCG/collections/58986579/public/

Summary of Evidence Update:
Evidence Update Process for topics not covered by ILCOR Task Forces

1. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

Organisation (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Touma, O *Resuscitation* 2013	Systematic review *<u>Inclusion criteria:</u>* Human, English language studies evaluating the relationship between EtCO2 during cardiac arrest and outcomes *<u>Limitation:</u>* Few smaller studies did not limit to adult population - exact n not reported but appears to represent relatively small number overall	ETCO2 as a predictor of ROSC	23 (22 prospective observational, 1 RCT comparing chest compression device to standard CPR but also compared ETCO2 in survivors- given same weight as observational studies) 16 studies pre-hospital, 5 ED, 1 inpatient setting	ETCO2 < 1.33kPA (10 mm Hg) during CPR is a strong predictor against ROSC but not 100% sensitive. Strongest studies from pre-hospital setting and therefore not generalizable to ED/ hospital cardiac arrests	Use of ETCO2 < 1.33kPA during CPR cannot be used in isolation to predict ROSC
Hartmann, S *JICM* 2015	Systematic review and meta-analysis *<u>Inclusion criteria:</u>* Human, English language studies reporting ETCO2 with	ETCO2 and ROSC	20 studies (n = 6565) to determine average ETCO2 19 studies (n = 6550) in meta-analysis	Mean ETCO2 significantly higher in patients with ROSC (25.8 ± 9.8 mm Hg) compared to those without ROSC (13.1 ±8.2)	Overall difference between those with and without ROSC was 12.7 mm Hg ETCO2 level may be higher (25 mm Hg) than levels previously identified (10-20 mm Hg) to guide resuscitation

	and without ROSC *<u>Limitation</u>:* Included 1 small study (n=40) in pediatric cardiac arrest				Authors report GRADE guideline evidence quality is **<u>poor</u>** for heterogeneity
Paiva, E *Resuscitation* 2017	Systematic review and meta-analysis *Inclusion:* Adult, human studies of cardiac arrest reporting specific (rather than pooled) ETCO2 correlated with prognosis	Does ETCO2 level measured during CPR correlate with 1) ROSC 2) survival to discharge	17 studies (6198 patients) in qualitative review, 5 studies suitable for quantitative ETCO2 analysis	Consistent evidence for ETCO2 ≥ 10 mm Hg as prognostic factor for ROSC Initial ETCO2 ≥ 10-20 mm Hg or >20 mm Hg after 20 minutes CPR strong predictor of survival (but based on single study of 127 patients where as many as 14% had ROSC before ETCO2 measurement) ETCO2 < 10 mm Hg after 20 min CPR has 0.5% likelihood ROSC	Initial level ≥ 10 mm Hg correlates with ROSC and survival but initial level < 10 mm Hg does not predict futility Low level quality as all studies observational
Venkatesh, H *Emerg Med J* 2017	Best evidence topic report *<u>Inclusion:</u>*	Is ETCO2 value prognostic in ROSC	4 studies	ETCO2 of ≤ 10 mm Hg measured at 3-5 min is	Trend in ETCO2 more important than single measurement

	Adults, admitted to ED after OHCA, ETCO2 measured and correlated with ROSC *Limitation*: Small number of studies and includes Hartmann study above	in ED patients with OHCA		associated with poor prognosis	

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**
NONE	**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:**	
Davis, DP *Resuscitation* 2012	Observational analysis of prospectively collected data -created a derivation and validation set 145 patients with 588 compression pauses analyzed	EMS study of OHCA patients who had defibrillator and ETCO2 data prior to ED arrival	To identify threshold for heart rate and ETCO2 to predict ROSC Optimal threshold for ETCO2 identified at > 20 mm Hg in derivation set (along with HR > 40 bpm) Identified palpable pulses in 98 percent (95% CI 95-100) and absence of pulses in 99 percent (95 % 98-100)	Threshold ETCO2 > 20 mm Hg (along with HR >40) good predictors of ROSC
Rognas, L *Resuscitation* 2013	Analysis of prospectively collected observational data on pre-hospital advanced airway management 271 patients	OHCA patients who had airway placed and ETCO2 recorded	To determine if a cutoff value of ETCO2 of 1.3 kPa could be used to determine ROSC Of 22 patients with ETCO2 ≤ 1.3 kPa, 4 had ROSC	ETCO2 ≤ 1.3 kPa during pre-hospital CPR cannot be used as cutoff to determine ROSC
Akinci, E *Pak J Med Sci* 2014	Prospective collection of data on adult OHCA patients presenting to ED N =80 ROSC = 30%	ETCO2 measured at 5 minute intervals and AUROC for ROSC determined	To assess ETCO2 measured during CPR for predicting mortality 20 minute ETCO2 had best model characteristics (0.850 (95%CI 0.721-0.980)) with 68 patients Best intersection for distinguishing between survival/ death was 28 mmHg and no patients with ETCO2 < 14 mm Hg survived though numbers not reported	No absolute ETCO2 threshold identified

Sheak, KR *Resuscitation* 2015	Multicenter cohort study of OHCA and IHCA patients 583 patients	Patients who had time-synchronized ETCO2 data	To evaluate ETCO2 association with CPR quality Case-averaged mean ETCO2 values higher in patients with ROSC vs without (34.5 ± 4.5 vs 23.1 ± 12.9 mm Hg, p < .001) and in those who survived to hospital discharge vs did not (38.2 ±12.9 vs 26.1 ± 15.2 mm Hg, p < .001)	Higher average ETCO2in patients with ROSC and survival to hospital discharge but no cutoff threshold identified
Pearce, AK *Resuscitation* 2015	Cohort study of database of inpatient resuscitations at 2 urban hospitals. 50 patients	Inpatients with PEA arrest and ETCO2 recorded during CPR Excluded if ETCO2 obtained > 10 minutes into CPR or ROSC already obtained	To investigate association between initial ETCO2 and ROSC and survival to discharge Initial ETCO2 > 20 mm Hg associated with increased likelihood of ROSC (adjusted OR4.8, 95% CI 1.2-19.2) Initial ETCO2 > 10 mm Hg was not a predictor of ROSC (OR 2.49, 95% CI 0.64-9.63) Initial ETCO2 was not associated with survival to hospital discharge (p= 0.251)	Initial ETCO2 > 20 mm Hg is a significant predictor of ROSC but not survival to hospital discharge in inpatients with PEA arrest Small sample size (n=50)
Poon, KM *Resuscitation* 2016	Prospective cohort study Cardiac arrest registry of patients presenting to 2 EDs N= 319	Adult non-traumatic OHCA with ETCO2 recorded at 3 minutes post intubation in the ED	To evaluate if initial is ETCO2 prognostic of ROSC Pre-defined low ETCO2 as ≤ 10 mm Hg 3 min ETCO2 > 10 mm Hg was a predictor of	3 min ETCO2 > 10 mm Hg was a strong predictor of ROSC 3 minute ETCO2 ≤ 10 mm Hg associated with low chance of ROSC

	ROSC in 34% (n =108) Survival to discharge 2% (n=6)		ROSC with OR 18.16 (95% CI 4.79- 51.32) 4 percent of patients with ROSC (4/108) had ETCO2 ≤ 10 mm Hg	
Lui, CT *Resuscitation* 2016	Cross-sectional study N= 178 ROSC = 60	Adult non-traumatic OHCA patients with active CPR and intubation at 2 regional EDs	To evaluate association between an abrupt and sustained rise in ETCO2 to predict ROSC Evaluated rise of 10 and 20 mmHg and rise to level ≥ 40 mm Hg Both abrupt rise of 10 and 20 mm Hg and abrupt rise with subsequent ETCO2 level ≥ 40 mm Hg associated with ROSC vs no ROSC (all p <0.001)	Abrupt rise in ETCO2 during resuscitation associated with ROSC with good specificity but poor sensitivity
Sutton, RM *Resuscitation* 2016	Prospective observational cohort using AHA GWTG registry N= 803 for subset of patients with ETCO2 monitoring only	Adult index IHCA with CPR and invasive airway or arterial catheter in place at time of arrest	Evaluate ETCO2 and arterial diastolic blood pressures as marker for quality of CPR and association with outcomes ETCO2 > 10 mm Hg during CPR associated with improved survival to hospital discharge (OR 2.41, 95% CI 1.35-4.30) and survival with favorable neurologic outcome (OR 2.31, 95% CI 1/31- 4.09)	ETCO2 > 10 mm Hg during CPR favorably associated with both survival to hospital discharge and favorable neurologic outcome
Wang, AY Am J Emerg Med 2016	Retrospective cohort study N= 202	Adult ≥ 20 years with non-traumatic IHCA while in ED with ETCO2 monitoring	To evaluate initial ETCO2 association with sustained ROSC, survival to hospital discharge and favorable neurologic outcome	Initial ETCO2 > 25.5 mm Hg during CPR associated with sustained ROSC and survival to discharge but not neurologic outcome

			Cutpoint of ETCO2 of 25.5 mm Hg identified by ROC curve Initial ETCO2 > 25.5 mm Hg independent predictor of sustained ROSC (OR 2.64, 95% CI 1.43- 4.88) and survival to hospital discharge (OR 3.10, 95% CI 1.26-7.60) but not with favorable neurologic outcome	
Singer, AJ *Am J Emerg Med* 2017	Prospective cohort study N= 100 33% sustained ROSC 2 patients survived to hospital discharge	OHCA patients presenting to ED with both ETCO2 and cerebral oxygen saturations (rSO2) measured	To determine accuracy of ETCO2 and rSO2 to predict ROSC Used ROC characteristics to identify optimal cutoff of 19 mm Hg for ETCO2 ETCO2 20 mm Hg had 100 % sensitivity (95% CI 87-100) but poorly specific (45%, 33-57)	ETCO2 20 mm Hg highly sensitive but poorly specific for ROSC
Savastano, S *Resuscitation* 2017	Retrospective cohort study of OHCA (Pavia CARe) N= 62 patients, 207 shocks	OHCA patients with VT/VF arrest and ETCO2 monitoring prior to shock	To evaluate if ETCO2 1 min before shock delivery predicts termination of shockable rhythm 130 shocks (63%) were successful Tertiles of ETCO2: T1 $\leq$ 20 mm Hg, 20 > T2 $\leq$ 31 mm Hg, T3 > 31 mm Hg Survival T1 50%, T2 63% and T3 78% P value for trend <0.001	No shock effective when ETCO2 < 7 mm Hg and no shock ineffective at > 45 mm Hg

Brinkoff, P *Resuscitation* 2018	Retrospective case-control study N= 169 ROSC = 77	OHCA patients with ETCO2 in prehospital setting	To evaluate trends in ETCO2 levels and association with ROSC Patients with ROSC had more positive ETCO2 trends than non-ROSC patients (p= 0.003)	Study looked at ETCO2 trends over time and did not identify optimal cutoff value
Yilmaz, G *Am J Emerg Med* 2018	Prospective cohort N= 32	Adult OHCA and ED IHCA patients who had carotid bloof flow and ETCO2 measured during CPR	To evaluate if carotid artery peak systolic velocity (PSV) during CPR as alternate to ETCO2 to assess CPR efficacy Mean ETCO2 in ROSC group higher than non-survivors (26.3 ± 6.5 vs 19.1 ±7.8) (p <0.05) Nonsignificant correlation between PSV and ETCO2	No cutoff value for ETCO2 identified
Javaudin, F *Resuscitation* 2018	Retrospective cohort study of French National OHCA Registry (RéAC) N= 9405 ETCO2 measured = 6016	Adult non-traumatic OHCA who arrived to the hospital comatose	To evaluate association between prehospital ETCO2 and 30 day neurologic outcomes ETCO2 30-40 mm Hg used as reference range ETCO2 change of 10 mm Hg increments above and below reference range x 2 associated with worse neurologic outcomes (all p <0.001)	Prehospital ETCO2 between 30 and 40 mm Hg has best prognosis for favorable neurologic outcome
Chicote, B *Resuscitation* 2019	Retrospective cohort of OHCA patients N=214 ROSC = 76	VF arrest with concurrent ETCO2 data at delivery of at least 1 shock	To evaluate ETCO2 as predictor of shock success ETCO2 higher in successful shocks compared to failed shocks (31 vs 25 mmHg), (P <	ETCO2 predicts defibrillation success on first shocks No data on ROSC presented

			0.05), but only for first shocks Shocks with ETCO2 < 11 mm Hg always unsuccessful and those with ETCO2 > 40 mm Hg successful 60% of time	
Engel II, TW *Resuscitation* 2019	Prospective cohort study N= 125 complete data sets	Adult non-traumatic OHCA and ED cardiac arrest patients with ETCO2 and cerebral oximetry monitoring	To compare ETCO2 to cerebral oximetry to predict ROSC Cerebral oximetry superior to ETCO2 at various time points Cutoff ETCO2 in penultimate minute of resuscitation of 26.5 mm Hg had 74% sensitivity and 59.5% specificity for ROSC	No definite cutoff for ETCO2 established
Poppe, M *Eur J Anaesthesiol* 2019	Retrospective observational cohort of prehospital cardiac arrest N = 526	Adult OHCA patients with non-shockable rhythms and advanced airway within 15 minutes of start CPR	To evaluate predictive value of initial ETCO2 for ROSC and 30 day survival Groups divided into ETCO2 < 20, 20- 45 and > 45 mm Hg ETCO2 > 45 mm Hg group improved outcomes relative to other 2 groups: Any ROSC OR 2.58 (95% CI 1.64- 4.06) Sustained ROSC OR 3.59 (95% CI 2.19- 5.85) 30 day survival OR 5.02 (95% CI 2.25-11.23) There was no difference in survival between the <	Patients with non-shockable rhythms with initial ETCO2 of > 45 mm Hg had improved ROSC and 30 day survival compared to patients with ETCO2 < 20 or 20-45 mmHg

			20 and 20-45 mmHg groups	
Elola, A *Resuscitation* 2019	Retrospective cohort N= 426 ROSC = 117	PEA OHCA patients with thoracic impedance (TI), ECG and ETCO2 data available	To determine if ETCO2 can detect ROSC Machine learning, addition of ETCO2 to ECG and TI improves model test characteristics Mean ETCO2 in ROSC 31 (20-44) versus 16 (7-35) mm Hg in no-ROSC group ($p < 0.05$)	No definite cutoff identified
Javaudin, F *Prehospital Emerg Care* 2019	Retrospective analysis of prospective observational cohort from French OHCA registry (RéAC) N = 32,249	Mixed adult OHCA patients with a known maximum ETCO2 reported	To determine maximum value ETCO2 for ROSC and no survival Optimal cutoff values for ROSC: -suspected cardiac etiology = 24 mm Hg -suspected respiratory etiology 28 mm Hg For maximum ETCO2 < 10 mm Hg, 0.6 % (n=75) patients in the cardiac etiology group achieved ROSC and 0.1% (n=9) survived For suspected respiratory etiology with max ETCO2 < 10 mm Hg, 0.8% (n=45) achieved ROSC and 0.1% (n=4) survived	Threshold of <6 mm Hg identified for no 30 day survivors for OHCA of suspected cardiac and respiratory causes - large database used

Reviewer Comments (including whether meet criteria for formal review):
No ETCO2 level identified that can, in isolation, be used to determine futility in cardiac arrest resuscitation. ETCO2 of < 10 mm Hg during CPR was consistently, but not universally associated with poor outcomes.

Timing is also a factor as several papers looked at trend/ multiple timepoints in resuscitation. Lastly, multiple studies identified different cutoffs than the 10 and 20 mm Hg values from the past evidence review. There are multiple recent studies, so consideration of an updated systematic review is reasonable.

