Appendix B

Advanced Life Support – 2025 Evidence Updates
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2025 Evidence Update
ALS 3003 – Prone CPR

Worksheet Author(s): Katherine Berg
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / Research Question:
Population: Adults and children in any setting (in-hospital or out-of-hospital) with cardiac arrest occurring while in the prone position.
Intervention: Performing cardiopulmonary resuscitation (CPR) and / or defibrillation while the patient remains in the prone position.
Comparators: Turning the patient supine prior to initiation of CPR and / or defibrillation.
Outcomes: Arterial blood pressure during CPR (important-5), time to initiation of CPR (important-5), time to defibrillation for shockable rhythms during CPR (important-5), end-tidal capnography during CPR (important-5), ROSC (important-6), survival and survival with favorable neurologic outcome to discharge, 30 days or longer (critical-9).
Study Designs: Randomized controlled trials (RCTs) and non-randomized studies (non-randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies), case series and case reports are eligible for inclusion. Case series and reports will be included as the writing group is aware that the human data on prone CPR are extremely limited. Unpublished studies (e.g., conference abstracts, trial protocols), and editorials are excluded, although case reports published in letter form may be included. Scoping reviews and systematic reviews will be included for discussion and to ensure no primary papers are missed, but data will not be extracted primarily from these reviews.

Year of last full review: 2021
Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:

Search Strategy (for an existing PICOST) included in the attached approved PICOST
PubMed:
((Prone*[tiab] OR "Prone Position"[Mesh]) AND ("Cardiopulmonary Resuscitation"[Mesh] OR cardiopulmonary[tiab] OR CPR[tiab] OR resuscitation[tiab] OR chest compression*[tiab] OR cardioversion[tiab] OR defibrillation[tiab] OR supine[tiab] OR (reverse[tiab] AND (CPR[tiab] OR resuscitation[tiab])))) AND ((ventricular (fibrillation OR tachycardia)) OR Cardiac arrest[tiab] OR heart arrest[tiab] OR asystole OR cardiopulmonary[tiab] OR pulseless electrical[tiab] OR PEA[tiab])

Database searched: PUBMED
Time Frame: (existing PICOST) – Dec 9 2020-July 15 2024
Date Search Completed: July 15 2024
Search Results (Number of articles identified and number identified as relevant): 116 identified, with 2 identified as relevant, including 1 systematic review and one report of 2 cases

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews

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

Anez et al, 2021	Systematic review	Prone CPR in operating room or ICU	2 observational studies (17 patients total) and 32 case reports	Concluded that it is possible to perform adequate CPR in the prone position. All studies identified were also included in the prior ILCOR review.	N/A

RCTs: 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)**
Jacobsen et al, 2023	Study Type: Case report (two cases)	EMS report of two out-of-hospital cardiac arrest cases where dispatch gave instructions for CPRn in the prone position due to inability to move the patient.	Both patients were in VF when EMS arrived, after receiving bystander CPR in the prone position, and both survived to admission.	N/A

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

There is minimal new evidence, and an updated systematic review is not warranted at this time.

Reference list:

1. Anez C, Becerra-Bolanos A, Vives-Lopez A, Rodriguez-Perez A. Cardiopulmonary Resuscitation in the Prone Position in the Operating Room or in the Intensive Care Unit: A Systematic Review. Anesthesia and Analgesia, Vol 132 (2); pp 285-292, Feb 2021. PMID: 33086246
2. Jacobsen RC, Beaver B, Olola C, Briggs AM, Scott G, Patterson BA, Wash G, Clawsom JJ. Prone Dispatch-Directed CPR in Out-of-hospital Cardiac Arrest: two successful cases. Prehosp Emerg Care, 27(2):192-195, April 2022. PMID: 35353005

2025 Evidence Update
ALS 3201 – Antiarrhythmic Drugs during Cardiac Arrest

Worksheet Author(s): Alexandra Rose Gosling, Shinichiro Ohshimo, Peter Kudenchuk, Jasmeet Soar
Task Force: Advanced Life Support
Conflicts of Interest: Peter K. Lead Investigator for ROC-ALPS (2016) and ARREST (1999) RCTs.

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

Study Designs:
Year of last full review: 2018
Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
We suggest the use of amiodarone or lidocaine in adults with shock refractory VF/pVT (weak recommendation, low-quality evidence).

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

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

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

Search Strategy (for an existing PICOST) included in the attached approved PICOST
PubMed search 1 Jan 2017 to 14 July 2023: 930 titles

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

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

((((((((((((('heart'/exp OR heart) AND ('arrest'/exp OR arrest) OR 'cardiac'/exp OR cardiac) AND ('arrest'/exp OR arrest) OR sudden) AND ('cardiac'/exp OR cardiac) AND ('death'/exp OR death) OR 'cardiovascular'/exp OR cardiovascular) AND ('arrest'/exp OR arrest) OR cardiopulmonary) AND ('arrest'/exp OR arrest) OR cardiopulmonary) AND ('failure'/exp OR failure) OR 'resuscitation'/exp OR resuscitation OR cardiopulmonary) AND ('resuscitation'/exp OR resuscitation) OR cpr OR 'code'/exp OR code) AND ('blue'/exp OR blue) OR 'code'/exp OR code) AND 99 OR advanced) AND ('cardiac'/exp OR cardiac) AND ('life'/exp OR life) AND ('support'/exp

OR support) OR acls OR pulseless) AND electrical AND ('activity'/exp OR activity) OR ventricular) AND ('fibrillation'/exp OR fibrillation) OR 'asystole'/exp OR asystole OR pulseless) AND ventricular AND ('tachycardia'/exp OR tachycardia) OR 'in hospital') AND ('cardiac'/exp OR cardiac) AND ('arrest'/exp OR arrest) AND ('anti arrhythmia' AND agents OR 'amiodarone'/exp OR amiodarone OR 'lidocaine'/exp OR lidocaine OR 'procainamide'/exp OR procainamide OR nifekalant OR 'bretylium'/exp OR bretylium OR 'magnesium'/exp OR magnesium OR 'esmolol'/exp OR esmolol OR 'sotalol'/exp OR sotalol OR lignocaine OR 'lignocaine'/exp OR phenytoin OR 'phenytoin'/exp OR metoprolol OR 'metoprolol'/exp) AND [2017-2023]/py

Search Results

930 PubMed titles
753 Embase titles

After removal of duplicates and screening of titles and abstracts by two reviewers (RG and PK):
168 (128 PubMed + 40 Embase) articles for further review by RG/SO/PK/JS

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

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews

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

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
		retrospective studies	• 6 studies reported the dose of amiodarone (150–300 mg) 3 studies reported the dose of lidocaine (60 mg or 1.5 mg/kg)	was superior to placebo re survival to discharge • Amiodarone (OR 2.43, 95% CrI 1.61–3.68) and lidocaine (OR 1.62, 95% CrI 1.04–2.53) was superior to placebo re favourable neurological outcome	
Zeppenfeld K et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death Eur Heart J 2022 Oct 21;43(40):3997-4126	ESC Guideline 2022	Antiarrhythmic drugs	1155 referenced articles	• Isoprotereno l infusion, verapamil or quinidine for acute treatment of an electrical storm or recurrent ICD discharges should be considered in idiopathic VF (2a) • Quinidine should be considered for chronic therapy to suppress an electrical storm or recurrent ICD discharges in idiopathic VF (2a) • Isoprotereno l infusion should be considered	Isoproterenol, verapamil, quinidine, amiodarone, beta blockers recommended in management of electrical storm and recurrent VF, but should be guided by underlying pathology.