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C10. Cardiac Arrest in Pregnancy (ALS 436: EvUp)

Worksheet author(s): Carolyn M Zelop and Julie Arafeh
Council: 3CPR
Date Submitted:

PICO / Research Question: ALS 436 Pregnancy and cardiac arrest Among pregnant women who are in cardiac arrest in any setting (P), does any specific intervention(s) (I), compared with standard care (usual resuscitation practice) (C), change ROSC, Survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year, Survival with Favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year (O)?

Outcomes:
Maternal: ROSC, Survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year, Survival with Favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year
neonatal : ROSC, Survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year, Survival with Favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year

5-Important

Type (intervention, diagnosis, prognosis): Intervention
Additional Evidence Reviewer(s): Julie Arafeh
Conflicts of Interest (financial/intellectual, specific to this question): NA

Year of last full review: 2010 / 2015 / New question: 2015
Search Completed: August 11, 2014

Last ILCOR Consensus on Science and Treatment Recommendation:
We suggest delivery of the fetus by perimortem cesarean delivery for women in cardiac arrest in the second half of pregnancy (weak recommendation, very-low-quality evidence). There is insufficient evidence to define a specific time interval by which delivery should begin. High-quality usual resuscitation care and therapeutic interventions that target the most likely cause(s) of cardiac arrest remain important in this population. There is insufficient evidence to make a recommendation regarding the use of left lateral tilt and/or uterine displacement during CPR in the pregnant patient. Values, Preferences, and Task Force Insights In making this statement, we place value on maternal and neonatal survival, on the absence of data on left lateral tilt and uterine displacement in women with cardiac arrest, and on our uncertainty about the absolute effect of either uterine displacement or perimortem delivery during CPR on any of the assigned outcomes. The task force thought not making a recommendation for or against the use of left lateral tilt or uterine tilt is unlikely to change current practice or guidelines.

2010/2015 Search Strategy: 2015
("Pregnancy"[Mesh:NoExp] or "Pregnant Women"[Mesh] or "Pregnancy Complications"[Mesh:NoExp] or pregnant[TI] or pregnancy[TI] OR maternal[TI] OR parturient[TIAB] OR "Anesthesia, Obstetrical"[Mesh] OR "Perinatology"[Mesh] OR "Maternal Mortality"[Mesh]) AND ("Heart Arrest"[Mesh] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "asystole"[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR CPR[TIAB] OR "resuscitation"[Mesh] OR resuscitat*[TIAB] OR “chest compression”[TIAB] OR “chest compressions”[TIAB] OR “heart massage”[TIAB] OR “cardiac massage”[TIAB] OR “cardiac compression”[TIAB] OR “cardiac compressions”[TIAB] OR “thoracic compression”[TIAB] OR “thoracic compressions”[TIAB] OR “maternal resuscitation”[TIAB]) AND (“perimortem

cesarean section”[TIAB] OR “perimortem delivery”[TIAB] OR “left lateral”[TIAB] OR “lateral tilt”[TIAB] OR “uterine displacement”[TIAB] OR “aortocaval compression”[TIAB] OR "Patient Positioning"[Mesh] OR "Pregnancy Complications, Cardiovascular"[MeSH] OR pharmacokinetic*[TIAB] OR "Pharmacokinetics"[Mesh] OR "lipid resuscitation" OR "Thrombolytic Therapy"[Mesh] OR thrombolytic*[TIAB] OR Fibrinolytic*[TIAB] OR "Fat Emulsions, Intravenous"[Mesh] OR “fat emulsion”[TIAB] OR “fat emulsions”[TIAB] OR “lipid emulsion”[TIAB] OR “lipid emulsions”[TIAB] OR “cardiac output”[TIAB] OR "Hypothermia, Induced"[Mesh:NoExp] OR hypothermia[TIAB] OR emergenc*[TIAB] OR "Emergencies"[Mesh] OR "Emergency Medical Services"[Mesh] OR "Combined Modality Therapy"[Mesh:NoExp]) NOT (“animals”[Mesh] NOT “humans”[Mesh]) NOT ("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or Case Reports[ptyp] or news[ptyp])

2019 Search Strategy: same as above
Database searched: Pubmed
Date Search Completed: 10/26/19
Search Results (Number of articles identified / number identified as relevant): 286/ 8
Inclusion/Exclusion Criteria: descriptive reviews and limited case reports were excluded
Link to Article Titles and Abstracts (if available on PubMed):

Summary of Evidence Update:
Evidence Update Process for topics not covered by ILCOR Task Forces

1. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

Organisation (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)**
	Study Type:	**Inclusion Criteria:**	**1° endpoint:**	
Maternal Salvage with extracorporeal life support (ECLS) Lessons learned in a single center Biderman et al Anesthesia/ Analgesia 2017;123:1275-80	Retrospective case series; N=11	All cases of pregnant/peripartum women treated with ECLS for peripartum death or maternal near misses with imminent risk of death	Maternal survival was the primary outcome 3/11 were pregnant at 13, 20 and 33weeks gestation 2/3 resulted in fetal/neonatal deaths Of the 5 with cardiac arrest, 3 survived (66%) These received veno-arterial cannulation Overall, 7/11 or 64% survived Deaths were attributed to late sepsis 3/11 and 1/11 with oxygenator blockade	Details regarding survival not known Two unique clinical challenges were maintenance of high peripartum cardiac output (CO) and balancing anticoagulation with hemostasis
Utility and limitations of perimortem cesarean section: a nationwide survey in Japan Kabori et al J Obstet Gynecol Res Vol 45 No 2: 325-330 Feb 2019	Descriptive retrospective observational Study; N=18	Questionnaires sent to obstetric units throughout Japan regarding cases of perimortem cesarean section (PCS)* performed from 4/2010 to 4/2015 44% response rate Second survey sent to obtain more details *Terminology in this article used for perimortem cesarean delivery	Outcomes in women who had PCS performed in 18 10 were in hospital and 8 were out of hospital (50% return of spontaneous circulation [ROSC] with 1 death within 24 hours and 3 with hypoxic encephalopathy [HE]) 12/18 had ROSC who received PCS 6/18 who were discharged without major sequelae were compared to those who 12 who were nondischarged	Transporting patients for PCS appeared to have worse prognosis since it resulted in delays from time of arrest to delivery

			(deaths or vegetative state) Receiver operating characteristic (ROC) curve to detect onset of disseminated intravascular coagulation (DIC) from collapse Appeared to be 20 minutes 3/12 (25%) were discharged without sequelae had PCS 6 min(+/- 5.7) 3/12 (25%) died 24 hours post ROSC 5/12 (42%) developed HE with 2/5 improving with rehab and 1 had lower-limb disuse syndrome Those discharged without sequelae 6/18 had a statistically significant shorter median interval time from arrest to PCS 9 vs 34 min, P= 0.002 3/18 neonates were discharged without sequelae 6/18 neonates died in neonatal period and 9 developed HE	
The CAPS Study: incidence, management and outcomes of cardiac arrest in pregnancy in the United Kingdom (UK): a prospective, descriptive study.	Prospective, descriptive study using the UK Obstetric Surveillance System (UKOSS); study size = 66	All women who received basic life support in pregnancy between 07/01/2011 and 06/30/2014 **Inclusion Criteria:** cases with chest compressions following maternal collapse; in final	Cardiac arrest in pregnancy: Adding immediate postpartum (PP) cardiac arrests changed incidence from 2.8 (95% CI 2.2-3.6) to 6.3 (95% CI 4.7-8.4) arrests per 100,000 maternities, remains a rare event 28/66=42% (95% CI	1)Maternal survival related to location of arrest (less likely to survive if arrest at home vs hospital). 2)Delivery within five minutes of recognition of arrest without ROSC associated with improved survival rate.

Beckett VA, Knight M, Sharpe P *BJOG*. 2017.		year immediate postpartum and antenatal cases were included N= 66 which met inclusion criteria	30-55%) case fatality ROSC = 48/66 (72) Survival to discharge 38/66= 58% 16/38 (42% had morbidities with 6/38 having neurological Perimortem cesarean delivery (PMCD): Time from collapse to delivery in survivors = 7 min (IQR 2.5-17.5) versus 16 min (IQR 6.5-43.5) (P= 0.04) Aortocaval decompression In 29 women, N=21 had tilting of the pelvis N=4 was manual left uterine displacement (LUD) After review of cases, 2 women did not have PMCD when it would have been appropriate. 6/66 had ROSC and PMCD was not performed Maternal death: Characteristics compared for women who died vs those who survived: age, ethnicity, body mass index (BMI), paid employment, smoker, gestational age. Death more likely when cardiac arrest at home, woman moved to perform PMCD, and longer time from arrest noted to delivery No long term outcomes after discharge	3)Almost 25% of arrests related to anesthetic factors. 4)Regular training in maternal cardiac arrest needs to continue; LUD rarely done, basic life support (BLS) applied quickly but quality could not be assessed

			Data available for N= 58 24/25 neonates survived when PMCD performed witin 5 minutes compared with 7/10 when PMCD > 5 minutes, P= 0.059	
Maternal out of hospital cardiac arrest: a retrospective observational study Maurin et al. Resuscitation 2019 Feb;135:205-211	Retrospective cohort study including gravid women who sustained out of hospital maternal cardiac arrest (OHMCA); N=16	Inclusion criteria: Gravid women 18 years of age or older who sustained OHMCA from 2009-14 in Paris 16 cases overall	Prehospital teams captured clinical and therapeutic intervention sequence, automatic external defibrillator (AED) use and number of shocks, ROSC and survival Prehospital ROSC 3/5 less than 14 weeks 1/3 14-26/28 weeks 1/8 for 26/28 weeks 5 achieved circulation through a mechanical device 10 were admitted to the hospital 3/8 received in hospital PMCD 55min or greater from cardiac arrest (CA) 5 achieved circulation through a mechanical device 2 were alive at hospital Discharge day 21 and 30 1 surviving neonate after 7 week OHMCA	Difficult to apply resuscitation techniques No PMCD in time Only survivors were in the first trimester 33% of witnesses initially performed chest compressions

Maternal cardiac arrest (MCA) in the Netherlands: a nationwide surveillance Schaap et al. European J Ob Gyn and RB 237 (2019) 145-150	Prospectively collected cases of MCA using Netherlands Obstetrical Surveillance; N=38	Inclusion: All Dutch cases of MCA from 2013-16	Main outcomes: Incidence of MCA, use of PMCD and maternal death 7.6/100,000 pregnancies 38cases of MCA with 18 antepartum/20 postpartum Aortocaval compression relief in 4/14 (29%) and 11/14 (79%) had PMCD Survivors had shorter interval from MCA to PMCD, 10 minutes vs 60 minutes, p=0.004 22/38 or 58% case fatality rate (95% CI 42-72%)	Maternal death was associated with longer interval from MCA to delivery Location of collapse also correlated with death Analysis indicates need for widespread training
Emergent transesophageal echocardioagaphy (TEE) in hemodynamically unstable obstetric (OB) patients Burrage et al In J Ob Anesthesia 2015, 24, 131-136	Retrospective case series to explore utility of TEE during cases of obstetrical hemodynamic instability; N=10	Inclusion criteria Use of TEE in peripartum emergent instability cases including cardiac arrest between 1999-2014	10 patients had emergent TEE including 6 cases with MCA 6/10 had MCA as indication for TEE 3/6 survived to hospital discharge while 3 succumbed to neurological insults	TEE effect on management included: cardiac surgical management, drainage of a pericardial effusion, guided fluid resuscitation and use of medications,
Incidence, outcomes and guideline compliance of out of hospital MCA resuscitations: a population study Lipowicz et al Resuscitation 123 (2018), 127-132	Population cohort study using data from Toronto Regional RescuNET CA database; N=6	Inclusion criteria: OHMCA from 2010-2014	Incidence of OHMCA was 1.71:100,000 pregnant women (95% CI 0.21-6.18) 3/6 had ROSC Survival to hospital discharge was 16.7% and neonatal survival was 33%	Pregnancy specific guideline compliance was low

			0% uterine displacement was documented and 1/6 had uterine tilt documented 5/6 had PMCD but all were outside the 5 minute window	
Maternal Collapse: Challenging the four- minute rule: Benson et al. EBIOMedicine 6 (253-257)	Nested review with stepwise survival analysis; 80 articles	All cases of MCA that underwent PMCD including case reports that included clinical details and key time intervals as well as maternal and neonatal outcomes MCA without PMCD was excluded	Primary outcomes included maternal and neonatal injury free survival as a function of time from arrest to birth Maternal outcomes: 33 women died, 8 were injured and 33 had no sequelae. Neonatal outcomes: 17 died, 14 were injured and 42 survived without sequelae Injury free survival had a stepwise roughly linear decline with time of arrest to birth time for both mother and neonate Threshold for 50% injury free maternal survival rate was 25 minutes and 26 minutes for neonatal 50% injury free survival rate Secondary outcome of interest was arrest to birth time interval Out of 34 neonates for which the data was known, 4 newborns or 11% were born within	Proceed with PMCD as quickly as possible once decision is made to deliver

			5 minutes or less, 12 or 35.5% were delivered between 5-11 minutes, 8 or 23.5% were delivered from 11-21 minutes and 10 or 29.4% delivered more than 21 minutes after maternal cardiac arrest	

Reviewer Comments (including whether meet criteria for formal review):

Overall quality of the studies is fair to modest with substantial limitations including lack of granularity and the presence of bias and confounding. The researchers are hampered by the inability to construct large scale prospective or randomized study design.

In the very limited data identified (small observational studies with the above limitations), PMCD at or greater than 20 weeks uterine size appears to improve outcomes of MCA when high quality resuscitative care does not result in ROSC. Shorter time intervals from arrest to delivery appear to lead to improved maternal and neonatal outcomes. Due to the characteristics of the newer studies identified, it is not clear that an updated systematic review would lead to increased certainty of recommendations.

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C11 Opioid Toxicity (ALS 441: EvUp)

Worksheet author(s): James Paxton, Brian O'Neil #COI -12
Taskforce: ALS

Council: ALS
Date Submitted: 1/18/2020

PICO/Research Question: ALS 441: Opioid Toxicity. Among adults who are in cardiac arrest or respiratory arrest due to opioid toxicity in any setting (P), does any specific therapy (e.g., naloxone, bicarbonate, or other drugs) (I), compared with usual ALS (C), change (O)?

Outcomes: The focus will be on clinical outcomes, including, but not necessarily limited to, return of spontaneous circulation (important – 5), survival/survival with a favorable or unfavorable neurological outcome at hospital discharge (critical-9), and survival/survival with a favorable or unfavorable neurological outcome after hospital discharge (critical-8) at 90 days, 180 days, 1 year).

Type (intervention, diagnosis, prognosis): Intervention

Additional Evidence Reviewer(s): Anthony Lagina, Katherine Akers, Ian Drennan
Conflicts of Interest (financial/intellectual, specific to this question): None stated

Year of last full review: 2010 / 2015 / New question: 2015

Last ILCOR Consensus on Science and Treatment Recommendation: We recommend the use of naloxone by IV, intramuscular, subcutaneous, IO, or intranasal routes in respiratory arrest associated with confirmed or suspected opioid toxicity (strong recommendation, very-low-quality evidence). The dose of naloxone required will depend on the route of administration.
We can make no recommendation regarding the modification of standard ALS in opioid-induced cardiac arrest.