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

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

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
			placebo (6 RCTs)		survival to hospital admission
Zhao H et al. Amiodarone and/or lidocaine for cardiac arrest: Bayesian network meta-analysis. Am J Emerg Med 2020;38:2185-93	Bayesian network meta-analysis – studies from inception to 1/21/2020 evaluating survival to discharge, survival to hospital admission/24 h and favorable neurological outcome	• Primary endpoint survival to discharge • Secondary endpoints survival to hospital admission/24 h and favorable neurological outcome • Amiodarone, lidocaine, placebo and combinations of same	• 9 studies (10,972 patients) meeting criteria: Dx refractory VF/VT cardiac arrest (in and out of hospital), age ≥18 yrs, assessed amiodarone, lido, amio+lido or placebo and full text articles • Included 4 RCTs, 4 RS (retrospective studies) and 1 PS (prospective study). • Cochrane bias risk assessment & Newcastle-Ottawa scale used to access quality of RCT & observational studies • Primary endpoint survival to hospital discharge; secondary endpoints survival to hospital admission/24 h and favorable neurological outcome (modified	• Head-to-head studies Survival to hospital admission/24h – 8 studies: • Lidocaine (Lido OR 3.12 (95% CI) 1.08, 9.98)) and amiodarone (Amio OR 2.96 (95% CI) (1.02, 8.53)) each individually better vs combination of the two drugs • NSD between amiodarone vs lidocaine (Amio OR 0.95 95% CI (0.67,1.34)) • NSD Amio vs placebo (Amio OR 1.34 95% CI (0.95, 1.90)) • NSD Lidocaine vs placebo (Lido OR 1.42 95% CI (0.97, 2.06)) • NSD Amiodarone plus lidocaine vs placebo (Amio+Lido OR 0.45 95% CI (0.15, 2.35))	• In head-to-head studies lido and amio significantly better than placebo in survival to hospital discharge; amiodarone more effective than placebo in favorable neurological outcome; lido and amiodarone individually more effective than lido plus amio in survival to hospital admission/24h • Amiodarone and lidocaine are superior to the combination of the two drugs in admission rates and superior to placebo in discharge rates. • The probability analysis revealed that lidocaine is the most effective agent for hospital admission and survival to discharger.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
			Rankin scale 0-3) • Bayesian network meta-analysis performed • Pooled outcome measures determined using random effects model	Survival to discharge -9 studies: • Amio vs placebo (Amio OR 1.18 95% CI (1.03, 1.35)) • Lido vs placebo (Lido OR 1.22 95% CI (1.06, 1.41)) • NSD Amio vs amio plus lidocaine (Amio OR 2.25 95% CI (0.93, 5.44) • NSD Amio vs lidocaine (Amio OR 0.96 (0.86,1.07)) • NSD Amio plus lido vs lido (Amio+lido OR 0.43 (0.18,1.03)) • NSD Amio plus lido vs placebo (Amio+lido OR 0.52 (0.21, 1.27)). Favorable neurological survival - 4 studies: • Amio vs placebo (Amio OR 1.2 95% CI (1.02,1.41)) • NSD amio vs lidocaine (Amio OR 1.09 (0.92, 1.29)) • NSD Lido vs placebo	• Regarding favorable neurological outcome, amiodarone is superior to placebo. • The probability analysis revealed that amiodarone was superior to lidocaine and placebo in neurological outcome.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				(Lido OR 1.1 (0.93,1.30)) • Markov chain Monte Carlo modeling (MCMC) was used to estimate relative ranking probability of treatments – lidocaine was most effective for survival to hospital admission and discharge; amiodarone as most effective for favorable neuro outcome • These findings are different from those of 2 previous meta-analyses. One of these - a conventional meta-analysis - concluded that amiodarone and lidocaine had the same beneficial effect on survival to hospital admission, and both were better than placebo. It also concluded that there was no significant difference among the three interventions in survival to hospital discharge. The	

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				second study – a network meta-analysis - concluded that lidocaine had the best effect in survival to hospital discharge, with no significant difference in survival to hospital admission. • In a retrospective study comparing amiodarone with lidocaine (without a placebo comparison) we performed a Bayesian network meta-analysis to obtain more evidence. The proportions of patients surviving to hospital admission and discharge were not different between patients who received lidocaine, amiodarone, or a combination of the two drugs. However, the combination regimen was the least effective in our study, even less effective than placebo. This may be because only one	

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				study with 41 patients was included. Another reason may be that amiodarone and lidocaine have different pharmacological mechanisms, and the combination of the two drugs could increase side effects and inhibit the sinoatrial and atrioventricular nodes.	
Ludwin K et al. Effect of amiodarone and lidocaine on shock-refractory cardiac arrest: A systematic review and meta-analysis. Kardiol Pol 2020;78:999-1007	Systematic review and meta-analysis	• Amiodarone vs lidocaine	• Studies were included if they met the following criteria: 1) randomized and quasi-randomized controlled trials, cohort and cross-sectional studies; 2) intravascular access; 3) comparison of amiodarone and placebo, lidocaine and placebo, or amiodarone and lidocaine; 4) reporting at least return of spontaneous circulation (ROSC) outcome; 5) adult patients	• An insignificantly higher number of cases with return of spontaneous circulation was observed in the amiodarone group compared with the lidocaine group (OR, 1.03; 95% CI, 0.87–1.21; P = 0.75). • A similar relationship was observed for survival to hospital discharge (OR, 1.12; 95% CI, 0.92–1.38; P = 0.26), as well as survival with favorable neurological outcome (OR, 1.11; 95% CI, 0.89, 1.39; P = 0.35).	• No statistically significant survival benefit of resuscitation with amiodarone compared with lidocaine.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
			with cardiac arrest • 682 unique references → 8 selected • 1° outcome of this systematic review was ROSC. • 2° outcome was survival to hospital discharge and survival to hospital discharge with favorable neurological outcome. Favorable neurological outcome was defined as the patient discharged home or for rehabilitation, Cerebral Performance Categories Scale score of 1 or 2, or a modified Rankin Scale score of 1 or 2 • 8 studies selected (5 retrospective observational and 3 randomized) but authors mistook Daya IV vs IO ALPS		

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
			substudy as updated ALPS for the main ALPS analysis		
Ali MU, et al. Effectiveness of antiarrhythmic drugs for shockable cardiac arrest: A systematic review. Resuscitation 2018:132:63-72	Systematic review and meta-analysis (Medline, Embase, and Cochrane Library)	P: shockable cardiac arrest in adults I: antiarrhythmic drugs C: other antiarrhythmic drugs or placebo O: survival to hospital discharge; discharge with good neurological function; ROSC T: from inception to August 15, 2017	14 RCTs and 17 observational studies	For the critical outcomes of survival to hospital discharge and discharge with good neurological function, none of the anti-arrhythmic drugs showed any difference in effect compared with placebo, or with other anti-arrhythmic drugs. For the outcome of return of spontaneous circulation, the results showed a significant increase for lidocaine compared with placebo (RR = 1.16; 95% CI, 1.03–1.29, p = 0.01).	The high level evidence supporting the use of antiarrhythmic drugs during CPR for shockable cardiac arrest is limited and showed no benefit for critical outcomes. Original ILCOR SR.
Chowdhury A et al. Antiarrhythmics in Cardiac Arrest: A Systematic Review and Meta-Analysis. Heart Lung Circ 2018;27:280-290	Systematic review and meta-analysis (CINAHL, SCOPUS, PubMed, Web of Science, Medline(Ovid) and the Cochrane Clinical Trials Registry)	P: adult cardiac arrests (OHCA and IHCA, over 18 yo) I: 8 antiarrhythmic drugs (amiodarone, lidocaine, magnesium, esmolol, nifekalant, bretylium,	31 studies (13 RCTs; 7 prospective cohort studies; 11 retrospective cohort studies; n= 42,808)	For any outcome, amiodarone, lidocaine and magnesium showed no significant effect either against placebo or each other. For ROSC, esmolol showed a near significant	There has been no conclusive evidence that any antiarrhythmic agents improve rates of ROSC, survival to admission, survival to discharge or neurological outcomes.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
		vasopressin, sotalol) C: other antiarrhythmic drugs or placebo O: ROSC; survival to hospital admission for OHCA patients, survival to hospital discharge; neurologic outcomes at discharge T: from inception to March, 2017		increase (OR = 17.59; 95%CI = 0.87–356.81; p = 0.06). For survival to admission, bretylium showed a significant benefit compared to placebo (OR = 4.04; 95%CI = 1.22–13.43; p = 0.02; Figure 3) For survival to admission, nifekalant showed a significant increase compared to lidocaine (OR = 2.91; 95%CI = 1.44–5.87; I2 = 34%; p = 0.003). On sensitivity analysis, both amiodarone and lidocaine had a significant increase in survival to admission, with no effect on survival to discharge.	
McLeod SL et al. Comparative effectiveness of antiarrhythmics for out-of-hospital cardiac arrest: A systematic	Systematic review and network meta-analysis (Medline, Embase, and Cochrane Library)	P: adult patients experiencing out-of-hospital cardiac arrest (OHCA). I: 5 antiarrhythmic drugs	8 RCTs (n=4,464)	For ROSC, lidocaine was associated with a significant increase in ROSC compared to placebo (1.15; 95% CI: 1.03-1.28), and was	Amiodarone and lidocaine were the only agents associated with improved survival to hospital admission. For the