2015 Search Strategy:

PubMed: (Search Completed: March 23, 2014) ((((((analgesics, opioid) OR ((oxycodone OR hydrocodone OR heroin OR morphine OR methadone OR codeine OR fentanyl OR opiate* OR opioid* OR hydromorphone OR vicodin OR demerol OR oxycontin OR tramadol OR meperidine OR opium) .tw.)) OR exp opioid-related disorders/)))) AND ((((((asphyxial arrest) OR ((ROSC[TIAB] OR "return of spontaneous circulation"[TIAB] OR "Heart Arrest"[Mesh] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR "cardiovascular arrests"[TIAB] OR asystole*[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR "cardio- pulmonary arrest"[TIAB] OR "cardio-pulmonary arrests"[TIAB] OR "Out-of-Hospital Cardiac Arrest"[Mesh] OR "Out of Hospital Cardiac Arrest"[TIAB] OR "Out-of- Hospital Cardiac Arrest"[TIAB] OR "Out of Hospital Cardiac Arrests"[TIAB] OR "Out-of-Hospital Cardiac Arrests"[TIAB] OR (("out-of-hospital"[TIAB] OR "out of hospital"[TIAB] OR "outside of hospital"[TIAB]) AND cardiac[TIAB] AND arrest*[TIAB]) OR "resuscitation"[Mesh:noexp] OR resuscitation[TIAB] OR "cardiopulmonary resuscitation"[Mesh] OR "cardiopulmonary resuscitation"[TIAB] OR CPR[TIAB] OR "basic life support"[TIAB] OR BLS[TIAB] OR "Advanced Cardiac Life Support"[TIAB] OR "ACLS"[TIAB] OR "advanced life support"[TIAB] OR "Life Support Care"[Mesh] OR "cardiorespiratory resuscitation"[TIAB] OR "Heart Massage"[Mesh] OR heart massage*[TIAB] OR cardiac massage*[TIAB] OR chest compression*[TIAB] OR cardiac compression*[TIAB])))) OR Ventricular Fibrillation))))) AND ((((((naloxone) OR Buprenorphine) OR Subutex) OR Suboxone))))))) NOT (animals[mh] NOT humans[mh]) NOT ("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or Case Reports[ptyp])))

Embase: (Search Completed: March 23, 2014) 'narcotic analgesic agent'/exp OR 'opiate'/exp OR 'oxycodone':ab,ti OR 'hydrocodone':ab,ti OR 'heroin':ab,ti OR 'morphine':ab,ti OR 'methadone':ab,ti OR 'codeine':ab,ti OR 'fentanyl':ab,ti OR 'opium':ab,ti

OR 'opioid':ab,ti OR 'hydromorphone':ab,ti OR 'vicodin':ab,ti OR 'demerol':ab,ti OR 'oxycontin':ab,ti OR 'tramadol':ab,ti OR 'meperidine':ab,ti AND ('heart arrest'/exp OR 'asphyxial arrest':ab,ti OR 'heart arrest':ab,ti OR 'cardiac arrest':ab,ti OR 'asystole':ab,ti OR 'cardiovascular arrest':ab,ti OR 'resuscitation'/exp AND 'advanced life support':ab,ti OR 'heart massage'/exp) AND ('naloxone'/exp OR 'naloxone':ab,ti OR 'buprenorphine':ab,ti OR 'subutex':ab,ti OR 'suboxone':ab,ti) AND [embase]/lim

Cochrane: (Search Completed: March 23, 2014) ([mh "analgesics, opioid"] or "Oxycodone":ti,ab or "hydrocodone":ti,ab or "heroin":ti,ab or "fentanyl":ti,ab or "Hydromorphone":ti,ab or "vicodin":ti,ab or "Demerol ":ti,ab or "oxycontin":ti,ab or "Tramadol":ti,ab or "Meperidine":ti,ab or "opium":ti,ab) AND ([mh "Heart Arrest"] OR "cardiac arrest":ti,ab OR "cardiovascular arrest":ti,ab or "heart arrest":ti,ab or "cardiopulmonary arrest":ti,ab or "cardio pulmonary arrest":ti,ab or "respiratory arrest":ti,ab)

Other: (Search Completed:) ? is there a sepperate tox database?
Main Topics/Key Terms: Cardiac arrest, asphyxial arrest, opiates, naloxone, ROSC and neurologic outcomes

2020 Search Strategy:

PubMed: (“analgesics, opioid”[MeSH Terms] OR opiate*[tiab] OR opioid*[tiab] OR “opium”[MeSH Terms] OR opium[tiab] OR “opium dependence”[MeSH Terms] OR “morphine derivatives”[MeSH Terms] OR codeine[tiab] OR hydrocodone[tiab] OR oxycodone[tiab] OR dihydromorphine[tiab] OR heroin[tiab] OR hydromorphone[tiab] OR morphine[tiab] OR oxymorphone[tiab] OR thebaine[tiab] OR “methadone”[MeSH Terms] OR methadone[tiab] OR “fentanyl”[MeSH Terms] OR fentanyl[tiab] OR vicodin[tiab] OR meperidine[MeSH Terms] OR meperidine[tiab] OR demerol[tiab] OR oxycontin[tiab] OR tramadol[MeSH Terms] OR tramadol[tiab] OR “opioid-related disorders”[MeSH Terms] OR “narcotics”[MeSH Terms] OR narcotic*[tiab]) AND (“heart arrest”[MeSH Terms] OR “out-of-hospital cardiac arrest”[MeSH Terms] OR “heart arrest”[tiab] OR “cardiac arrest”[tiab] OR “cardiovascular arrest”[tiab] OR “cardiopulmonary arrest”[tiab] OR “asphyxial arrest”[tiab] OR asystole*[tiab] OR ROSC[tiab] OR "return of spontaneous circulation"[tiab] OR "pulseless electrical activity"[tiab] OR "resuscitation"[MeSH Terms] OR resuscitat*[tiab] OR CPR[tiab] OR "life support"[tiab] OR BLS[tiab] OR ALS[tiab] OR ACLS[tiab] OR "life support care"[MeSH Terms] OR “heart massage”[tiab] OR “cardiac massage”[tiab] OR “chest compression”[tiab] OR “chest compressions”[tiab] OR “cardiac compression”[tiab] OR “cardiac compressions”[tiab] OR “ventricular fibrillation”[MeSH Terms] OR “ventricular fibrillation”[tiab] OR “atrial fibrillation”[tiab] OR “heart fibrillation”[tiab] OR “cardiac fibrillation”[tiab] OR “electric countershock”[MeSH Terms] OR cardioversion[tiab] OR defibrillat*[tiab]) AND (“narcotic antagonists”[MeSH Terms] OR “narcotic antagonist”[tiab] OR “narcotic antagonists”[tiab] OR “opioid antagonist”[tiab] OR “opioid antagonists”[tiab] OR “opioid receptor antagonist”[tiab] OR “opioid receptor antagonists”[tiab] OR “naloxone”[MeSH Terms] OR naloxone[tiab] OR narcan[tiab] OR evzio[tiab] OR nalmefene[tiab] OR naltrexone[tiab] OR “buprenorphine”[MeSH Terms] OR buprenorphine[tiab] OR subutex[tiab] OR “buprenorphine, naloxone drug combination”[MeSH Terms] OR suboxone[tiab] OR “sodium bicarbonate”[MeSH Terms] OR bicarbonate[tiab]) NOT (“animals”[mh] NOT “humans”[mh]) NOT ("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or “case reports”[ptyp])

Embase: ('narcotic analgesic agent'/exp OR ‘narcotic dependence’/exp OR ‘narcotic agent’/exp OR narcotic*:ti,ab OR ‘opiate addiction’/exp OR ‘opiate derivative’/exp OR opiate*:ti,ab OR opioid*:ti,ab OR 'morphine derivative'/exp OR codeine:ti,ab OR hydrocodone:ti,ab OR oxycodone:ti,ab OR dihydromorphine:ti,ab OR heroin:ti,ab OR hydromorphone:ti,ab OR morphine:ab,ti OR oxymorphone:ti,ab OR thebaine:ti,ab OR methadone:ti,ab OR fentanyl:ti,ab OR vicodin:ti,ab OR meperidine:ti,ab OR demerol:ti,ab OR oxycontin:ti,ab OR tramadol:ti,ab) AND ('heart arrest'/exp OR ‘out of hospital cardiac arrest’/exp OR 'asphyxial arrest':ti,ab OR 'heart arrest':ti,ab OR 'cardiac arrest':ti,ab OR asystole:ti,ab OR 'cardiovascular arrest':ti,ab OR ‘cardiopulmonary arrest’:ti,ab OR ‘return of spontaneous circulation’/exp OR ROSC:ti,ab OR ‘return of spontaneous circulation’:ti,ab OR ‘pulseless electrical activity’:ti,ab OR 'resuscitation'/exp OR resuscitat*:ti,ab OR CPR:ti,ab OR ‘life support’:ti,ab OR BLS:ti,ab OR ALS:ti,ab OR ACLS:ti,ab OR ‘heart stimulation’/exp OR ‘heart massage’:ti,ab OR ‘cardiac massage’:ti,ab OR ‘chest compression’:ti,ab OR ‘chest compressions’:ti,ab OR ‘cardiac compression’:ti,ab OR ‘cardiac compressions’:ti,ab OR ‘heart fibrillation’/exp OR ‘ventricular fibrillation’:ti,ab OR ‘atrial fibrillation’:ti,ab OR ‘heart fibrillation’:ti,ab OR ‘cardiac fibrillation’:ti,ab OR cardioversion/exp OR cardioversion:ti,ab OR ‘defibrillation’/exp OR ‘defibrillator’/exp OR defibrillat*:ti,ab) AND (‘narcotic antagonist’/exp OR ‘narcotic antagonist’:ti,ab OR ‘narcotic antagonists’:ti,ab OR ‘opioid antagonist’:ti,ab OR ‘opioid antagonists’:ti,ab OR ‘opioid receptor antagonist’:ti,ab OR ‘opioid receptor antagonists’:ti,ab OR 'naloxone'/exp OR naloxone:ti,ab OR narcan:ti,ab OR evzio:ti,ab OR nalmefene:ti,ab OR naltrexone:ti,ab OR ‘buprenorphine’/exp OR buprenorphine:ti,ab OR subutex:ti,ab OR suboxone:ti,ab OR ‘buprenorphine plus naloxone‘/exp OR ‘bicarbonate’/exp OR bicarbonate:ti,ab) NOT ([animals]/lim NOT [humans]/lim) NOT (‘case report’/de OR ‘letter’/it OR ‘editorial’/it OR ‘conference abstract’/it OR ‘conference paper’/it OR ‘conference review’/it)

CINAHL Complete: (MJ narcotics OR TI narcotic* OR AB narcotic* OR MJ ‘analgesics, opioid’ OR TI opioid* OR AB opioid* OR TI opium OR AB opium OR TI opiate* OR AB opiate* OR TI morphine OR AB morphine OR TI codeine OR AB codeine OR TI hydrocodone OR AB hydrocodone OR TI oxycodone OR AB oxycodone OR TI dihydromorphine OR AB dihydromorphine OR TI heroin OR AB heroin OR TI hydromorphone OR AB hydromorphone OR TI morphine OR AB morphine OR TI oxymorphone OR AB oxymorphone OR TI thebaine OR AB thebaine OR TI methadone OR AB methadone OR TI fentanyl OR AB fentanyl OR TI vicodin OR AB vicodin OR TI meperidine OR AB meperidine OR TI demerol OR AB demerol OR TI oxycontin OR AB oxycontin OR TI tramadol OR AB tramadol) AND (MJ ‘heart arrest’ OR TI ‘heart arrest’ OR AB ‘heart arrest’ OR TI ‘cardiac arrest’ OR AB ‘cardiac arrest’ OR TI ‘asphyxial arrest’ OR AB ‘asphyxial arrest’ OR TI asystole OR AB asystole OR TI ‘cardiovascular arrest’ OR AB ‘cardiovascular arrest’ OR TI ‘cardiopulmonary arrest’ OR AB ‘cardiopulmonary arrest’ OR TI ‘return of spontaneous circulation’ OR AB ‘return of spontaneous circulation’ OR TI ROSC OR AB ROSC OR MJ resuscitation OR TI resuscitat* OR AB resuscitat* OR TI CPR OR AB CPR OR TI ‘life support’ OR AB ‘life support’ OR TI BLS OR AB BLS OR TI ALS OR AB ALS OR TI ACLS OR AB ACLS OR TI ‘heart massage’ OR AB ‘heart massage’ OR TI ‘cardiac massage’ OR AB ‘cardiac massage’ OR TI ‘chest compression’ OR AB ‘chest compression’ OR TI ‘chest compressions’ OR AB ‘chest compressions’ OR TI ‘cardiac compression’ OR AB ‘cardiac compression’ OR TI ‘cardiac compressions’ OR AB ‘cardiac compressions’ OR MJ ‘atrial fibrillation’ OR TI ‘atrial fibrillation’ OR AB ‘atrial fibrillation’ OR MJ ‘ventricular fibrillation’ OR TI ‘ventricular fibrillation’ OR AB ‘ventricular fibrillation’ OR TI cardioversion OR AB cardioversion OR MJ defibrillation OR MJ defibrillators OR TI defibrillat* OR AB defibrillat*) AND (MJ ‘narcotic antagonists’ OR TI ‘narcotic antagonist’ OR AB ‘narcotic antagonist’ OR TI ‘narcotic antagonists’ OR AB ‘narcotic antagonists’ OR TI ‘opioid antagonist’ OR AB ‘opioid antagonist’ OR TI ‘opioid antagonist’ OR AB ‘opioid antagonist’ OR TI ‘opioid receptor antagonist’ OR AB ‘opioid receptor antagonist’ OR TI ‘opioid receptor antagonist’ OR AB ‘opioid receptor antagonist’ OR MJ naloxone OR TI naloxone OR AB naloxone OR TI narcan OR AB narcan OR TI evzio OR AB evzio OR TI nalmefene OR AB nalmefene OR TI naltrexone OR AB naltrexone OR TI buprenorphine OR AB buprenorphine OR TI subutex OR AB subutex OR TI suboxone OR AB suboxone OR MJ ‘sodium bicarbonate’ OR TI bicarbonate OR AB bicarbonate)

Cochrane Library: Title Abstract Keyword (opioid* OR opiate* OR opium OR narcotic* OR morphine OR codeine OR hydrocodone OR oxycodone OR dihydromorphine OR heroin OR hydromorphone OR oxymorphone OR thebaine OR methadone OR fentanyl OR vicodin OR meperidine OR demerol OR oxycontin OR tramadol)
AND Title Abstract Keyword (“heart arrest” OR “cardiac arrest” OR “cardiovascular arrest” OR “cardiopulmonary arrest” OR “asphyxial arrest” OR asystole* OR ROSC OR "return of spontaneous circulation" OR "pulseless electrical activity" OR resuscitat* OR CPR OR "life support" OR BLS OR ALS OR ACLS OR “heart massage” OR “cardiac massage” OR “chest compression” OR “chest compressions” OR “cardiac compression” OR “cardiac compressions” OR “ventricular fibrillation” OR “atrial fibrillation” OR “heart fibrillation” OR “cardiac fibrillation” OR “electric countershock” OR cardioversion OR defibrillat*)
AND Title Abstract Keyword (“narcotic antagonist” OR “narcotic antagonists” OR “opioid antagonist” OR “opioid antagonists” OR “opioid receptor antagonist” OR “opioid receptor antagonists” OR naloxone OR narcan OR evzio OR nalmefene OR naltrexone OR buprenorphine OR subutex OR suboxone OR bicarbonate)

Databases searched: PubMed, Embase, CINAHL Complete, Cochrane Library

Date Search Completed: September 13, 2019

Search Results (Number of articles identified / number identified as relevant): 1195 / 4

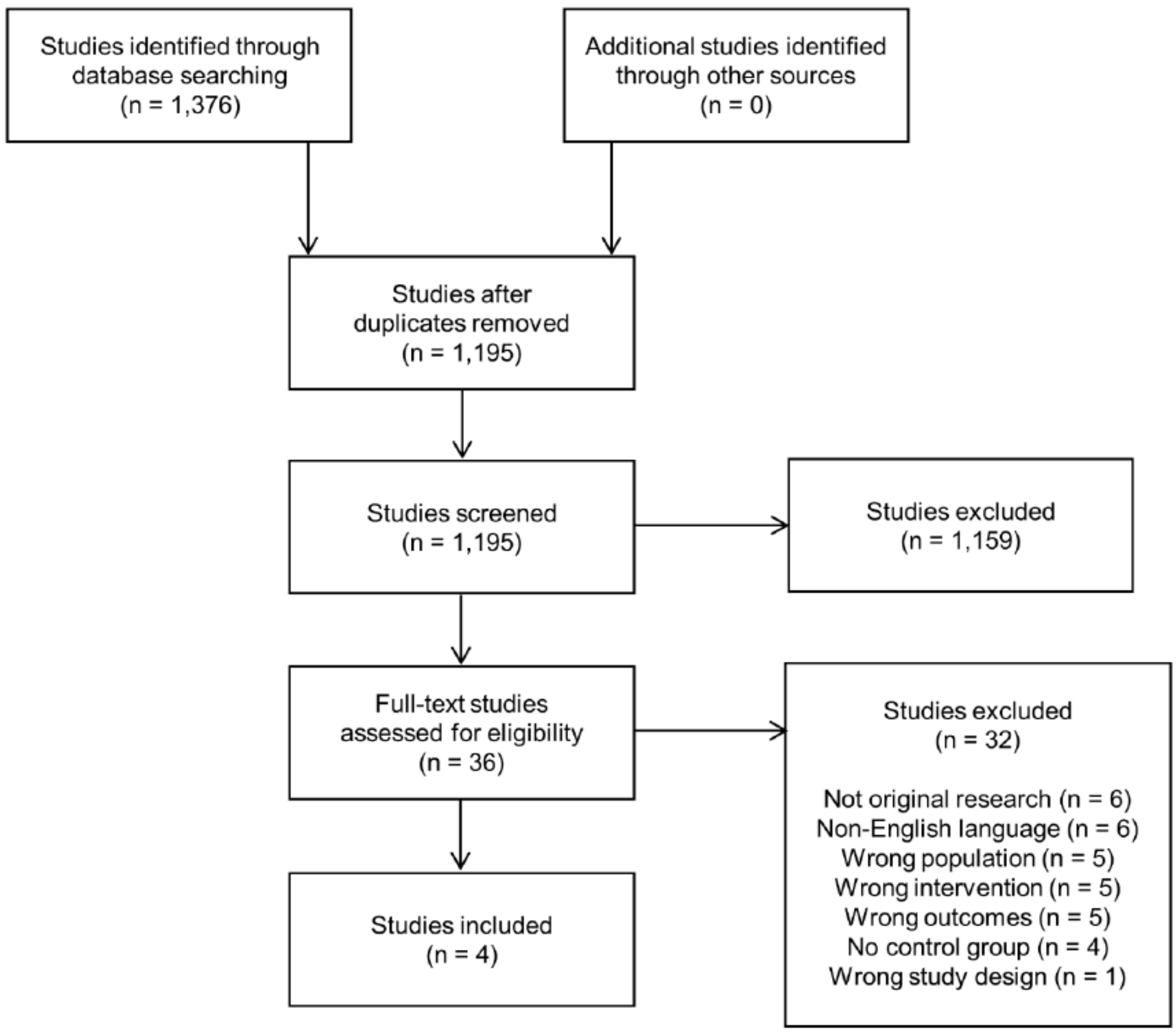
Inclusion/Exclusion Criteria:

Inclusion:
1. Studies including adult human patients in cardiac or respiratory arrest due to opioid toxicity in any setting
2. Studies comparing a specific therapy (e.g., naloxone; intervention group) vs. advanced life support (control group)
3. Studies reporting one of the following outcomes: return of spontaneous circulation; survival at discharge, 30 days, 60 days, 180 days, or 1 year; or survival with favorable neurological or functional outcome at discharge, 30 days, 60 days, 180 days, or 1 year
4. RCTs, non-randomised (i.e., cohort) studies (both prospective and retrospective), registries, prognosis studies based on RCT data, and case-control studies

Exclusion
1. Studies of animals or pediatric patients

2. Letters to the editor, commentaries, editorials, case series or reports, narrative reviews, and unpublished studies (e.g., conference abstracts, trial protocols)

PRISMA Flow Diagram:



Link to Article Titles and Abstracts: The 4 chosen included opiate only overdose. Due to the small sample the inclusion criteria was extended to cardiac arrest due to an overdose that included opiate overdose as a subgroup. The final 15 included manuscripts also included articles referred by the committee. *Only 2 were included from the 2015 search*

Donohue-2019	Orkin-2017
Kim-2016	Engdahl-2002
Katimura-2014	Smith-2018
Ormseth-2019	Salcido-2015
Sakhuja-2017	Elmer-2015
Katz-2015	Koller-2014
Walley-2013	
Sporer-1996	

Boyd-2006

Summary of Evidence Update:

Evidence Update Process for topics not covered by ILCOR Task Forces: This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

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**
Alqahtani 2019	Systematic review observational and interventional studies from medline, Embase, Emcare, EMB Reviews and CINAHL	Incidence and outcomes of adult OHCA precipitated by drug OD between 1990 and 2018	12 total articles 6-North America 4-Europe 2- Asia	Pooled results: incidence of EMS treated OHCA: 1.4/100,000 Survival: 9% Neuro: 6 % Drug OD associated with improved survival to discharge: odds ration 2.2	No specific recommendations but supports incidence and improved outcomes associated with OHCA from drug OD and broad regional variation

Nonrandomized Trials, Observational Studies

	Methods	Participants	Interventions	Comparisons	Outcomes	Notes
Katimura 2014	Prospective Observational Cohort Study	14,164 OHCA of Non-cardiac origin resuscitated by ems and transported to hospital (≥20 yo), "included, stroke, hanging , falls	Tracked outcomes and temporal trends	To other non-cardiac and to cardiac arrest out	Noted 1-month survival was 5.3% overall with respiratory cause, 0.6.5%, malignant tumors-0.8%, 4.9% in strokes and 4.1% in other,	Did not break out the type of drug overdose, drug overdose made up only drug overuse in 1/6% of cases, did not specifically note opiates

		drowning etc. (Jan 2009-Feb 2014)			external causes included asphyxia 14.3%, hanging 0.7%, fall 1.11%, drowning 1.6%, Traffic accident, 3.7% with drug overdose Did note no change in outcomes over time,	
Ormseth, 2019	Retrospective Review of cases of a single institution Database	Data from 2012-2017, OHCA > 18 yo chosen if Hx suggests or OD, needed to have ROSC and not awake, Only included those admitted to hospital.	300 OHCA with 28 (9%) from drug OD, 54 % of these were opiates	OD vs Non-OD cardiac arrest	OD OHCA were younger (40 vs. 59, p < 0.001), less likely to be witnessed by a bystander (36% vs. 80%, p < 0.001), had a higher rate of brain death (43% vs. 6 %, p < 0.001) Inpatient mortality was similar 79% v 73% OD v Non OD, and those that survived to discharge there was no difference	Outcomes were more brain death with similar inpatient

					between the CPC 1-2 or mRS of 0-3	
Sakhuja, 2017	Retrospective Cohort Study, from the National Inpatient Sample Database	3,835,448 hospital admissions for drug overdose. 2000-2013 (≥20 yo),	None, studied opiate induced cardiac arrest cardiac arrest and mortality and outcomes trends over time	To heroin v Prescriptions opiates and other non-opiate poisonings	16.4% of admissions were Rx meds, 2.3% due to heroin, cardiac arrest was more common with heroin v Rx v non opioid: 3.8%v 1.4% v 0.6% p, 0.001	Found rate of cardiac arrest is increasing disproportionally in opiate OD, Both Rx opioids and heroin OD were both independent risk factors for cardiac arrest and mortality
Katz 2015	Retrospective cohort study, utilizing the Penn Alliance for TTM, 28 hospitals contribute	hospital admissions for cardiac arrest due drug overdose. 2005-2013, OD based upon the reports of the provider, EMS, UDS	None, studied OD induced cardiac arrest, from registry	Demographics and outcome of cardiac arrest patients with OD vs non-OD	64/2584-3.5% due to OD, similar to previous, OD were, younger, male, unwitnessed and no bystander CPR c/w non- OD. 16/25 OD patients with UDS, 69% opioids and 50% cocaine positive	Noted similar rates of ROSC, survival, and good CPC outcomes c/w non-OD

Reference	**Methods**	**Participants**	**Interventions**	**Comparisons**	**Outcomes**	**Notes**
Walley 2013	Interrupted time series analysis of opiate	19 Massachusetts counties, with at least 5 OD CA/yr,	Implementation of the Opiate education and naloxone, distribution	High: > 100/100,00, vs low 1-100/100,00.	2912 trained 327 rescues, absolute model for	Found opiate death rates were reduced in communitie

	deaths and acute care utilization			no implementation of an OEND with respect to death and acute care utilization rates.	Rate ratios for opioids deaths were for low implementation and 0.93 and for high implementation it was 0.82 for the reduction of opiate induced death	s that implemented OEND, us of acute care facilities was unchanged

Reference	Methods	Participants	Interventions	Comparisons	Outcomes	Notes
Elmer 2015	Retrospective Observational Cohort Study	591 OHCA (≥18 yrs), including 85 deemed "recreational drug-overdose related." Excluded IHCA, trauma, stroke, or SAH. Pittsburgh, PA, USA (Jan 2009-Feb 2014)	85 pts with OD OHCA, including 40 pts who received Naloxone	506 pts with non-OD OHCA	OD OHCA pts were younger (39 vs. 50 yrs), had fewer comorbidities, more likely non-shockable initial rhythms, had worse baseline neurological function (GCS) and less often received cath. However, overall survival, neurological outcomes and LOS did not vary between OD and non-OD groups. OD OHCA patients who survived to discharge had a significantly higher rate of favorable discharge dispositions (83% of OD	Outcomes for all 85 OD OHCA pts are lumped together (not presented separately for those who received Naloxone and those who did not). Both opiates and benzos found in 49% of the pts with positive urine tox screens.

					OHCA survivors discharged to home or acute rehabilitation vs 62% of non-OD OHCA (P = 0.03)).	
Reference	**Methods**	**Participants**	**Interventions**	**Comparisons**	**Outcomes**	**Notes**
Koller 2014	Retrospective Review of ROC Database	2342 EMS-treated OHCA pts, including 180 pts with suspected OD OHCA. Data obtained from Pittsburgh (PA) ROC records (2006 to late 2008 and late 2009 to 2011). Excluded cases identified as DOA by EMS, as well as cases from late 2008 to late 2009 (during the multisite ROC PRIMED clinical trial for which the data were embargoed).	180 OD OHCA cases, including 168 who received Naloxone	2162 Non-OD OHCA cases	OD OHCA were younger (45 vs. 65, p < 0.001), less likely to be witnessed by a bystander (29% vs. 41%, p < 0.005), and had a higher rate of survival to hospital discharge (19% vs. 12%, p = 0.014) than non-OD OHCA. Suspected overdose cases had a higher overall chest compression fraction (0.69 vs. 0.67, p = 0.018) and higher probability of adrenaline, sodium bicarbonate, and atropine administration	Outcomes for all 180 OD OHCA pts are lumped together (not presented separately for those who received Naloxone and those who did not).

					($p < 0.001$). Suspected overdose status was predictive of survival to hospital discharge when controlling for other variables ($p < 0.001$).	

Reference	**Methods**	**Participants**	**Interventions**	**Comparisons**	**Outcomes**	**Notes**
Orkin 2017	Retrospective Observational Cohort Study of the Toronto Regional RescuNet Epistry database (which is comprised of data points from both the ROC database and Strategies for Post Arrest Resuscitation Care (SPARC) database).	21,497 OHCA patients with presumed cardiac etiology (2007-2013), including 378 (1.8%) drug-related and 21,119 (98.2%) non-drug OHCA.	378 (1.8%) OD OHCA patients, including description of interventions in Table 2 (epinephrine, amiodarone, airway placement, defibrillation; etc). Naloxone or other OD-specific interventions were not reported anywhere in the article.	21,119 (98.2%) non-drug OHCA, with the same interventions in Table 2.	Primary outcome was survival to discharge. OD OHCA patients were younger and less likely to receive bystander resuscitation, have initial shockable cardiac rhythms, or be transported to hospital. Compared to non-OD OHCA, there were no significant differences in EMS response times, ROSC, or survival to discharge. Standardized case fatality rates confirmed	"Drug-related" included intentional or accidental OD, including prescribed meds, OTC meds, illicit substances and alcohol. Exclusions included chemical poisoning (carbon monoxide, methanol etc.), paramedic –witnessed arrest, DNR.

					that these effects were not due to age / sex differences. Adjusting for known predictors of survival, OD OHCA was associated with increased odds of survival to hospital discharge (OR1.44, 95% CI 1.15±1.81).	
Reference	**Methods**	**Participants**	**Interventions**	**Comparisons**	**Outcomes**	**Notes**
Kim 2019	Retrospective Observational Cohort Study	193 non-cancer in-hospital cardiac arrest (IHCA) pts, including 58 (30%) pts who received any opiates within 24 hrs of CA, and 135 pts who did not receive opiates within 24 hrs of IHCA event. All subjects were enrolled from a single center in Seoul, South Korea (2008-2012).	58 pts who received opiate analgesics within 24 hrs of IHCA. There is no mention of naloxone (or other specific targeted therapy vs. OD) in the article.	135 pts who did not receive opiates within 24 hrs of IHCA event.	Survival rate did not differ significantly between groups. In the opioid group, as-needed opioid administration was associated with a lower 24-hour survival rate than regular opioid administration (9 [33.3%] of 27 patients vs 20 [64.5%] of 31 patients; P = .030). In multivariate logistic regression analysis, as-needed opioid	Excluded OHCA and any IHCA outside of the general medical floor (e.g., MICU, OR etc). Excluded cancer or DNR pts.

					administration was negatively associated with 24-hour survival.	

Reference	Methods	Participants	Interventions	Comparisons	Outcomes	Notes
Donohue 2009	Retrospective Observational Cohort Study	3084 OHCA 35 years and less, between April 1,2003 and March 31 2007 in London	267 pts with OD OHCA, 9-17 yrs(3male 2 female) 18-35 yrs (196 male, 59 female). Naloxone use not recorded	2817 pts with non-OD OHCA	OD OHCA pts were highly represented in the non-traumatic OHCA group subsisting mostly of males age 18-35	Outcomes for all 267 OD OHCA pts are lumped together
Engdahl 2002	Retrospective Review of EMS records	5415 EMS-treated OHCA pts, non cardiac etiology 1360, cardiac etiology 4055 including 180 pts with suspected OD OHCA. Data collected from Goteborg Sweden October 1, 1980 to October 1, 2000	180 OD OHCA cases, naloxone not recorded	5505 OHCA with attempted resuscitation Compared to 1180 no cardiac and 4055 cardiac	OD OHCA were younger (ages not clarified), In the various subgroups survival was highest in those with drug abuse (6.8%) Increased CPC score noted among OD OHCA upon hospital discharge compared to cardiac and surgical etiology	Outcomes for all 180 OD OHCA pts are lumped together (not presented separately for those who received Naloxone and those who did not).