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
review and network meta-analysis. Resuscitation 2017:121:90-97		C: other antiarrhythmic drugs or placebo O: ROSC; survival to hospital admission; survival to hospital discharge; neurologically intact survival T: from inception to March, 2017		also superior to bretylium (1.61; 95% CI: 1.00-2.60). For survival to hospital admission, both amiodarone (1.18; 95% CI: 1.08-1.30) and lidocaine (1.18; 95% CI: 1.07-1.30) were associated with a significant increase compared to placebo. For survival to hospital discharge or neurologically intact survival, no antiarrhythmic was more effective than placebo. For any outcome, no antiarrhythmic was convincingly superior to any other.	outcomes most important to patients, survival to hospital discharge and neurologically intact survival, no antiarrhythmic was convincingly superior to any other or to placebo.
Sato S, et al. Meta-analysis of the efficacies of amiodarone and nifekalant in shock-resistant ventricular fibrillation and pulseless ventricular	Systematic review and meta-analysis (PubMed, Cochrane Central Register of Controlled Trials, and Igaku Chuo Zasshi)	P: adult patients with OHCA/IHCA and had VF or pVT) I: amiodarone or nifekalant C: lidocaine, placebo, or a non-treatment antiarrhythmic drug	33 studies (7 RCTs; 6 observational studies; 20 retrospective studies)	For both short-term (OR: 1.25, 95% CI: 0.91–1.71) and long-term survival (OR: 1.00, 95% CI: 0.63–1.57), amiodarone showed no significant benefit compared to control	Nifekalant may be more beneficial than amiodarone for both short-term and long-term survival in these conditions. However, the efficacy of amiodarone in

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
tachycardia. Sci Rep 2017;7:12683.		O: short-term survival (defibrillation success, VF/pVT termination, return to spontaneous circulation, survival until admission to the hospital/intensive care unit, and three-hour survival) and long-term survival (30-day survival, 1-year survival, and survival until discharge from hospital) T: from inception to December 2016		treatments. For both short-term (OR: 3.23, 95% CI: 2.21–4.72)and long-term survival (OR: 1.88, 95% CI: 1.36–2.59), nifekalant showed a significant benefit compared to control treatments. There was no significant difference in short-term (OR: 0.85, 95% CI: 0.63–1.15) or long-term survival (OR: 1.25, 95% CI: 0.67–2.31) between amiodarone- and nifekalant-treated patients.	either outcome remains unclear.
Khan SU, et al. Amiodarone, lidocaine, magnesium or placebo in shock refractory ventricular arrhythmia: A Bayesian network meta-analysis. Heart Lung 2017;46:417-424	Systematic review and Bayesian network meta-analysis (PubMed/MEDLINE, EMBASE and Cochrane Central Register of Controlled Clinical Trials)	P: adult patients with OHCA/IHCA and had VF or VT) I: amiodarone, lidocaine, and magnesium C: , placebo O: survival to hospital discharge, survival to hospital admission/24 h and ROSC T: from 1981 to February 2017	11 studies (7 RCTs; 2 prospective observational studies; 2 retrospective observational studies)	For survival to hospital discharge, lidocaine was significantly better than amiodarone (OR, 2.18; 95% Cr.I. 1.26–3.13), MgSO4 (OR, 2.03; 95% Cr.I. 0.74–4.82) and placebo (OR, 2.42; 95% Cr.I. 1.39–3.54). For survival to hospital admission/24 h,	We conclude that lidocaine may be the most effective anti-arrhythmic agent for survival to hospital discharge in patients with pulseless VT or VF.

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				lidocaine was significantly superior to placebo (OR, 1.68; 95% CI, 1.03–2.75; P-value = 0.04; I2 = 0). For achievement of ROSC, lidocaine showed a significant benefit compared to placebo (OR, 1.51; 95% Cr.I. 1.06–2.37), with a trend favoring lidocaine over both amiodarone (OR, 1.43; 95% Cr.I. 0.98–2.42) and MgSO4 (OR, 1.51; 95% Cr.I. 0.86–2.88). A sensitivity analysis was conducted on the included RCTs for OHCA due to ventricular arrhythmia, lidocaine was superior to both amiodarone (OR, 2.42; 95% Cr.I. 1.25–3.39) and placebo (OR, 3.01; 95% Cr.I. 1.60–4.30) in survival to hospital discharge.	
Bretylium					
AHA Part III: Adult Advanced	1992 AHA Guideline	• Bretylium	• 10 references	• Bretylium tosylate is a	• Bretylium is useful in

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Cardiac Life Support JAMA 1992;286:2199-2241				quaternary ammonium compound used in the treatment of resistant VT and VF unresponsive to defibrillation, epinephrine, and lidocaine. Its cardiovascular actions are complex and include a release of catecholamines initially on injection, followed by a postganglionic adrenergic blocking action that frequently induces hypotension. • There are data documenting the primary antifibrillatory effect of bretylium in animals, although this concept has recently been challenged.	treating both VF and VT but no better than lidocaine in direct comparisons. • Bretylium should not be used as a first-line antiarrhythmic agent. This simplifies selection of a therapy and precludes potential adverse hemodynamic effects.
AHA Part 6: Advanced cardiovascular life support; Section 5: Pharmacology I: Agents for Arrhythmias. Circulation 2000;102:I-112-28.	AHA Guideline	• Bretylium	• 6 references cited	• AHA has dropped reference to bretylium because of tis limited utility and availability. • In 1999 bretylium was unavailable from	• After 1999 bretylium was been removed from ACLS treatment algorithms and guidelines because of a high occurrence of side effects, the availability