Katz 2015	Retrospective Observation study	2584 OHCA (≥18 yrs), US cardiac arrest registry, the Penn Alliance for Therapeutic hypothermia 2005-2013 64/2584 OHCA from OD	64 pts with OD OHCA,	2520 pts with non-OD OHCA	OD OHCA pts were younger (40 vs. 66 yrs), mostly male more likely non-shockable initial rhythms (8 vs 25%), less witnessed (20 vs 72%) and less bystander CPR (9 vs 34%). OD OHCA had similar rates of ROSC (39 vs 47) of survival (16 vs19) and category CPC 1-2 upon discharge (13 vs 16)	Outcomes for all 64 OD OHCA Narcan not recorded UDS data showed for OD with ROSC 69% opiates, 50% cocaine,

Smith 2018	Retrospective observational cohort study	18,562 OHCA pts, including 971 pts with suspected OD OHCA. Age >18 EMS OHCA resuscitations in Arizona between January 1,2010 and December 31, 2015	971 OD OHCA	2162 Non-OD OHCA cases	OD OHCA pts were younger (38 vs. 66 yrs P<0.0001), witnessed (25 vs 44% p<0.0001) more likely non-shockable initial rhythms (7vs 23% p<0.0001), OD OHCA higher rates of survival (18.6 vs 11.9% p<0.0001)	After risk adjustment for age, gender, bystander CPR, witnessed arrest, BCPR, ems response time, and shockable rhythm an aOPR of 2.1 (1.8-2.6) for survival compared to cardiac OHCA
Salcido 2015	Retrospective cohort study of ROC database	56,272 OHCA presented to ROC from 2006-2010 with 1351 OHCA from OD Regional variation between 0.5 and 2.7 per 100,000 person years	1351 pts with OD OHCA,	54,921 pts with non-OD OHCA	OD OHCA pts were younger (41 vs. 67 yrs), more likely non-shockable initial rhythms (8.2 vs 23.3%), less witnessed (21.8 vs 44.4%) OD OHCA higher rates of ROSC (33.5 vs 30.7) and survival (12.7 vs 8.9%)	No Narcan data recorded Increased survival of OD OHCA in this study

Reference	Methods	Participants	Interventions	Comparisons	Outcomes	Notes
Sporer 1996	Retrospective Cohort Study	726 patients receiving naloxone by EMS. Needed 3/5 criteria to meet definition of opiate OD, most presumed IV heroin	Tracked EMS response, complications and deaths	none	84% with pulse and BP, 14% will clear signs of death, 2.2% with cardiac arrest, 2/16 with CA had ROSC, no survivors of opiate induced CA	Assumed IV heroin, no other interventions or comparisons
Boyd-2006	Retrospective cohort study,	94 patients from Helsinki from 1997-2000, EMS treated suspected OD	94 CA due to OD, 19 with heroin, 3 heroin only others mixed, 53 other poisonings	Heroin v other OD	24% w/o resuscitation, 16% of Heroin OD and 11% of other OD DC from hospital	All opiate OD survivors either had EMS witnessed arrest of EMS call prior to arrest

Reviewer Comments (including whether meet criteria for formal review):

Patients with drug overdoses which included opiate overdose as compared with other arrests overall were younger, unwitnessed, receive less bystander CPR and less likely to be in a shockable rhythm. Survival to discharge and neurologic outcomes compared with other arrest etiologies varied, though most showed equivalent to improved outcomes.

There are no studies comparing specific therapies in opioid induced cardiac arrest compared with usual ALS care and the effect on outcomes. Consideration of an updated SysRev was suggested.

	Approval Date
Evidence Update coordinator	
ILCOR board	

***Once approval has been made by Evidence Update coordinator, worksheet will go to ILCOR Board for acknowledgement.**

Reference List

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C12 Postresuscitation Hemodynamic Support (ALS 570: EvUp)

Worksheet author(s): Michael Parr
Council: ANZCOR
Date Submitted: November 2019

PICO / Research Question: Postresuscitation hemodynamic support (ALS 570)

Among adults with ROSC after cardiac arrest in any setting (P), does titration of therapy to achieve a specific hemodynamic goal (e.g., MAP greater than 65 mm Hg) (I), compared with no hemodynamic goal (C), change survival or survival with favourable neurologic outcome at discharge, 30 days or longer(O)?

Type (intervention, diagnosis, prognosis): intervention

Additional Evidence Reviewer(s):
Conflicts of Interest (financial/intellectual, specific to this question): none

Year of last full review: 2015

Last ILCOR Consensus on Science and Treatment Recommendation:

There are no RCTs addressing hemodynamic goals after resuscitation. Titration of Therapy to Achieve a Specific Hemodynamic Goal (eg, MAP of More Than 65 mm Hg) Compared With No Hemodynamic Goal For the critical outcome of survival with favorable neurologic/functional outcome, very-low-quality evidence (downgraded for risk of bias and publication bias) from 1 multicenter retrospective nonintervention study including 8736 subjects showed post–cardiac arrest SBP less than 90 mm Hg was associated with higher mortality (65% versus 37%) and diminished discharge functional status in survivors (49% versus 38%).(Trzeciak 2009, 2895) For the critical outcome of survival, very-low-quality evidence (downgraded for risks of bias and publication bias) from 2 retrospective single-center studies including 2282 patients showed reduced survival for patients with post-ROSC SBP less than 90 mm Hg(Bray 2014, 509) and less than 100 mm Hg.(Kilgannon 2008, 499) Bundle of Therapies With a Specific Blood Pressure Target Compared With No Bundle For the critical outcome of survival with favorable neurologic/functional outcome, we found very-low-quality evidence (downgraded for risks of bias and publication bias) from 7 studies that included 813 subjects. One pre-/poststudy of early goal-directed therapy of 36 patients with a MAP target greater than 80 mm Hg showed no difference in mortality or neurologic outcome at hospital discharge.(Gaieski 2009, 418) One prospective observational study of 118 patients using historic controls showed that aiming for MAP greater than 65 mm Hg increased survival to hospital discharge with a favorable neurologic outcome at 1 year in 34 of 61 (56%) versus 15 of 58 (26%) in the control period (OR, 3.61; CI, 1.66–7.84; P=0.001).(Sunde 2007, 29-39) One cohort study of 148 patients showed no difference in neurologic outcome at hospital discharge when a MAP less than 75 mm Hg was a threshold for intervention.(Laurent 2002, 2110-2116) One retrospective study of 136 patients identified groups with MAP greater than 100 mm Hg or less than 100 mm Hg after ROSC. Good neurologic recovery was independently and directly related to MAP measured during 2 hours after ROSC (r2=0.26).(Mullner 1996, 59) One before-and-after observational study of a care bundle, including 55 subjects aiming for a MAP greater than 65 mm Hg within 6 hours, showed no change of in-hospital mortality (55.2% [bundle] versus 69.2% [prebundle]) or CPC 1 or 2 (31% versus 12%).(Walters 2011, 360-366) In 1 prospective single-center observational study of 151 patients receiving a bundle of therapies where 44 (29%) experienced good neurologic outcome, a time-weighted average MAP threshold greater than 70 mm Hg had the strongest association with good neurologic outcome (OR, 4.11; 95% CI, 1.34–12.66; P=0.014).(Kilgannon 2014, 2083-2091) One retrospective study of bundle therapy targeting a MAP greater than 80 mm Hg in 168 patients showed survivors had higher MAPs at 1 hour (96 versus 84 mm Hg), 6 hours (96 versus 90 mm Hg; P=0.014), and 24 hours (86 versus 78 mm Hg) when compared with nonsurvivors. Increased requirement for vasoactive drugs was associated with mortality at all time points. Among those requiring vasoactive drugs, survivors had higher MAPs than nonsurvivors at 1 hour (97 versus 82 mm Hg) and 6 hours (94 versus 87 mm Hg).(Beylin 2013, 1981) For the critical outcome of survival, we found very-low-quality evidence (downgraded for risks of bias and publication bias) from 2 studies including 91 patients that assessed the impact of postresuscitation goal-directed/bundles of care (including blood pressure targets) on survival. One pre-/poststudy of early goal-directed therapy of 36 patients including a MAP target greater than 80 mm Hg showed no difference in mortality at hospital discharge.(Gaieski 2009, 418) One pre-/postobservational study of a care bundle including 55 patients aiming for a MAP greater than 65 mm Hg within 6 hours resulted in an in-hospital mortality of 55.2% (bundle) versus 69.2% (prebundle) (P=0.29; RR, 0.80; 95% CI, 0.53–1.21).(Walters 2011, 360)

Treatment Recommendations (2015)
We suggest hemodynamic goals (eg, MAP, SBP) be considered during postresuscitation care and as part of any bundle of postresuscitation interventions (weak recommendation, low-quality evidence).

There is insufficient evidence to recommend specific hemodynamic goals; such goals should be considered on an individual patient basis and are likely to be influenced by post–cardiac arrest status and pre-existing comorbidities (weak recommendation, low-quality evidence).

2010/2015 Search Strategy:

Search ((((((((((heart arrest[MeSH Terms] OR heart arrest OR cardiac arrest OR cardiopulmonary resuscitation [MeSH Terms] OR CPR OR resuscitation))) AND ((return of spontaneous circulation OR (rosc) OR spontaneous circulation OR post resuscitation OR post cardiac arrest)))))) AND ((((hemodynamic goal OR physiological monitoring[MeSH Terms] or " goal directed therapy "OR titration OR drug therapy OR vasopressor OR inotrope OR titrate OR Algorithm[mh] OR ((goal OR target OR parameter) and hemodynamic))) OR (supranormal OR Lactate [mh] OR "Low cardiac output syndrome" or cardiac output)))) AND (((((((((((((((" patients "[MeSH Terms] OR " patients "[All Fields] OR " patient "[All Fields]) AND outcomes [All Fields])) OR ((" mortality "[Subheading] OR " mortality "[All Fields] OR " survival "[All Fields] OR " survival "[MeSH Terms]) OR (" survival rate "[MeSH Terms] OR (" survival "[All Fields] AND " rate "[All Fields]) OR " survival rate "[All Fields]))) OR outcomes) OR neurological function) OR length of stay)) AND Humans[Mesh])NOT (((" animals "[MH] NOT (animals[MH] AND human[MH]))))))))))))))) AND ("2013/12/01"[Date - Publication] : "3000"[Date - Publication])

2019 Search Strategy:
Pubmed:
Search ((((((((((heart arrest[MeSH Terms] OR heart arrest OR cardiac arrest OR cardiopulmonary resuscitation [MeSH Terms] OR CPR OR resuscitation))) AND ((return of spontaneous circulation OR (rosc) OR spontaneous circulation OR post resuscitation OR post cardiac arrest)))))) AND ((((hemodynamic goal OR physiological monitoring[MeSH Terms] or " goal directed therapy "OR titration OR drug therapy OR vasopressor OR inotrope OR titrate OR Algorithm[mh] OR ((goal OR target OR parameter) and hemodynamic))) OR (supranormal OR Lactate [mh] OR "Low cardiac output syndrome" or cardiac output)))) AND (((((((((((((((" patients "[MeSH Terms] OR " patients "[All Fields] OR " patient "[All Fields]) AND outcomes [All Fields])) OR ((" mortality "[Subheading] OR " mortality "[All Fields] OR " survival "[All

Fields] OR " survival "[MeSH Terms]) OR (" survival rate "[MeSH Terms] OR (" survival "[All Fields] AND " rate "[All Fields]) OR " survival rate "[All Fields]))) OR outcomes) OR neurological function) OR length of stay)) AND Humans[Mesh])NOT (((" animals "[MH] NOT (animals[MH] AND human[MH])))))))))))))) AND ("2013/12/01"[Date - Publication] : "3000"[Date - Publication])

Cochrane:

([mh "heart arrest"] OR "heart arrest":ti,ab OR "cardiac arrest":ti,ab OR [mh "resuscitation, cardiopulmonary"]) AND ("return of spontaneous circulation":ti,ab or "ROSC":ti,ab) AND ([mh "hemodynamics"] OR "hemodynamic goal:":ti,ab or [mh "physiological monitoring"] OR "goal directed therapy":ti,ab or "Vasopressors":ti,ab OR "inotrope":ti,ab or [mh "algorithm"] OR "lactate":ti,ab)

Database searched: PUBMED

Date Search Completed: September, 2019

Search Results (Number of articles identified / number identified as relevant): 772/14

Inclusion/Exclusion Criteria: RCTs, non-randomised controlled trials, comparative cohort studies (either prospective or retrospective). Additional studies designs included to align with included designs in prior search for ILCOR 2015: descriptive cohort studies (either prospective or retrospective), regression analyses of associations between survival/neurologically intact survival and haemodynamics.

Relevant systematic reviews were also identified for the purpose of checking reference lists for additional eligible studies.

Timeframe: Search included December 2013-September 2019

Summary of Evidence Update:

Evidence Update Process for topics not covered by ILCOR Task Forces

1. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

Organisation (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 ID	Title	Comment
	RCTs	
Ameloot 2019	Early goal-directed haemodynamic optimization of cerebral oxygenation in comatose survivors after cardiac arrest: The Neuroprotect post-cardiac arrest trial.	Trial name: Neuroprotective Goal Directed Hemodynamic Optimization in Post-cardiac Arrest Patients (NEUROPROTECT) NCT02541591 Authors' conclusion: Targeting a higher MAP in post-CA patients was safe and improved cerebral oxygenation but did not improve the extent of anoxic brain damage or neurological outcome.
Jakkula 2018	Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomised pilot trial.	Trial name: Carbon dioxide, Oxygen and Mean arterial pressure After Cardiac Arrest and REsuscitation (COMACARE) NCT02698917 Authors' conclusion: Targeting a specific range of MAP was feasible during post-resuscitation intensive care. However, the blood pressure level did not affect the NSE concentration at 48 h after cardiac arrest, nor any secondary outcomes [includes neurologic outcome at 6 months).

Nonrandomized Trials, Observational Studies

Study ID	Title	Comment
Post hoc analyses of target temperature management RCTs		
Topijan 2018	Association of early postresuscitation hypotension with survival to discharge after targeted temperature management for pediatric out-of-hospital cardiac arrest secondary analysis of a randomized clinical trial. Trial name: Post-hoc analysis of Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA)	Authors' conclusion: In this post hoc secondary analysis of the THAPCA trial, 26.7% of participants had hypotension within 6 hours after temperature intervention. Early post-cardiac arrest hypotension was associated with lower odds of discharge survival, even after adjusting for covariates of interest.
Bro-Jeppesen 2015	Hemodynamics and vasopressor support during targeted temperature management at 33 degrees C Versus 36 degrees C after out-of-hospital cardiac arrest: a post hoc study of the target temperature management trial. Trial name: Post-hoc analysis of Target Temperature Management After Cardiac Arrest (TTM) NTC01020916	Authors' conclusion: Targeted temperature management at 33 degrees C was associated with hemodynamic alterations with decreased heart rate, elevated levels of lactate, and need for increased vasopressor support compared with targeted temperature management at 36 degrees C. Low mean arterial pressure and need for high doses of vasopressors were associated with increased mortality independent of allocated targeted temperature management.
Prospective observational studies		
Grand 2019	Cardiac output, heart rate and stroke volume during targeted temperature management after out-of-hospital cardiac arrest: Association with mortality and cause of death. *Prospective substudy within TTM trial*	Authors' conclusion: Cardiac index during TTM after resuscitation from OHCA is not associated with mortality. Future studies should investigate whether certain subgroups of patients could benefit from targeting higher goals for cardiac index.
Huang 2017	Association of hemodynamic variables with in-hospital mortality and favorable neurological outcomes in post-cardiac arrest care with targeted temperature management.	Authors' conclusion: Our results indicate that lower MAP and HR more than 93/min are associated with in-hospital mortality during the initial 48 h after ROSC. Cardiac index at 12 h < 2.5 $l/min/m^2$ is associated with survival but not with neurological outcome. During the course of post-cardiac arrest TTM, these markers of hemodynamic status may be useful predictors of outcomes.
Laurikkalaa 2016	Mean arterial pressure and vasopressor load after out-of-hospital cardiac arrest: Associations with one-year neurologic outcome. *Prospective substudy within FINNRESUSCI study*	Authors' conclusion: Hypotension occurring during the first six hours after cardiac arrest is an independent predictor of poor one-year neurologic outcome. High vasopressor load was not associated with poor outcome and further randomized trials are needed to define optimal MAP targets in OHCA patients
Ameloot 2015a	Hemodynamic targets during therapeutic hypothermia after cardiac arrest: A prospective observational study.	Authors' conclusion: we showed that a MAP range between 76–86 mmHg and SVO_2 range between 67% and 72% were associated with maximal survival.[1]