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				the manufacturer.	of safer agents at least as efficacious and the limited supply and availability of the drug.
Beta Blockers					
Miraglia D et al. Esmolol in the management of prehospital refractory ventricular fibrillation: A systematic review and meta-analysis Am J Emerg Med 2020;38:1921-34	Systematic review and meta-analysis	• Esmolol	• 3253 unique records, of which 2 observational studies were found to be in accordance with the research purpose, totaling 66 patients, of whom 33.3% (n=22) received esmolol • We considered for inclusion any controlled clinical study design (randomized controlled trials [RCTs] and controlled non-randomized trials [CnRTs]), and observational studies (cohort studies and case control studies) with a control group (i.e. patients not receiving esmolol) published in English as full-text articles in	Esmolol was likely associated with: • An increased rate of survival to discharge (RR 2.82, 95% CI 1.01–7.93, p = 0.05) (GRADE: Very low). There was no statistical significance at the individual study level but there was modest statistical significance at the meta-analysis level • Survival with favorable neurological outcome (RR 3.44, 95% CI 1.11–10.67, p = 0.03) (GRADE: Very low). • Return of spontaneous circulation (ROSC) (RR 2.63, 95% CI 1.37–5.07, p = 0.004) (GRADE: Very low) • Survival to intensive care unit (ICU)/hospital	• Effectiveness of esmolol for refractory VF/pVT remains unclear; evidence is inconclusive. • We are uncertain of the effects of esmolol on any of the reported outcomes as a result of this assessment; additionally, the optimal information size was not achieved for the meta-analysis, and sequential testing on an accumulated number of participants did not surpass trial sequential monitoring boundaries. Therefore, the conclusion should be that the intervention might be beneficial, but larger sample sizes are needed as the estimates

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
			indexed journals between January 2000 and December 2019 that reported survival rates and neurological outcome in adults (≥18 years) resuscitated from prehospital cardiac arrest on-scene or in the emergency department (ED). • 1° outcomes of the study were survival to discharge and survival with favorable neurological outcome. • 2° outcomes included sustained ROSC, survival to intensive care unit (ICU)/hospital admission, survival at 30 days and one year, and survival with favorable neurological outcome at 30 days and one year	admission (RR 2.63, 95% CI 1.37–5.07, p = 0.004) (GRADE: Very low). • The GRADE quality of evidence was graded as very low for each outcome and as having a high risk of confounding. • The overall risk of bias within individual studies was judged as serious for both studies, with confounding bias, selection of participants, and measurement of outcomes being the primary sources. • The overall risk of bias within both studies was judged as serious because they included at least one category with serious risk of bias. • Both studies were at moderate risk of selection bias. • Both studies were at overall low risk of bias for classification of interventions and deviations from	are still inconclusive • At this time, there is inadequate evidence to either support the use of esmolol during refractory cardiac arrest or the routine use of a β-blocker after cardiac arrest.

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

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

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				control in both studies; review of actual studies indicates this was only true in the Lee study	
Long DA et al. Does B-Blockade for treatment of refractory ventricular fibrillation improve outcomes? Ann Emerg Med 2020;76:42-45	Clinical synopsis of: Gottlieb M, Dyer S, Peksa A. Betablockade for the treatment of cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia: a systematic review and meta-analysis. Resuscitation. 2020;146:118-25	• Beta blockade in refractory VF/pulseless VT • Refractory VF/VT defined as refractory to ≥ 3 shocks, or electrical storm (≥ 4 episodes/hr or ≥20 episodes VF/VT qd) • Esmolol, propranolol, left stellate ganglion block evaluated	• 3 studies (n=115): 2 performed in ED and 1 unspecified location; 1 study prospective and observational; 2 retrospective observational • Esmolol, propranolol, left stellate ganglion block as interventions • None of studies assessed adverse events	• Based on GRADE certainty of evidence low to very low Pooled data meta-analysis results: • Temporary ROSC (n=66) 86.5% (BB) vs 31.8% (OR 14.46 95% CI (3.63,57.57)) • Sustained ROSC (n=66) 59.1% vs 22.7% (OR 5.76 95% CI (1.79,18.52)) • Admission survival (n=66) 59.1% vs 22.7% (OR 5.76 95% CI (1.79,18.52)) • Survival to discharge (n=115) 53.1% vs 10.6% (OR 7.92 95% CI (1.85,33.89)) • Survival with favorable neuro outcome (n=66) 27.3% vs 9.1% (OR 4.42 95% CI (1.05,18.56))	• Results of this meta-analysis suggest that b-blockade in patients with cardiac arrest caused by refractory ventricular fibrillation or pulseless ventricular tachycardia may lead to increased rates of return of spontaneous circulation, survival to discharge, and survival with a favorable neurologic outcome • Given the paucity of studies found and included through screening of the literature in this meta-analysis and the low confidence of the results, further high-quality clinical investigations are necessary to evaluate the efficacy

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

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				potential confounding	
Miraglia D et al. The evolving role of novel treatment techniques in the management of patients with refractory VF/pVT out-of-hospital cardiac arrest Am J Emerg Med 2020;38:648-54	Comprehensive literature search (systematic review) of observational studies	• Outcomes of extracorporeal membrane oxygenation, esmolol, double sequential defibrillation and stellate ganglion block • This assessment limited to esmolol findings (2 observational studies)	• 2 observational studies on esmolol	Esmolol: • Driver (2014) - n=6 esmolol recipients – 66.7% temporary ROSC, 66.7% sustained ROSC and admission to ICU, 50% survival, 50% survival with CPC ≤2 • Lee (2016) n=16 esmolol recipients – 66.7% temporary ROSC, 56.3% sustained ROSC and ICU admission, 18.8% survival; 18.8% survival with CPC ≤2	• Insufficient evidence to support effects of evaluated techniques (and in particular esmolol) in treatment of refractory VF/pVT OHCA
Other Antiarrhythmics					
Sharma A et al. Analysis of the 2018 American Heart Association Focused Update on Advanced Cardiovascular Life Support Use of Antiarrhythmic Drugs During and Immediately After Cardiac Arrest. J Cardiothoracic Vasc Anesth 2020;34:537-44	Analysis of 2018 AHA Focused update	• Antiarrhythmic drugs in cardiac arrest: amiodarone, lidocaine, nifekalant, bretylium, Mg, sotalol	• Review of articles cited in 2018 AHA focused update	• Nifekalant vs lidocaine – NSD in survival to discharge • Bretylium vs lidocaine – NSD in ROSC or survival to discharge • Sotalol vs lidocaine – NSD in ROC, survival to discharge or neurologically favorable survival • Amiodarone vs lidocaine – NSD	• Amiodarone or lidocaine may be useful for VF/pVT unresponsive to defibrillation • Mg may be useful for polymorphic VT due to torsade • Role of beta blockers uncertain • No proven benefit of nifekalant, sotalol or bretylium

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
				in survival to discharge or neurologically favorable outcome in ALPS • Subsequent systematic review/meta-analysis showed improved survival to hospital admission with either lidocaine or amiodarone without improved survival discharge with either drug; no differences in outcome between amiodarone and lidocaine for any outcome • Nifekalant vs amiodarone – no difference in hospital mortality • Insufficient evidence to support or refute beta blockers • Mg – no benefit in ROSC or survival to discharge; limited evidence in torsade based on only 2 observational studies	compared to existing agents
Dyer S et al. Electrical storm: A focused review	Descriptive review of electrical storm defined as ≥3	• Antiarrhythmic drugs (amiodarone,	• 84 referenced articles	• Descriptive only	• Mainly a narrative review suggesting use

Organization (if relevant); Author; Year Published	**Guideline or systematic review**	**Topic addressed or PICO(S)T**	**Number of articles identified**	**Key findings**	**Treatment recommendations**
for the emergency physician Am J Emerg Med 2020;38:1481-87	episodes VF/VT/ICD shocks over 24 hrs	procainamide), beta blockers (esmolol, propranolol, metoprolol), isoproterenol			of antiarrhythmic agent and beta blocker as treatment agents without further formal analyses

RCTs:

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

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
				[OR], 0.91; 95% CI, 0.90–0.93 per min), lidocaine (OR, 0.93; 95% CI, 0.91–0.96), and placebo (OR, 0.91; 95% CI, 0.90–0.93). • Improved survival times administering amiodarone at any point compared to placebo (OR, 1.32; 95% CI, 1.05–1.65). Lidocaine only improved survival at later time points compared with placebo (p = 0.048).	
Lupton JR et al. Survival by time-to-administration of amiodarone, lidocaine, or placebo in shock-refractory out-of-hospital cardiac arrest. Acad Emerg Med. 2023 Mar 4	• Evaluate effect of time between EMS arrival to drug administration on efficacy of amiodarone and lidocaine compared to placebo. • Post-hoc analysis of 10-site, 55-	Initial shockable rhythm (VF, pVT) who received amiodarone, lidocaine or placebo before achieving ROSC	ALPS RCT examined effects of amiodarone, lidocaine and placebo.	• Patients receiving amiodarone (compared to placebo) had increased survival to admission (62% v 48.5% p = 0.001, OR 1.76 95% CI 1.24-2.5), survival to discharge	This is a post-hoc analysis of a previous RCT, only uses proportion of original study number.