Study ID	Title	Comment
Ameloot 2015b	An observational near-infrared spectroscopy study on cerebral autoregulation in post-cardiac arrest patients: Time to drop 'one-size-fits-all' hemodynamic targets?	Authors' conclusion: Cerebral autoregulation showed to be disturbed in 35% of post-CA patients of which a majority had pre-CA hypertension. Disturbed cerebral autoregulation within the first 24. h after CA is associated with a worse outcome. In contrast to uniform MAP goals, the time spent under a patient tailored optimal MAP, based on an index of autoregulation, was negatively associated with survival.
Retrospective observational studies		
Annoni 2018	The impact of diastolic blood pressure values on the neurological outcome of cardiac arrest patients.	Authors' conclusion: In CA patients admitted to the ICU, low DAP during the first 6 h is an independent predictor of unfavourable neurological outcome at 3 months.
Chiu 2018	Impact of hypotension after return of spontaneous circulation on survival in patients of out-of-hospital cardiac arrest.	Authors' conclusion: Among the patients who experienced ROSC after OHCA, post-ROSC hypotension was an independent predictor of survival.
Russo 2018	Optimal mean arterial pressure in comatose survivors of out-of-hospital cardiac arrest: An analysis of area below blood pressure thresholds	Authors' conclusion: Hypotension occurring during the first six hours after cardiac arrest is an independent predictor of poor one-year neurologic outcome. High vasopressor load was not associated with poor outcome and further randomized trials are needed to define optimal MAP targets in OHCA patients.
Janiczek 2016	Hemodynamic Resuscitation Characteristics Associated with Improved Survival and Shock Resolution After Cardiac Arrest.	Authors' conclusion: Early post-return of spontaneous circulation hemodynamic resuscitation achieving higher MAP using fluid preferentially over vasopressors is associated with improved survival to hospital discharge as well as better lactate clearance.
Young 2015	Higher achieved mean arterial pressure during therapeutic hypothermia is not associated with neurologically intact survival following cardiac arrest.	Authors' conclusion: We did not observe a relationship between higher achieved MAP during TH and neurologically intact survival. However, shock at the time of admission was clearly associated with poor outcomes in our study population. These data do not support the use of vasopressors to artificially increase MAP in the absence of shock. There is a need for prospective, randomized trials to further define the optimum blood pressure target during treatment with TH.

Reviewer Comments (including whether meet criteria for formal review):

RCTs have not been able to show benefit of higher vs lower hemodynamic targets. Due to the existence of two new RCTs and several observational studies since the prior review, consideration of a SysRev may be warranted.

Reference list

Ameloot K, De Deyne C, Ferdinande B, Dupont M, Palmers PJ, Petit T et al. (2017). Mean arterial pressure of 65 mm Hg versus 85-100 mm Hg in comatose survivors after cardiac arrest: Rationale and study design of the Neuroprotect post-cardiac arrest trial. Am Heart J. 191:91-98.

Ameloot K, Genbrugge C, Meex I, Jans F, Boer W, Vander Laenen M et al. (2015b). An observational near-infrared spectroscopy study on cerebral autoregulation in post-cardiac arrest patients: Time to drop 'one-size-fits-all' hemodynamic targets? Resuscitation. 90:121-126.

Ameloot K, Meex I, Genbrugge C, Jans F, Boer W, Verhaert D et al. (2015a). Hemodynamic targets during therapeutic hypothermia after cardiac arrest: A prospective observational study. Resuscitation. 91:56-62.

Bro-Jeppesen J, Annborn M, Hassager C, Wise MP, Pelosi P, Nielsen N et al. (2015). Hemodynamics and vasopressor support during targeted temperature management at 33 degrees C Versus 36 degrees C after out-of-hospital cardiac arrest: a post hoc study of the target temperature management trial*. Crit Care Med. 43(2):318-327.

Chiu YK, Lui CT, Tsui KL. (2018). Impact of hypotension after return of spontaneous circulation on survival in patients of out-of-hospital cardiac arrest. Am J Emerg Med. 36(1):79-83.

Grand J, Kjaergaard J, Bro-Jeppesen J, Wanscher M, Nielsen N, Lindholm MG et al. (2019). Cardiac output, heart rate and stroke volume during targeted temperature management after out-of-hospital cardiac arrest: Association with mortality and cause of death. Resuscitation. 142:136-143.

Huang CH, Tsai MS, Ong HN, Chen W, Wang CH, Chang WT et al. (2017). Association of hemodynamic variables with in-hospital mortality and favorable neurological outcomes in post-cardiac arrest care with targeted temperature management. Resuscitation. 120:146-152.

Janiczek JA, Winger DG, Coppler P, Sabedra AR, Murray H, Pinsky MR et al. (2016). Hemodynamic Resuscitation Characteristics Associated with Improved Survival and Shock Resolution After Cardiac Arrest. Shock. 45(6):613-619.

Meyer AS, Ostrowski SR, Kjaergaard J, Johansson PI, Hassager C. (2016). Endothelial Dysfunction in Resuscitated Cardiac Arrest (ENDO-RCA): safety and efficacy of low-dose prostacyclin administration and blood pressure target in addition to standard therapy, as compared to standard therapy alone, in post-cardiac arrest syndrome patients: study protocol for a randomized controlled trial. Trials. 17:378.

Topjian AA, Moler FW, Telford R, Holubkov R, Nadkarni VM, Berg RA et al. (2018). Association of early postresuscitation hypotension with survival to discharge after targeted temperature management for pediatric out-of-hospital cardiac arrest secondary analysis of a randomized clinical trial. JAMA Pediatrics. 172(2):143-153.

Young MN, Hollenbeck RD, Pollock JS, Giuseffi JL, Wang L, Harrell FE et al. (2015). Higher achieved mean arterial pressure during therapeutic hypothermia is not associated with neurologically intact survival following cardiac arrest. Resuscitation. 88:158-164.

C13 Postresuscitation Steroids (ALS 446: EvUp)

Worksheet author(s): Tonia Nicholson, Mike Parr
Council: ANZCOR
Date Submitted: Dec 2019

PICO / Research Question: In adult patients with ROSC after cardiac arrest (prehospital or in-hospital) (P), does treatment with corticosteroids (I) as opposed to standard care (C), improve outcome (O) (eg. survival)?

Outcomes: Survival to Hospital discharge with good neurological outcome / Survival to hospital discharge (+/- Time to Shock Reversal / Shock Reversal)

Type (intervention, diagnosis, prognosis): Intervention

Additional Evidence Reviewer(s): N/A

Conflicts of Interest (financial/intellectual, specific to this question): N/A

Year of last full review: 2010 (but similar literature search done to address 2015 PICOT 433)

Last ILCOR Consensus on Science and Treatment Recommendation:

Consensus on Science : There were no human or animal studies that directly ad- dressed the use of the estrogen, progesterone, insulin, or insulin-like growth factor in cardiac arrest. Early observational studies of the use corticosteroids during cardiac arrest suggested possible benefit (LOE 4).[229,230] One complex randomized pilot study (LOE 1)[231] and 1 nonrandomized human study (LOE 2)[232] suggested benefit with corticosteroids, whereas 1 small, older, human prehospital controlled clinical trial suggested no benefit (LOE 1).[233] One animal study of corticosteroids suggested possible benefit (LOE 5).[234]

Treatment Recommendation : There is insufficient evidence to support or refute the use of corticosteroids alone or in combination with other drugs during cardiac arrest.

2010 Search Strategy: Cochrane Library search:
("Heart Arrest"[Mesh] OR "Cardiopulmonary Resuscitation"[Mesh]) AND ("Pituitary-Adrenal System"[Mesh] OR "Adrenal Insufficiency"[Mesh] OR "Adrenal Cortex Hormones"[Mesh] OR "Glucocorticoids"[Mesh] OR "Hydrocortisone"[Mesh] OR "Cortisone"[Mesh] OR "Prednisolone"[Mesh] OR "Prednisone"[Mesh] OR "Methylprednisolone"[Mesh] OR "Dexamethasone"[Mesh] OR "Betamethasone"[Mesh]). 5 results.

PubMed search:
("Heart Arrest"[Mesh] OR "Cardiopulmonary Resuscitation"[Mesh]) AND ("Pituitary-Adrenal System"[Mesh] OR "Adrenal Insufficiency"[Mesh] OR "Adrenal Cortex Hormones"[Mesh] OR "Adrenal Cortex Hormones "[Pharmacological Action] OR "Glucocorticoids"[Mesh] OR "Hydrocortisone"[Mesh] OR "Cortisone"[Mesh] OR "Prednisolone"[Mesh] OR "Prednisone"[Mesh] OR "Methylprednisolone"[Mesh] OR "Dexamethasone"[Mesh] OR "Betamethasone"[Mesh]). 184 results.

EMBASE search:
('heart arrest'/exp/mj OR 'resuscitation'/exp/mj) AND 'corticosteroid'/exp/mj 347 results.

AHA Endnote database search: (“arrest” OR “CPR”) AND (“adrenal” OR “glucocorticoids” OR ”steroid” OR “hydrocortisone” OR “cortisone” OR “prednisolone” OR “prednisone” OR “methylprednisolone” OR “dexamethasone” OR “betamethasone”): 379 results. Titles and abstracts (where appropriate) of all results were examined for relevance. Where doubt existed the full papers were reviewed to identify relevant papers.

The reference lists of relevant papers were searched for other relevant papers. Forward searching of relevant papers was performed using SCOPUS.

2019 Search Strategy: Table Error! No text of specified style in document.**.1 Explanation of search strategy approach**

This search includes studies published in 2014 or later – the rationale for this is that there was another PICO done in 2015 (ALS 433) regarding the use of steroids *during* CPR, which used a very similar search strategy used to address the 2010 PICO, which captured all relevant articles up to July 2014.

#	Search string (developed for the EMBASE.com platform, which includes Medline and Embase databases)	Explanation
#1	'heart arrest'/exp 'heart arrest$':ti,ab 'cardiac arrest$':ti,ab 'cardiovascular arrest$':ti,ab 'cardiopulmonary arrest'/exp 'cardiopulmonary arrest$':ti,ab 'cardio-pulmonary arrest$':ti,ab 'resuscitation'/exp rosc:ti,ab 'post-rosc':ti,ab 'post-resuscitation':ti,ab 'return of spontaneous circulation':ti,ab resuscitat*:ti,ab	**Population – Cardiac arrest** Terms related to cardiac arrest and/or ROSC should be the focus of the article, so these terms must appear in either the title or the abstract, or the article must be tagged with EMTREE terms for cardiac arrest or ROSC. Note, general terms for life support such as 'basic life support' (as used in prior search) or ''advanced cardiac life support' were considered too generic, and terms relating to CPR techniques such as chest compressions and heart massage were considered too specifically focusing on the process of CPR rather than the post-ROSC patient.
#2	#1 NOT ('animal'/exp NOT 'human'/exp OR 'nonhuman'/exp OR 'rodent'/exp OR 'animal experiment'/exp OR 'experimental animal'/exp OR rat:ti,ab OR rats:ti,ab OR mouse:ti,ab OR mice:ti,ab OR dog$:ti,ab OR pig$:ti,ab OR porcine:ti,ab OR swine:ti,ab OR chick$:ti,ab)	**Exclude non-human studies** The search results must include citations from the newborn population string, so a 'non-human studies' filter was applied to it.
#3	#2 NOT ([conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [book]/lim OR 'case report'/de)	**Exclude publication types** Conference abstracts and other ineligible study types were removed here.
#4	#3 AND [2014-2020]/py	**Date limit** The date of the last ILCOR search was 18 July 2014. This search string can be combined with intervention strings or other population strings to produce a final number of records.
#5	'steroid'/de 'corticosteroid'/de 'mineralocorticoid'/de corticosteroid$:ti,ab mineralocorticoid$:ti,ab steroid$:ti,ab prednisone:ti,ab prednisolone:ti,ab methylprednisolone:ti,ab fludrocortisone:ti,ab hydrocortisone:ti,ab dexamethasone:ti,ab	**Intervention terms – steroids** To identify steroid studies. These terms must appear in the title or abstract, or the article must be tagged with EMTREE terms for steroids. Note, the EMTREE terms were not exploded as that includes a large number of irrelevant interventions. Instead, studies coded directly to the steroid EMTREE term (or the corticosteroid EMTREE term, etc.) were captured, along with studies that include these terms as free text, or include the specific drugs that were included in the search for the 2015 ILCOR CoSTR (hydrocortisone was added to this set of specific drugs as it is mentioned in the 2015 Consensus on science).
#6	#4 AND #5	**Population + intervention**
#7	(((after OR post) NEAR/4 (rosc OR spontaneous OR circulation OR resuscitation OR cardiac OR arrest)):ti,ab) OR postarrest:ti,ab OR 'post-arrest':ti,ab OR 'post-rosc':ti,ab OR (surviv* NEAR/3 (cardiac OR arrest OR resuscitation OR ohca OR 'oh ca' OR ihca OR 'ih ca'))	**Post-arrest terms** This string is useful to stratify studies according to whether they include reference to post-ROSC status. However, this string could potentially exclude relevant studies, and should not be relied upon to filter the identified studies.
#8	#6 AND #7	**Population + intervention + post-arrest terms**
#9	#6 NOT #8	**Population + intervention (minus + post-arrest terms)**

Database searched: EMBASE.com platform (includes Medline and EMBASE)/Cochrane Reviews

Date Search Completed: 02 Dec 2019

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

Embase/Medline 702
Cochrane: 99
Trials Registry 281

Inclusion/Exclusion Criteria:
Inclusion – Adults (>18yrs) with non-traumatic cardiac arrest

Exclusions - Steroids given only during CPR (ie. Prior to ROSC), paediatric patients, animal studies, letters, commentaries, editorials, case series, poster presentations only, journal club reviews, interim analyses.