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
	EMS-agency double-blind RCT for amiodarone, lidocaine, or placebo in OHCA (ALPS) n = 2802 patients			(37.1% v 28% p = 0.021, OR 1.56 95% CI 1.07-2.29) and functional survival (31.6% v 2.23% p = 0.029, OR 1.55 95% CI 1.04-2.32) • No significant difference between lidocaine <8min and placebo (p>0.05) Amiodarone or lidocaine ≥8 min had no significant difference in outcome compared to placebo (p>0.05)	
Lane DJ et al. Bayesian analysis of amiodarone or lidocaine versus placebo for out-of-hospital cardiac arrest Heart. 2022 Oct 28;108(22):1777-1783.	• To assess the probability of improved survival or improved neurological outcome. • Post-hoc Bayesian analysis of ALPS RCT n = 3026 adult patients enrolled in RCT	Adult patients with OHCA with refractory VF or pVT (all patients enrolled to ALPS RCT)	Randomly assigned to receive amiodarone, lidocaine or placebo	• Improved survival with amiodarone ranged from 83% (strong prior) to 95% (weak prior) compared with placebo and from 78% (strong) to 90% (weak) for lidocaine. • Probability of improved	This is a post-hoc analysis of a previous RCT.

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
				neurological outcome from amiodarone ranged from 96% (weak) to 99% (strong) compared with placebo and from 88% (weak) to 96% (strong) for lidocaine. In conclusion, amiodarone had high probabilities of improved survival and neurological outcome whereas treatment with lidocaine had a more modest benefit.	
Rahimi M et al. Effect of Time to Treatment With Antiarrhythmic Drugs on Return of Spontaneous Circulation in Shock-Refractory Out-of-Hospital Cardiac Arrest J Am Heart Assoc. 2022 Mar 15;11(6):e023958	• Evaluate effect of time to treatment (drug/placebo administration) with ROSC at hospital arrival. • Post-hoc analysis of ROC ALPS RCT n = 1112 patients achieved ROSC at hospital arrival (total 3026 enrolled in RCT)	Adults with non-traumatic OHCA and an initial rhythm of VF or pVT refractory to at least one defibrillation attempt	Randomly assigned to receive amiodarone, lidocaine or placebo	• 36.7% patients achieved ROSC at hospital arrival (350 amiodarone, 396 lidocaine, 366 placebo) • Proportion of patients with ROSC decreased as time to medication increased: amiodarone	This is a post-hoc analysis of a previous RCT, only uses proportion of original study number.

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
				(OR 0.92 95%CI 0.9-0.94), lidocaine (OR 0.95 95% CI 0.93-0.96) and placebo (OR 0.95 95% CI 0.93-0.96) With shorter times to drug administration, the proportion with ROSC was higher in amiodarone versus placebo recipients.	
Salcido DD, et al. Effects of intra-resuscitation antiarrhythmic administration on rearrest occurrence and intra-resuscitation ECG characteristics in the ROC ALPS trial. Resuscitation 2018:129:6-12	To investigate the relationship between rearrest and intra-resuscitation antiarrhythmic drugs in the context of the Resuscitation Outcomes Consortium (ROC) amiodarone, lidocaine, and placebo (ALPS) trial. Pospective, randomized, controlled, double-blind trial conducted from February 2013 to January 2017 n=1,144	Patients 18 years or older with nontraumatic OHCA, documented persistent, or recurring VF/VT after ≥1 shock	I: lidocaine (n=420), amiodarone (n=363) C: placebo (n=361) O: rearrest, survival to hospital discharge, good neurologic function at hospital discharge (MRS <=3), quantitative ECG measures at first analyzable VF, immediately prior to ROSC, and at onset of first rearrest.	Rearrest rate was 44.0% overall; 42.9% for placebo, 45.7% for lidocaine, and 43.0% for amiodarone.	Rearrest rates did not differ between antiarrhythmic and placebo treatment groups. ECG waveform characteristics were correlated with treatment group and rearrest. Rearrest was inversely associated with survival and neurologic outcomes.

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
Kudenchuk PJ, et al. Antiarrhythmic Drugs for Nonshockable-Turned-Shockable Out-of-Hospital Cardiac Arrest: The ALPS Study (Amiodarone, Lidocaine, or Placebo). Circulation 2017;136:2119-2131	To evaluate the effectiveness of amiodarone and lidocaine for OHCA due to shock-resistant VF/VT (The Amiodarone, Lidocaine or Placebo Study (ALPS)). Prospective, randomized, double-blind, placebo-controlled multicenter trial n=4,089	Patients 18 years of age or older with atraumatic out-of-hospital cardiac arrest, established intravenous or intraosseous vascular access, and persistent (nonterminating) or recurrent (restarting after successful termination) VF/VT after one or more shocks.	I: lidocaine (n=420), amiodarone (n=363) C: placebo (n=361) O: The primary outcome of the trial was survival to hospital discharge. Secondary outcome were survival to discharge with favorable neurological functional status, defined on the modified Rankin scale as 3 or less, and adverse drug-related effects.	Active-drug recipients in this cohort required fewer shocks, supplemental doses of their assigned drug, and ancillary antiarrhythmic drugs than recipients of a placebo (P<0.05). In all, 16 (4.1%) amiodarone, 11 (3.1%) lidocaine, and 6 (1.9%) placebo-treated patients survived to hospital discharge (P=0.24). No significant interaction between treatment assignment and discharge survival occurred with the initiating OHCA rhythm (asystole, pulseless electric activity, or VF/VT). Survival in each of these categories was consistently higher with active drugs, although the trends were not statistically	Although not statistically significant, point estimates for survival were greater after amiodarone or lidocaine than placebo, without increased risk of adverse effects or disability and consistent with previously observed favorable trends from treatment of initial shock-refractory VF/VT with these drugs.