Link to Article Titles and Abstracts (if available on PubMed):

Summary of Evidence Update:
Evidence Update Process for topics not covered by ILCOR Task Forces

Relevant Guidelines or Systematic Reviews

Organisation (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
1) Donnino, MW, Andersen, LW, Berg, KM, Chase, M, Sherwin, R, Smithline, H, Carney, E, Ngo, L, Patel, PV, Liu, X and et al. 2016	**Study Aim:** To determine whether the provision of corticosteroids improves time to shock reversal and outcomes in patients with post-cardiac arrest shock. **Study Type:** Randomized, double-blind trial **Study Size:** 50 patients	**Inclusion Criteria:** >18 yrs, OHCA or IHCA, post cardiac vasopressor dependence for at least 1hr	**Intervention:** Hydrocortisone 100 mg IV or placebo every 8 hours for 7 days or until shock reversal. **Comparison:** Placebo given every 8 hrs or 7 days or until shock reversal	**1° endpoint:** Time to shock reversal There was no difference in time to shock reversal between groups: Hazard ratio: 0.83 [95 % CI: 0.40–1.75], p = 0.63	Shock reversal, Survival with good neurological outcome, Survival to hospital discharge. There was no difference in secondary outcomes of shock reversal (52 % vs. 60 %, p = 0.57), good neurological outcome (24 % vs. 32 %, p = 0.53) or survival to d/c (28 % vs. 36 %, p = 0.54) between the hydrocortisone and placebo groups. **Study Limitations:**

					Small sample size. Heterogeneity of study sample -didn't allow for analysis of subsets that may have benefitted. Most patients died from neurological causes rather than hemodynamic compromise. Nº of patients with either relative or absolute adrenal insufficiency was too small for definitive conclusions in this important subgroup
2) Vasopressin,steroids and epinephrine and neurologically favourable survival after in-hospital cardiac arrest. Menzelopoulos SD, Malachias S, Chamos C et al . 2013	**Study Aim:** To determine if the combination of vasopressin-epinephrine-steroids during CPR & hydrocortisone if there is shock 4 hrs after ROSC improve survival to hospital discharge with good neurological outcome. **Study Type:** Randomized, double-blind trial placebo-controlled **Study Size:** 268 patients 130 in intervention group and 138 in control	**Inclusion Criteria:** >18 yrs; IH vasopressor-requiring cardiac arrest (across 3 Greek tertiary care hospitals) **Exclusion Criteria:** Terminal illness (ie. life expectancy < 6 weeks), DNR status, CA due to exsanguination (eg. Ruptured AAA), OOHCA, Rx with IV corticosteroids before arrest, previous enrollment/ exclusion from study.	**Intervention: Vasopressin** 20IU per CPR cycle + epinephrine (1mg/CPR cycle)& methylprednisolone (40mg during 1st CPR cycle) . In the presence of post-resuscitation shock at 4hrs, IV hydrocortisone 300mg/day for 7 days, then 200mg/d, 100mg/day & stopped. **Comparison:** Epinephrine (1mg/CPR cycle) & saline placebo, then if post-resuscitation shock at 4hrs, IV normal saline 100ml daily for 7 days	**1° endpoint:** ROSC for >20mins: VSE Group 109/130 vs control 91/138 = OR 2.98 (1.39-6.4). Survival to hospital d/c with good neurological outcome (CPC score of 1 or 2) 18/130 vs 7/138 = OR 3.28 (1.17-9.2, p = 0.02)	**2° Endpoints:** 1)Arterial pressure during and approximately 20 mins after CPR. 2)Arterial pressure and CV oxygen saturation during days 1-10 after randomization. 3) Number of organ failure-free days during days 1-60. 4)Potentially steroid-associated complications eg. Hyperglycaemia, infection, bleeding PU, paresis. **Study Limitations:** Only included patients with IHCA. Low overall survival rates for IHCA (in comparison with other Post resuscitative steroids

					administered in addition to VSE during CPR – not possible to separate the 2 effects. No determination of pre-vasopressor CPR hemodynamics, baseline stress hormone concentrations, physiological variables at multiple post- ROSC time points, and post-arrest myocardial function.

Although the initial screen of abstracts selected 8 articles for review, all except the 2 RCTs above were excluded from further review for the following reasons:
1) Articles were journal club discussions of Mentzelopoulos, 2013:
-Botnaru, T, Altherwi, T and Dankoff, J. (2015). Improved neurologic outcomes after cardiac arrest with combined administration of vasopressin, steroids, and epinephrine compared to epinephrine alone. Canadian Journal of Emergency Medicine. 17(2):202-205.

-Hwang, JY, Arredondo, AF and Paul, TK. (2014). Lung cancer screening, targeted temperature after cardiac arrest, and vasopressin and steroids in cardiac arrest. American Journal of Respiratory and Critical Care Medicine. 189(8):995-996.

2)Studies involved steroids being given during cardiac arrest (not post-ROSC)
-Bolvardi, E, Seyedi, E, Seyedi, M, Abbasi, AA, Golmakani, R and Ahmadi, K. (2016). Studying the influence of epinephrine mixed with prednisolone on the neurologic side effects after recovery in patients suffering from cardiopulmonary arrest. Biomedical and Pharmacology Journal. 9(1):209-214.

-Niimura, T, Zamami, Y, Koyama, T, Izawa-Ishizawa, Y, Miyake, M, Koga, T, Harada, K, Ohshima, A, Imai, T, Kondo, Y, Imanishi, M, Takechi, K, Fukushima, K, Horinouchi, Y, Ikeda, Y, Fujino, H, Tsuchiya, K, Tamaki, T, Hinotsu, S, Kano, MR and Ishizawa, K. (2017). Hydrocortisone administration was associated with improved survival in Japanese patients with cardiac arrest. Scientific reports. 7(1):17919.

-Tsai, MS, Chuang, PY, Huang, CH, Tang, CH, Yu, PH, Chang, WT and Chen, WJ. (2019). Postarrest Steroid Use May Improve Outcomes of Cardiac Arrest Survivors. Critical care medicine. 47(2):167-175.

3) Article was reanalysis of data from studies done in 2009 and 2013:
Mentzelopoulos, SD, Koliantzaki, I, Karvouniaris, M, Vrettou, C, Mongardon, N, Karlis, G, Makris, D, Zakynthinos, E, Sourlas, S, Aloizos, S, Xanthos, T and Zakynthinos, SG. (2018). Exposure to Stress-Dose Steroids and Lethal Septic Shock After In-Hospital Cardiac Arrest: Individual Patient Data Reanalysis of Two Prior Randomized Clinical Trials that Evaluated the Vasopressin–Steroids–Epinephrine Combination Versus Epinephrine Alone. Cardiovascular Drugs and Therapy. 32(4):339-351.

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: **Study Size**	**Inclusion Criteria:**	**1° endpoint:**	

Reviewer Comments (including whether meet criteria for formal review):

The previous 2010 COSTR concluded – "There is insufficient evidence to support or refute the use of corticosteroids alone or in combination with other drugs during cardiac arrest."

At that time there were no RCTs that directly addressed the utility of steroids only post-cardiac arrest (rather than during or during and after arrest). The 2016 Donnino study is, although small, an RCT directly addressing this question. Menzelopoulos et al have also recently completed an RCT on steroids after ROSC, which is pending publication. An updated SysRev once those results are available may be useful.

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C14 Targeted Temperature Management (ALS 455, 790, 791, 802, 879: EvUp)

Worksheet author(s): Sarah Perman
Council: AHA
Date Submitted: 12.4.2019

PICO / Research Question: ALS 790 Targeted Temperature Management
Among patients with ROSC after cardiac arrest in any setting (P), does inducing mild hypothermia (target temperature 32°C–34°C) (I), compared with normothermia (C), change (O)?
Outcomes:
9-Critical
Survival with Favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year

8-Critical
Survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year

Type (intervention, diagnosis, prognosis): Intervention
Additional Evidence Reviewer(s):
Conflicts of Interest (financial/intellectual, specific to this question):

Year of last full review: 2010 / 2015 / New question: 2015
Search Completed: January 14, 2014

Last ILCOR Consensus on Science and Treatment Recommendation:
We recommend selecting and maintaining a constant target temperature between 32°C and 36°C for those patients in whom temperature control is used (strong recommendation, moderate-quality evidence). Whether certain subpopulations of cardiac arrest patients may benefit from lower (32°C–34°C) or higher (36°C) temperatures remains unknown, and further research may help elucidate this. We recommend TTM as opposed to no TTM for adults with OHCA with an initial shockable rhythm who remain unresponsive after ROSC (strong recommendation, low-quality evidence). We suggest TTM as opposed to no TTM for adults with OHCA with an initial nonshockable rhythm who remain unresponsive after ROSC (weak recommendation, very-low-quality evidence). We suggest TTM as opposed to no TTM for adults with IHCA with any initial rhythm who remain unresponsive after ROSC (weak recommendation, very-low-quality evidence). Values, Preferences, and Task Force Insights In making these recommendations, we place a higher value on the potential for increased survival with good neurologic outcome as compared with the possible risks (which appear to be minimal) and the cost of TTM. We emphasize that the mortality after cardiac arrest is high and the treatment options are limited. Although the evidence for TTM compared with no temperature management is of low quality, it is the only post-ROSC intervention that has been found to improve survival with good neurologic outcome. We have, therefore, made our recommendation strong in spite of the low-quality evidence.

2010/2015 Search Strategy: 2015
("paramedic cooling"[TIAB] OR "field hypothermia"[TIAB] OR "Hypothermia, Induced"[Mesh] OR "targeted temperature management"[TIAB] OR "therapeutic hypothermia"[TIAB] OR "hypothermia therapy"[TIAB] OR "whole body cooling"[TIAB] OR "whole-body cooling"[TIAB] OR ((cool*[TIAB] OR cold[TIAB] OR "target temperature"[TIAB] OR "Body Temperature"[Mesh] OR "body temperature"[TIAB]) AND ("Brain Injuries"[Mesh] OR "brain injury"[TIAB] OR "brain injuries"[TIAB] OR "neurological status"[TIAB] OR "neurological outcome"[TIAB] OR "neurological outcomes"[TIAB] OR "functional outcome"[TIAB] OR "functional outcomes"[TIAB] OR neuroprotect*[TIAB] OR "Hypoxia-Ischemia, Brain"[Mesh]

OR “hypoxic-ischemic encephalopathy”[TIAB] OR “cognitive impairment”[TIAB] OR “cognitive impairments”[TIAB] OR “cognitive function”[TIAB] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "Treatment Outcome"[Mesh] OR "Glasgow Outcome Scale"[Mesh]))) AND ("Out-of-Hospital Cardiac Arrest"[Mesh] OR “Out of Hospital Cardiac Arrest”[TIAB] OR “Out-of-Hospital Cardiac Arrest”[TIAB] OR "return of spontaneous circulation"[TIAB] OR ROSC[TIAB] OR "Heart Arrest"[Mesh] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR "cardiovascular arrests"[TIAB] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "asystole"[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR "Advanced Cardiac Life Support"[Mesh] OR "Advanced Cardiac Life Support"[TIAB] OR "ACLS"[TIAB] OR "Ventricular Fibrillation"[Mesh] OR "cardiopulmonary resuscitation"[Mesh] OR "cardiopulmonary resuscitation"[TIAB] OR CPR[TIAB] OR "Heart Massage"[Mesh]) NOT ((animal[mesh] NOT humans[mesh])) NOT ("letter"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] or Case Reports[Publication Type])

2019 Search Strategy:

("paramedic cooling"[TIAB] OR "field hypothermia"[TIAB] OR "Hypothermia, Induced"[Mesh] OR "targeted temperature management"[TIAB] OR "therapeutic hypothermia"[TIAB] OR "hypothermia therapy"[TIAB] OR "whole body cooling"[TIAB] OR "whole-body cooling"[TIAB] OR ((cool*[TIAB] OR cold[TIAB] OR "target temperature"[TIAB] OR "Body Temperature"[Mesh] OR “body temperature”[TIAB]) AND ("Brain Injuries"[Mesh] OR “brain injury”[TIAB] OR “brain injuries”[TIAB] OR “neurological status”[TIAB] OR “neurological outcome”[TIAB] OR “neurological outcomes”[TIAB] OR “functional outcome”[TIAB] OR “functional outcomes”[TIAB] OR neuroprotect*[TIAB] OR "Hypoxia-Ischemia, Brain"[Mesh] OR “hypoxic-ischemic encephalopathy”[TIAB] OR “cognitive impairment”[TIAB] OR “cognitive impairments”[TIAB] OR “cognitive function”[TIAB] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "Treatment Outcome"[Mesh] OR "Glasgow Outcome Scale"[Mesh]))) AND ("Out-of-Hospital Cardiac Arrest"[Mesh] OR “Out of Hospital Cardiac Arrest”[TIAB] OR “Out-of-Hospital Cardiac Arrest”[TIAB] OR "return of spontaneous circulation"[TIAB] OR ROSC[TIAB] OR "Heart Arrest"[Mesh] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR "cardiovascular arrests"[TIAB] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "asystole"[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR "Advanced Cardiac Life Support"[Mesh] OR "Advanced Cardiac Life Support"[TIAB] OR "ACLS"[TIAB] OR "Ventricular Fibrillation"[Mesh] OR "cardiopulmonary resuscitation"[Mesh] OR "cardiopulmonary resuscitation"[TIAB] OR CPR[TIAB] OR "Heart Massage"[Mesh]) NOT ((animal[mesh] NOT humans[mesh])) NOT ("letter"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] or Case Reports[Publication Type])

*Deploying a filter to exclude non-english studies, non-human studies and studies published greater than 5 years ago

Database searched: Pubmed
Date Search Completed: 12/2/2019
Search Results (Number of articles identified / number identified as relevant): 2792
Inclusion/Exclusion Criteria:
Excluded studies not in English (2479)
Excluded studies not on Humans (2331)
Excluded studies not in the last 5 years (1090)

On review, 14 articles met criteria given intervention and outcomes specified. Please see discussion below. Pediatric focused manuscripts were not included in this update (THAPCA, NEJM, PMID: 25913022)

Link to Article Titles and Abstracts (if available on PubMed):
https://www.ncbi.nlm.nih.gov/sites/myncbi/1PgE4WBCzHi505/collections/58987559/public/
https://www.ncbi.nlm.nih.gov/sites/myncbi/1PgE4WBCzHi505/collections/58987568/public/
Summary of Evidence Update:
Evidence Update Process for topics not covered by ILCOR Task Forces

1. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

Organisation (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Gao et al. 2015. PMID: 26021513	Systematic Review and Meta-analysis	Effectiveness of mild hypothermia on patients with cardiac arrest	6	All studies examined were published prior to 2010. MTH associated with survival (RR 1.23, 95%CI: 1.02-1.48) and neurological function (RR 1.33, 95%CI: 1.08-1.65)	Mild hypothermia can improve the survival rate and neurological function of patients with cardiac arrest after 6 months.
Yu et al. 2015. PMID: 25786101	Systematic Review and Meta-analysis	Role of mild hypothermia in adult patients after cardiac arrest	7	MTH associated with worse survival to hospital discharge (RR 0.94, 95%CI: 0.85-1.03)	Outcomes driven by TTM Trial as this trial had the most subjects included in this analysis. This analysis also included Kim et al. and studies that explored pre-hospital initiation of TTM.
ILCOR Donnino et al. 2015 PMID: 26449873	Guideline Statement, ILCOR	TTM in post-cardiac arrest management		The task force recommends targeted temperature management for adults with out-of-hospital cardiac arrest with an initial shockable rhythm at a constant temperature between 32 °C and 36 °C for at least 24 hours	
Song et al. 2016 PMID : 27847808	Systematic review and Meta-analysis	TH in patients who have an OHCA due to nonshockable rhythm	25	TTM is associated with better short term survival (RR = 1.42, 95% CI: 1.28-1.57) and neurological function (RR = 1.63, 95% CI: 1.39-1.91)	

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
HYPERION Lascarrou et al. 2019 PMID:	**Study Aim:** To measure the effect of TH on patients with OHCA due to nonshockable initial rhythms **Study Type:** Open label RCT	**Inclusion Criteria:** Study subjects were OHCA patients who had ROSC, comatose and were admitted to the ICU	**Intervention:** TH to temp of 33C for 24 hours of maintenance. Device was not prespecified **Comparison:** Similar subjects who had targeted normothermia to 37C	**1° endpoint**: On day 90, a total of 29 of 284 patients (10.2%) in the hypothermia group were alive with a CPC score of 1 or 2, as compared with 17 of 297 (5.7%) in the normothermia group (difference, 4.5 percentage points; 95% confidence interval [CI], 0.1 to 8.9; P = 0.04). Mortality at 90 days did not differ significantly between the hypothermia group and the normothermia group (81.3% and 83.2%, respectively; difference, -1.9 percentage points; 95% CI, -8.0 to 4.3).	**Study Limitations:** Fragility index was measured at 1, however, 3 patients withdrew consent after randomization from the intervention arm. Large proportion of patients had moderate temp variability because study did not require feedback device (pragmatic trial) and therefore, their temps may not have been as tightly regulated.
Scales et al. 2017. PMID: 28988962	**Study Aim:** To determine if pre-hospital initiation of hypothermia was associated with better rates of successful initation of TH. Study Type: RCT of pre-hospital TH versus usual care	**Inclusion Criteria:** OHCA with pre-hospital ROSC	**Intervention:** Pre hospital cold saline, ice packs and wrist band reminder to use TH **Comparison:** Usual care	**1° endpoint:** There was no difference in rate of successful initiation of TTM (30% vs 25%; RR, 1.17; 95% confidence interval [CI] 0.91-1.52; p=0.22), and no difference in the secondary outcome of survival with good neurological outcome (29% vs 26%; RR, 1.13,	**Study Limitations:** Primary outcome was a process measure (i.e. rate of successful initiation of TTM) and not a clinically significant outcome measure (i.e. neurologic recovery)

				95%CI 0.87-1.47; p=0.37).	