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

Nonrandomized Trials, Observational Studies

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
	Study Type:	Inclusion Criteria:	1° endpoint:	
Amiodarone and/or Lidocaine				
Perry E et al. The impact of time to amiodarone administration on survival from out-of-hospital cardiac arrest. Resusc Plus. 2023 Jun 7;14:100405	• Retrospective cohort study of adult patients with shock refractory VF/pVT using Ambulance Registry Data • n = 2,026 adults with VF/pVT OHCA • Time-dependent	• n= 2,026 adults with shock refractory VF/pVT treated by EMS between January 2010-Decmber 2019 1,393 (68.8%) received amiodarone during the shock-refractory VF/pVT	• 1° outcome was survival to hospital discharge • 2° outcomes: pre-hospital ROSC, event survival (a pulse on arrival at hospital) • Amiodarone administration within 28	• Administration of amiodarone within 28 minutes associated with improved ROSC and event survival outcomes and increased survival to hospital discharge • No documentation

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)
	propensity score matching	episode, all after 3 defibrillations had been administered (as per EMS guidelines)	minutes of the emergency call was associated with a higher likelihood of ROSC (≤18 minutes: RR = 1.031 (95% CI 1.018–1.043) and event survival (≤18 minutes: RR = 1.046 (95% CI 1.025–1.067) Amiodarone administration within 23 minutes of the emergency call was associated with increased likelihood of survival to hospital discharge (≤18 minutes: RR = 1.166 (95% CI 1.092–1.244)	of neurological outcome of patients who survived to discharge • Excluded patients with initial defibrillation by first responder/public, who were a higher-survival cohort
Kishihara Y et al. Comparison of the effects of lidocaine and amiodarone for out-of-hospital cardiac arrest patients with shockable rhythms: a retrospective observational study from a multicenter registry. BMC Cardiovasc Disord. 2022 Nov 5;22(1):466	• Retrospective observational propensity-matched record-review study using OHCA registry. n = 1970 adult patients with VF/pVT who were administered amiodarone or lidocaine	• Adult cardiogenic OHCA with VF/pVT treated by EMS who received either amiodarone or lidocaine during resuscitation n = 105 administered lidocaine, 1865 amiodarone	• 1° outcome was 30-day survival • 2° outcome: good neurological outcome at 30 days (CPC score 1-2) • Amiodarone used as reference • 30-day survival following lidocaine: OR 1.44 (95% CI 0.58-3.61) 30-day good neurological outcome following	• No significant differences in both 30-day survival or good neurological outcomes between amiodarone and lidocaine • Only 5.3% patients received lidocaine, whereas 94.7% were administered amiodarone • Only OHCA with cardiogenic cause included

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			lidocaine: OR 1.77 (95% CI 0.59-5.29)	
Wissa J et al. Time to amiodarone administration and survival outcomes in refractory ventricular fibrillation Emerg Med Australas. 2021 Dec;33(6):1088-1094	• Retrospective observational record review of ambulance service database for adult OHCA with refractory VF n = 502 patients	Adult OHCA of medical aetiology with refractory VF treated by ambulance service & received amiodarone	• 1° outcome: survived event, discharged alive, 30 day survival • Time to amiodarone negatively associated with survival (OR 0.93 for event survival; 95% CI 0.89–0.97) Optimal time window for amiodarone administration is within 23 min after arrest.	• Patients receiving amiodarone within the optimal time had significantly better survival (survived event 38.3% vs 20.6%, p< 0.001; discharge survival 25.5% vs 9.7%, p< 0.001; 30-day survival 25.1% vs 9.7%, p< 0.001) No data on neurological outcomes
Wagner D et al. Comparative Effectiveness of Amiodarone and Lidocaine for the Treatment of In-Hospital Cardiac Arrest Chest. 2023 May;163(5):1109-1119	• Retrospective cohort study of adult patients with in-hospital cardiac arrest with refractory VF/pVT. n = 14,630 patients	• Adult in-hospital cardiac arrest with refractory VF/pVT receiving amiodarone or lidocaine. • January 2000 – December 2014 • 68.7% (n= 10,058) treated with amiodarone 31.3% (n=4572) treated with lidocaine	• 1° outcome: ROSC • 2° outcomes: 24h survival, survival to hospital discharge and favourable neurologic outcome When compared with amiodarone, lidocaine associated with statistically significant increased rates of: ROSC (OR 1.15, p=0.01), 24h survival (OR 1.16, p=0.004) survival to discharge (OR 1.19, p <0.001) and favourable neurologic	Compared with amiodarone, lidocaine is associated with statistically significant higher rates of ROSC, 24h survival, survival to hospital discharge and favourable neurologic outcome, in patients with in-hospital cardiac arrest with refractory pVT/VF.

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)
			outcome (OR 1.18, p<0.001)	
Lee DK et al. Impact of early intravenous amiodarone administration on neurological outcome in refractory ventricular fibrillation: Retrospective analysis of prospectively collected prehospital data. Scan J Trauma Resus Emerg Med 2019; 27: 109-117	• Retrospective analysis of prospectively collected prehospital data • n=134 adults presenting with VF and nonresponsive to ≥3 shocks • Patients divided into 2 groups based on CPC 1-2 vs not at hospital discharge	• Adult OHCA due to initial VF • Persistent VF despite 3 shocks → 300 mg IV amiodarone + 150 mg if required	• 1°: Good neurological outcome at hospital discharge based on elapsed time from call-to-amiodarone (CPC 1-2) • 2°: Prehospital ROSC, total ROSC, survival to admission, survival to discharge based on call-to-amiodarone administration time • In univariate logistic regression, probability of good neurological outcome at hospital discharge decreased as the call-to amiodarone administration interval increased (OR 0.89 [95% CI = 0.80–0.99]) • In multivariate logistic regression TTM (OR 5.86 (1.27,27.09) & call-to-amio ≤ 20 min (OR 10.12 (1.37, 74.92) independently associated with better neurological outcome • Age, sex, public place,	• Early amiodarone administration (call-to-amiodarone administration interval ≤ 20 min) was an independent factor associated with good CPC at discharge in OHCA patients with initial VF and subsequent refr VF • Notably only 15 of 134 (11%) of patients were discharged with CPR 1-2 • Other system efficiencies could also account for benefit from earlier treatment (i.e. everything done sooner and more responsive substrate to any intervention)

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			witnessed arrest, bystander CPR, targeted temperature management (TTM), the call-to-epinephrine administration interval, and the call-to-amiodarone administration interval were included in the multivariable logistic regression analysis	
Daya MR et al. Survival after IV versus IO amiodarone, lidocaine or placebo in out-of-hospital shock-refractory cardiac arrest. Circulation 2020;141:188-198	• Prespecified observational analysis of a randomized placebo-controlled clinical trial • n=3019 adults with nontraumatic OHCA due to VF randomized to amiodarone, lidocaine or placebo	• n=3019 adults with nontraumatic OHCA due to VF randomized to amiodarone, lidocaine or placebo • 2358 received assigned drugs IV; 661 IO	• 1° survival to hospital discharge • 2° survival to hospital admission, favorable neurological survival (modified Rankin scale 0-3). • Unadjusted and adjusted analyses were similar • Adjusted analysis for IV administration – amiodarone vs placebo 1.26 (1.06,1.50), lidocaine vs placebo 1.21 (1.02,1.45); for IO NSD • Statistically significant interaction between route of vascular access and	• Effects of amiodarone and lidocaine were significantly greater for IV than IO route across all outcomes and beneficial only for the IV route • Study underpowered to statistically significant interactions

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			survival not evident (p=0.32) • Adjusted analysis for survival to hospital admission, survival with mRS ≤ 3 all showed significant benefit amiodarone vs placebo; lidocaine vs placebo; NSD for IO	
Benz P et al. Frequency of advanced cardiac life support medication use and association with survival during in-hospital cardiac arrest. ClinTher2020;42:121-129	• Retrospective single-center medical record review • n=181 in hospital cardiac arrest events	• Adults with in-hospital cardiac arrest between Jan 2017-March 2018	• 1° = frequency and quantity of medications used during resuscitation • 2° = median time to defibrillation, frequency of bicarbonate use • Use of meds: epinephrine 86.7% mean 4.2 mg; sodium bicarbonate 63.5% mean 9 grams (1.9 amps); amiodarone 30.9% mean 311.8 mg (70% of resuscitations with shockable initial rhythms). Lidocaine use surprisingly infrequent (<5% overall; 10% in shockable rhythms) • Amiodarone ROSC 0.63 (0.29,1.4); survival to discharge 0.94 (0.41, 2.16)	• Inconclusive for benefit of amiodarone on ROSC or survival to hospital discharge