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)**
Perman et al. 2015. PMID: 26572795	**Study Type:** Retrospective cohort study (n=519) using propensity matching to explore the utility of TH in patients with initial NS rhythms.	**Inclusion Criteria:** Subjects who had a cardiac arrest due to an initial non-shockable rhythm	**1° endpoint:** Survival to hospital discharge (OR 2.8; 95%CI: 1.6-4.7) and neurologic recovery (OR 3.5; 95%CI: 1.8-6.6) were better in patients who had TH versus those who did not have TH.	Retrospective cohort study using advanced statistical methods. Small cohort of patients. Included both in and out of hospital cardiac arrest.
Benson-Cooper et al. 2015. PMID: 26914002	**Study Type:** Retrospective observational study (n=179) of patients in the pre- and post- TH era.	**Inclusion Criteria:** OHCA in single center in NZ. Subjects were cooled to 33 for 12 hours if they were treated with TH.	**1° endpoint:** Neurologic recovery at hospital discharge was the primary endpoint. This study explored various factors associated and found that TH was correlated with better neurologic recovery (OR 2.8 [1.2-6.2], p=0.01)	This was a small single center before and after cohort. There is no discussion on how the normothermia arm was maintained.
Doshi et al. 2016. PMID: 26670621	**Study Type:** Retrospective observational cohort of OHCA patients with initial NS rhythms (n=696). Subjects were propensity matched to measure effects of TTM on outcome	**Inclusion Criteria:** Houston EMS data for patients with OHCA due to NS initial rhythm	**1° endpoint:** Survival to hospital discharge was measured and after propensity matching there was no association between TTM and improved rates of survival (OR 1.07; 95%CI: 0.71-1.60)	This single EMS source data set found no survival benefit to patients with initial NS rhythms who received TTM. The identified outcome of survival is not as impactful as neurologic recovery. The total cohort of eligible patients was approximately 1700 and only 696 had TTM data.
Sung et al. 2016. PMID: 26264064	**Study Type:** Retrospective cohort study of patients (n=1432) with OHCA due to NS initial rhythms.	**Inclusion Criteria:** Subjects had OHCA due to NS rhythm and were transported to a TH capable center. TH was initiated at the discretion of the treating physician	**1° endpoint:** Good neurological recovery (CPC 1 or 2) was primary outcome. Survival with good neurologic outcome was 14% in the group receiving TH, compared with 5% in those not treated with TH (risk difference = 8%, 95% CI 5-12%). The adjusted OR for a CPC 1 or	Large retrospective cohort that found benefit to TH in patients with initial NS rhythm. Data is consistent with outcomes from future RCT (Hyperion).

			2 with TH was 2.9 (95% CI 1.9-4.4).	
Chan et al. GWTG-R. 2016. PMID: 27701659	**Study Type:** Retrospective large registry study of in-patient cardiac arrest within the GWTG-R data	**Inclusion Criteria:** Inhospital cardiac arrest patients over 65 years of age with a sentinel event (n=26183, of which only 6% were treated with TTM). Measured the effect of TTM in survival and neurologic recovery.	**1° endpoint:** The primary endpoint was survival to hospital discharge where TTM was associated with a relative risk 0.88 [95% CI, 0.80 to 0.97] and a relative risk of 0.79 [95% CI, 0.69 to 0.90] for neurologic survival.	While this was a large cohort, very few (6%) underwent TTM. Data was only analyzed for patients greater than 65 years of age as medicare linked data was used for long term outcomes. Ventilation was used as a surrogate for being comatose, which may result in misclassification of patients as candidates for TTM.
Wang et al. 2016 PMID: 27820847	**Study Type:** Retrospective observational study of single center data.	**Inclusion Criteria:** Inhospital cardiac arrest patients (n=678) but only 22 individuals received TTM.	**1° endpoint:** TTM use was significantly associated with favourable neurological outcome (OR: 3.74, 95% confidence interval [CI]: 1.19-11.00; p-value = 0.02), but it was not associated with survival (OR: 1.41, 95% CI: 0.54-3.66; p-value = 0.48)	Small single center study.
Nurnberger, 2017. PMID: 28407232	**Study Type:** Secondary analysis of patients enrolled in the CIRC Trial who had OHCA and initiation of TH to 33C.	**Inclusion Criteria:** Subjects had OHCA and TH initiated out of the hospital, in hospital or not at all. 1812 were eligible but only 850 were analyzed.	**1° endpoint:** The odds ratio for survival comparing no cooling to out-of- plus in-hospital cooling was 0.53 [95%CI: 0.46-0.61, and comparing to in-hospital cooling only was OR 0.67 (95% CI: 0.50-0.89, P = 0·006)	Secondary analysis of trial data showing improved outcomes in patients who received TH. Outcome measured was dichotomous outcome of survival.
Martinell et al. 2017. PMID: 28465012	**Study Type:** Retrospective cohort study of patients who suffered OHCA and survived to hospital admission in one Swedish community over 12 years.	**Inclusion Criteria:** Subjects included were OHCA patients (n=871) who received mild induced hypothermia vs those who had not.	**1° endpoint:** Primary endpoint was 30 day survival, OR 1.33 (95% CI 0.83-2.15; p=0.24). Propensity score analysis and imputation of missing data was completed.	Single center study with moderate findings on unadjusted analysis that did not persist when imputing missing data and accounting for propensity score. Outcome measure was 30day survival.

Reviewer Comments (including whether meet criteria for formal review):

The question regarding therapeutic hypothermia (or temperature management at a goal of 32-34° C) was explored during the past 5 years in observational trials and one randomized controlled trial. Suggest Systematic review in next 1-2 years pending TTM2 publication.

Reference list

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C15 Targeted Temperature Management -Duration (ALS 455, 790, 791, 802, 879: EvUp)

Worksheet author(s): Sarah Perman
Council: AHA- 3CPR
Date Submitted: 1.6.2019

PICO / Research Question: ALS 791 Duration of TTM

In patients with ROSC after cardiac arrest in any setting (P), does does induction and maintenance of hypothermia for any duration other than 24 hours (I), compared with compared with induction and maintenance of hypothermia for a duration of 24 hours (C), change Survival with Favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year, Survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year (O)?

Outcomes:

9-Critical
Survival with Favorable neurological/functional outcome at discharge, 30 days, 60 days, 180 days AND/OR 1 year

7-Critical
Survival only at discharge, 30 days, 60 days, 180 days AND/OR 1 year

Type (intervention, diagnosis, prognosis): Intervention
Additional Evidence Reviewer(s):
Conflicts of Interest (financial/intellectual, specific to this question): none

Year of last full review: 2010 / 2015 / New question: 2015

Search Completed: December 11, 2013

Last ILCOR Consensus on Science and Treatment Recommendation:

We suggest that if TTM is used, duration should be at least 24 hours, as done in the 2 largest previous RCTs(HACA Study Group 2002, 549; Nielsen 2013, 2197) (weak recommendation, very-low-quality evidence). Values, Preferences, and Task Force Insights In making this recommendation, we place a high value on not changing current clinical practice, which most commonly is a TTM duration of 24 hours. We further note that the 2 largest trials related to TTM both used at least 24 hours, one of which found an outcome benefit when compared with not using TTM.

2010/2015 Search Strategy: 2015

("Hypothermia, Induced"[Mesh] OR "targeted temperature management"[TIAB] OR "therapeutic hypothermia"[TIAB] OR "hypothermia therapy"[TIAB] OR "whole body cooling"[TIAB] OR "whole-body cooling"[TIAB] OR ((cool*[TIAB] OR cold[TIAB]) AND ("Brain Injuries/prevention and control"[Mesh] OR neuroprotection[TIAB] OR "Hypoxia-Ischemia, Brain/prevention and control"[Mesh] OR “hypoxic-ischemic encephalopathy”[TIAB]))) AND ("Heart Arrest"[Mesh] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR "cardiovascular arrests"[TIAB] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "asystole"[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR "Advanced Cardiac Life Support"[Mesh] OR "Advanced Cardiac Life Support"[TIAB] OR "ACLS"[TIAB] OR "Ventricular Fibrillation"[Mesh] OR "cardiopulmonary resuscitation"[Mesh] OR "cardiopulmonary resuscitation"[TIAB] OR CPR[TIAB] OR "Heart Massage"[Mesh]) AND (prolong*[TIAB] OR hour*[TIAB] OR hrs[TIAB] OR duration*[TIAB] OR "Time Factors"[Mesh]) NOT ("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or Case Reports[ptyp])

2019 Search Strategy:

("Hypothermia, Induced"[Mesh] OR "targeted temperature management"[TIAB] OR "therapeutic hypothermia"[TIAB] OR "hypothermia therapy"[TIAB] OR "whole body cooling"[TIAB] OR "whole-body cooling"[TIAB] OR ((cool*[TIAB] OR cold[TIAB]) AND ("Brain Injuries/prevention and control"[Mesh] OR neuroprotection[TIAB] OR "Hypoxia-Ischemia, Brain/prevention and control"[Mesh] OR "hypoxic-ischemic encephalopathy"[TIAB]))) AND ("Heart Arrest"[Mesh] OR "cardiac arrest"[TIAB] OR "cardiac arrests"[TIAB] OR "cardiovascular arrest"[TIAB] OR "cardiovascular arrests"[TIAB] OR "heart arrest"[TIAB] OR "heart arrests"[TIAB] OR "asystole"[TIAB] OR "pulseless electrical activity"[TIAB] OR "cardiopulmonary arrest"[TIAB] OR "cardiopulmonary arrests"[TIAB] OR "Advanced Cardiac Life Support"[Mesh] OR "Advanced Cardiac Life Support"[TIAB] OR "ACLS"[TIAB] OR "Ventricular Fibrillation"[Mesh] OR "cardiopulmonary resuscitation"[Mesh] OR "cardiopulmonary resuscitation"[TIAB] OR CPR[TIAB] OR "Heart Massage"[Mesh]) AND (prolong*[TIAB] OR hour*[TIAB] OR hrs[TIAB] OR duration*[TIAB] OR "Time Factors"[Mesh]) NOT ("letter"[pt] OR "comment"[pt] OR "editorial"[pt] or Case Reports[ptyp])

Database searched: Pubmed
Date Search Completed: 12.5.19
Search Results (Number of articles identified / number identified as relevant): 1165
Inclusion/Exclusion Criteria:
English (1091)
Humans (760)
Last 5 years (410)

Link to Article Titles and Abstracts (if available on PubMed):
https://www.ncbi.nlm.nih.gov/sites/myncbi/1PgE4WBCzHi505/collections/58987589/public/

Summary of Evidence Update:
Evidence Update Process for topics not covered by ILCOR Task Forces

1. This evidence update process is only applicable to PICOs which are *not* being reviewed as ILCOR systematic and scoping reviews.

Relevant Guidelines or Systematic Reviews

Organisation (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
Kirkegaard et al. 2017.	**<u>Study Aim:</u>** Does temperature management at	**<u>Inclusion Criteria:</u>**	**<u>Intervention (n=176):</u>**	**<u>1° endpoint:</u>** 6 month neurologic follow up showed	**<u>Study Limitations:</u>** Sample size calculation was

PMID: 28742911	33C for 48 hours result in better neurologic outcome than 24 hours **<u>Study Type:</u>** Multicenter pragmatic randomized controlled trial	Comatose survivors of cardiac arrest admitted to the ICU with a presumed cardiac etiology to arrest.	Randomized to 48 hours of TTM at 33C **<u>Comparison (n=179):</u>** TTM for 24 hours of maintenance at 33C	no difference between the two arms (absolute difference, 4.9%; 95% CI, −5% to 14.8%; relative risk, 1.08; 95% CI, 0.93-1.25; *P* = .33)	based on an absolute difference of 15% between the two arms, which may have resulted in an underpowered study. 5% difference in improved outcome for the longer duration of treatment while not statistically significant, may have clinical implications.
Evald et al. 2018. PMID: 30572070	Does duration of treatment (24 v 48 hrs) result in different cognitive effects on survivors? **<u>Study Type</u>**: Substudy of Kirkegaard et al. TTM 24v48.	**<u>Inclusion:</u>** Same as above	Same as above	Multivariate regression analysis revealed that TTM48 was associated with a significant better performance on three of 13 cognitive tests specific to memory retrieval after adjusting for age at follow-up and time to return of spontaneous circulation. Overall, patients in the TTM24 group were almost three times more likely (RR = 2.9 (95% CI 1.1-7.4)), p = 0.02) to be cognitively impaired	Interesting implications given that further neurocognitive testing was done to truly clarify recovery. Subjects cooled for 48 hours had better memory retrieval, while patients in the 24 hour arm were more likely to be cognitively impaired.

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)
Kagawa et al. 2015. PMID: 26391133	**<u>Study Type:</u>** Observational data within single center registry (n=237)	**<u>Inclusion Criteria:</u>** Subjects were comatose survivors of cardiac arrest who underwent	**<u>1° endpoint:</u>** In adjusted analysis, there was no difference in survival with a good neurological recovery when patients were treated for a duration of therapy >28 hours (OR 3.20,	This was a small observational study where treatment duration was assigned by the treating physician. Subjects who were treated for 12 hours were considered the same as those who were treated for 24 hours,

		TTM. Patients were categorized as having a duration of therapy of <28 hours versus >28 hours.	95%CI: 0.37-70.83; p=0.312)	so difficult to interpret the outcomes for shorter duration.
	Study Type:	**Inclusion Criteria:**	**1° endpoint:**	

Reviewer Comments (including whether meet criteria for formal review):

This evidence review revealed a randomized controlled trial published in 2017 that explored the question of 24 versus 48 hours for duration of maintenance therapy in post-cardiac arrest temperature management. While the findings from this study did not reveal improved neurologic outcomes in the longer duration arm, it did provide further evidence to endorse 24 hours as the treatment duration. Unfortunately, this study may have been underpowered and therefore, the outcome of no difference may be called into question. Given this subject is the question posed in the upcoming multi-center trial ICECAP, there will be more data in the future to inform

Reference list

Evald L, Brønnick K, Duez CHV, Grejs AM, Jeppesen AN, Søreide E, Kirkegaard H, Nielsen JF. Prolonged targeted temperature management reduces memory retrieval deficits six months post-cardiac arrest: A randomised controlled trial. Resuscitation. 2019 Jan;134:1-9.

Kagawa E, Dote K, Kato M, Sasaki S, Oda N, Nakano Y, Miura K, Inoue I, Kihara Y. Do Lower Target Temperatures or Prolonged Cooling Provide Improved Outcomes for Comatose Survivors of Cardiac Arrest Treated With Hypothermia? J Am Heart Assoc. 2015 Sep 21;4(9).

Kirkegaard H, Søreide E, de Haas I, Pettilä V, Taccone FS, Arus U, Storm C, Hassager C, Nielsen JF, Sørensen CA, Ilkjær S, Jeppesen AN, Grejs AM, Duez CHV, Hjort J, Larsen AI, Toome V, Tiainen M, Hästbacka J, Laitio T, Skrifvars MB. Targeted Temperature Management for 48 vs 24 Hours and Neurologic Outcome After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. JAMA. 2017 Jul 25;318(4):341-350.