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)
Wang CH et al. Outcomes associated with amiodarone and lidocaine for the treatment of adult in hospital cardiac arrest with shock-refractory pulseless ventricular tachyarrhythmia. J Formosan Med Assoc 2020;119:327-34	• Retrospective study single medical center of patients with in-hospital cardiac arrest with VF/pVT • n = 130 Multivariate logistic regression analysis included all available independent variables were considered in the regression model, regardless of whether they were scored as significant in the univariate analyses.	• In-hospital adult nontraumatic cardiac arrest 2006-2015 from VF/pVT requiring > 1 shock • n= 113 who received amiodarone or lidocaine during resuscitation • 86.9% received amiodarone as first AA Rx (median 300 mg) ; 17 received lidocaine first (median 100 mg)	• 1° outcome termination of VF/pVT within three shocks. Termination of VF/pVT was defined as its displacement to a nonshockable rhythm (organised or asystole). • 2° outcomes included sustained ROSC, survival for 24 h, survival to hospital discharge, and a favourable neurological outcome at hospital discharge. A favorable neurological status was defined as a score of 1 or 2 on the Cerebral Performance Category (CPC) scale Multivariate logistic regression analyses: • Amiodarone-first group experienced a higher likelihood of terminating the VF/pVT within three shocks (odds ratio: 11.61, (95% CI 1.34,100.84); p-value = 0.03), as compared with the lidocaine-first group	• Amiodarone-first strategy seemed to be associated with the termination of VF/pVT using fewer shocks • Other outcomes inconclusive due to small study size • Study flawed in that amiodarone or lidocaine were administered after the 3rd shock – whereas primary outcome was termination within 3 shocks.

Study Acronym; Author; Year Published	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results (include P value; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
			• No significant differences between the amiodarone- and lidocaine-first groups in sustained return of spontaneous circulation (1.03 (0.29,3.71), survival for 24 h (0.66 (0.10,4.37), survival to discharge (0.12 (0.01, 1.47), or favourable neurological outcomes at hospital discharge (0.28 (0.02, 3.42).	
Lee BK. Effect of Prophylactic Amiodarone Infusion on the Recurrence of Ventricular Arrhythmias in Out-of-Hospital Cardiac Arrest Survivors: A Propensity-Matched Analysis. J Clin Med 2019;8:244-53	• Retrospective, observational propensity-matched record review study from 4 tertiary care hospital prospective databases • n= 295 hospitalized OHCA from shockable arrhythmias + 149 with nonshockable-turned-shockable arrhythmias undergoing TTM • Assess effectiveness of prophylactic IV amiodarone in preventing ventricular arrhythmia recurrences	• n= 295 hospitalized OHCA from shockable arrhythmias + 149 with nonshockable-turned-shockable arrhythmias undergoing TTM • 124 propensity-matched patients received prophylactic IV amiodarone vs 320 did not	• 1° VT recurrence • 2° survival to discharge, neurological outcome (CPC 1-2) … • 50/444 patients (11.3%) had VT recurrence most commonly during TTM induction • Recurrence of ventricular arrhythmia significantly higher in prophylactic amiodarone group than in non-prophylactic amiodarone group in multivariate (nonpropensity) analysis (16.9% vs.	• Prophylactic amiodarone after successful resuscitation from cardiac arrest with initial shockable or subsequently occurring shockable rhythm was not associated with the prevention of recurrent ventricular arrhythmias during TTM, improving survival or neurological outcome • Likely highly biased amiodarone treatment group owed to multiple risk factors, resulting in a higher VT recurrence rate in adjusted analyses that resolved when propensity-adjusted.

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)
	during TTM (33 and 36°)		9.1%, p = 0.02); no difference in survival to discharge or neurological outcome • 93 patients in each group were propensity matched… with NSD in VT recurrence, survival or favorable neurological outcome	
Bellut H. Early recurrent arrhythmias after out-of-hospital cardiac arrest associated with obstructive coronary artery disease: Analysis of the PROCAT registry. Resuscitation. 2019 Aug;141:81-87.	Retrospective single centre study, Paris, France, cardiac arrest centre - between January 2007 and December 2016 in the 24-bed medical ICU at Cochin University Hospital (Paris, France).	256 patients with primary OHCA with VF/VT and coronary angiogram and admitted to ICU. 29 major arrhythmia vs. 227 without major arrhythmia. 36 (14%) patients received a prophylactic AA treatment at admission in the ICU (which was amiodarone in all cases), with no significant difference between the 2 groups (4/29 in the major arrhythmia group vs 32/227 in controls	In multivariate analysis, treatment with prophylactic anti-arrhythmic in the ICU was not associated with a change in the risk of recurrence (OR 0.85 [0.21–3.65], p = 0.82).	Early recurrence of major arrhythmia was observed in more than 10% of post-cardiac arrest patients. These events happened mostly within the first 24 h. Too few patients to state whether prophylaxis was helpful.
Other Antiarrhythmics or combinations				
Lian R et al. The first case series analysis on efficacy of esmolol injection	• Retrospective case series analysis of adult IHCA	• Adult IHCA with refractory shockable	• Efficacy assessment: sustained ROSC (≥20	• Success rates of sustained ROSC, 24 h ROSC, 72 h ROSC, and

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)
for in-hospital cardiac arrest patients with refractory shockable rhythms in China Front Pharmacol. 2022 Sep 30;13:930245	with refractory VF/pVT treated with esmolol – no control n = 29	rhythms (VF/pVT) persisting after ≥3 defibrillation attempts, who received esmolol during CA • n = 9, given esmolol ≤5 defibrillation attempts n = 20, given esmolol bolus after 5th defibrillation attempt	minutes), ≥24h ROSC, ≥72h ROSC, survival to hospital discharge • Sustained ROSC: 79% • ≥24h ROSC: 62% • ≥72h ROSC: 59% • Survival to hospital discharge: 59% No statistically significant difference between those administered esmolol bolus ≤5 defibrillation attempts and those given it after >5 defibrillations, in any measured outcome	survival to hospital discharge were 79%, 62%, 59%, and 59%. • Small study size Less benefit seen in patients with end-stage heart failure
Patrick C et al. Feasibility of prehospital esmolol for refractory ventricular fibrillation J Am Coll Emerg Physicians Open. 2022 Apr 9;3(2):e12700	• Retrospective observational analysis of esmolol for adult out-of-hospital cardiac arrest with refractory VF • n = 63 with cardiac arrest and refractory VF (control) n = 70 with cardiac arrest and RVF received single bolus 0.5mg/kg esmolol (intervention)	Adult out-of-hospital cardiac arrest with refractory VF who received ≥3 EMS defibrillations between June 2017 and June 2020	• 1° outcome: to assess 'feasibility' defined as >75% of patients meeting RVF criteria receiving prehospital esmolol • 2° outcome: ROSC during EMS encounter, 24h hospital survival, survival to hospital discharge • 38% patients who received	• 87% eligible patients with cardiac arrest and refractory VF received esmolol prehospitally • OR 1.99 (95% CI 0.89-4.47) of ROSC during EMS encounter for those who received esmolol, compared to those who did not. This was not statistically significant. • Small sample size • Lower proportion of patients received antiarrhythmics

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)
			esmolol achieved prehospital ROSC compared to 24% in the control group (p=0.09). 24h survival and survival to discharge were the same in both groups.	after the addition of esmolol to the protocol
Stupca K et al. Esmolol, vector change, and dose-capped epinephrine for prehospital ventricular fibrillation or pulseless ventricular tachycardia Am J Emerg Med. 2023 Feb;64:46-50.	• Retrospective, multicentre, cohort study of prehospital cardiac arrest with refractory VF/pVT • Patients receiving 'EMS bundle' – esmolol, vector change defibrillation, dose-capped epinephrine of 3mg – compared to standard ACLS care n = 83 patients	• Prehospital cardiac arrest with VF/pVT having received ≥3 defibrillations, ≥3 epinephrine and 300mg amiodarone. • n = 36, standard ACLS care n = 47, 'EMS bundle'	• 1° outcome: sustained ROSC (>20 mins without recurrence of cardiac arrest) • 2° outcome: incidence of ROSC, survival to hospital arrival, survival to hospital discharge and neurologically intact survival at hospital discharge • Those who received standard ACLS care achieved significantly higher rates of sustained ROSC (58.3% vs 17%, p < 0.001), any ROSC (66.7% vs 19.1%, p < 0.001), and survival to hospital arrival (55.6% vs 17%, p < 0.001)	• Those who received the EMS bundle achieved significantly less likely to achieve sustained ROSC or survive to hospital admission Neurologically intact survival rates were low and similar between groups

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)
			Survival to hospital discharge (16.7% vs 6.4%, p=0.17) and neurologically intact survival at hospital discharge (5.9% vs 4.3%, p=1.00) were not significantly different between groups	
Huebinger R Time to Antiarrhythmic and Association with Return of Spontaneous Circulation in the United States Prehosp Emerg Care. 2023;27(2):177-183.	• Retrospective observational analysis of national EMS database n = 11,939 patients	• Adult non-traumatic cardiac arrests with initial shockable rhythm and received an antiarrhythmic • n = 9236 received amiodarone n = 1327 received lidocaine	• Outcomes: time to antiarrhythmic administration, ROSC • Median time to initial amiodarone dose was 19.9 minutes (IQR 15.8-25.6) • Median time to initial lidocaine dose was 19.5 minutes (IQR 15.2-25.4) • Rate of ROSC higher for lidocaine (30.2%) than amiodarone (24.5%) Increased time to initial antiarrhythmic associated with decreased rates of ROSC for amiodarone (OR 0.9, 95% CI 0.9-0.94) and lidocaine (OR 0.9 95% CI 0.8-0.97)	Longer time to administration of antiarrhythmic associated with decreased rate of ROSC
Li DL et al.	• Retrospective analysis of	Adult inpatients receiving first-time	• 1° outcome: first	• Quinidine can be useful as a short-

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)
Quinidine in the Management of Recurrent Ventricular Arrhythmias: A Reappraisal JACC Clin Electrophysiol. 2021 Oct;7(10):1254-1263.	single tertiary centre of patients with in-hospital recurrent sustained ventricular arrhythmias n = 37 patients	quinidine for recurrent sustained ventricular arrhythmias (VT and VF)	recurrence of VA, ICD shock and repeated VA ablation (and/or other procedures for VA suppression) • 2° outcomes: death, orthotopic heart transplant • Quinidine reduced acute VA from median of 3 episodes (IQR 2-7.5) to 0 (IQR 0-0.5) during median 3 days before and 4 days after initiation ($p < 0.001$) • Decreased from median 10.5 episodes/day (IQR 5-15) to 0.5 (IQR 0-4) in those with electrical storm ($p=0.004$) Of those discharged on quinidine, 54.2% has VA recurrence, median 138 days.	term therapy in patients with recurrent VAs and structural heart disease • 24.3% patients experienced adverse effects that led to drug discontinuation. • Small cohort
Funakoshi H Nifekalant versus Amiodarone for Out-Of-Hospital Cardiac Arrest with Refractory Shockable	• Post-hoc analysis of nationwide, multi-centre observational study n = 1317	• Adult OHCA with refractory VF/pVT receiving nifekalant or amiodarone	• 1° outcome: admission after ROSC • 2° outcomes: 30 day survival, 30 day favourable	Nifekalant not associated with improved outcomes re admission after ROSC, 30 day survival or 30 day favourable neurological outcome

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)
Rhythms; a Post Hoc Analysis Arch Acad Emerg Med. 2022 Jan 1;10(1):e6.		after arrival to hospital • June 2014-December 2017 • n = 1275 received amiodarone n = 42 received nifekalant	neurological outcome (CPC 1 or 2) For nifekalant (compared to amiodarone): admission after ROSC (-5.9%, 95% CI -7.1 to 22.4, p =0.57), 30 day favorable neurological outcome (0.1%, 95% CI -14 to 13.9, p=0.99, 30 day survival (-3.9%, 95% CI -19.8 to 12, p=0.63)	when compared with amiodarone.
Huebinger R Procainamide for shockable rhythm cardiac arrest in the Resuscitation Outcome Consortium Am J Emerg Med. 2022 May;55:143-146	• Retrospective observational study evaluating procainamide for OHCA from the Resuscitation Outcomes Consortium n = 3087 patients	• Adult OHCA with initial shockable rhythm and received an antiarrhythmic from ROC Epistry 3 • n = 51 procainamide • n = 1776 amiodarone n = 1418 lidocaine	• Prehospital ROSC, ROSC at ED arrival, survival to hospital discharge • Compared to procainamide, amiodarone had similar prehospital ROSC (OR 0.7, 95% CI 0.3–1.8), ED ROSC (OR 0.6, 95% CI 0.3–1.3), and survival (OR 1.0, 95% CI 0.3–3.1). Lidocaine also had a similar prehospital ROSC (OR 0.9, 95% CI 0.4–2.2), ED ROSC (OR 1.2, 95% CI 0.5–2.7), and survival (OR 1.4, 95% CI 0.5–4.0)	While associated with increased prehospital ROSC when compared with amiodarone using multivariable regression, procainamide otherwise had similar prehospital ROSC, ED ROSC, and survival.
Viskin S et al. Quinidine-	• Retrospective observational	• n= 43 adults within days of uncomplicated	• 1° outcome termination of	• The specific form of polymorphic VT described (in

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)
Responsive Polymorphic Ventricular Tachycardia in Patients With Coronary Heart Disease. Circulation 2019;139:2304-14.	study of patients with polymorphic VT and coronary artery disease – no control • n= 43	AMI or coronary revascularization with polymorphic VT deteriorating to VF or storm who failed conventional AA Rx including amiodarone, lidocaine and Mg • n=23 had polymorphic VT/VF storm	polymorphic VT/VF storm • 17 of 23 patients in storm received quinidine (1200-2000 mg qd) responded vs 6 pts who received non-quinidine therapies (p<0.0001)	context of recent AMI or coronary revascularization) may be responsive to quinidine. • Study non-randomized • Benefit of quinidine may be limited to a specific ischemic patient group
Schupp T, et al. Prognostic impact of beta-blocker compared to combined amiodarone therapy secondary to ventricular tachyarrhythmias. Int J Cardiol 2019:277:118-124	A large retrospective registry analysis, propensity-score matching (before matching, n=1,354; after matching, n=372)	P: patients surviving at least one episode of ventricular tachyarrhythmias I: beta-blocker (before matching, n=1,144; after matching, n=186) C: beta-blocker with amiodarone (before matching, n=210; after matching, n=186) O: all-cause mortality T: from 2002 until 2016	BB associated with improved long-term survival compared to BB-AMIO (univariable: HR = 0.550; p = 0.001, multivariable: HR = 0.712; statistical trend, p = 0.052). After propensity-score matching, BB therapy was still associated with improved survival compared to BB-AMIO (mortality rate 18% versus 26%; log rank p = 0.042; HR = 0.634; 95% CI = 0.407-0.988; p = 0.044). Prognostic superiority of BB was mainly observed in patients with LVEF>= 35% (HR = 0.463; 95% CI = 0.215-0.997; p = 0.049) and in those without atrial fibrillation (non-AF)	BB therapy is associated with improved secondary long-term prognosis compared to BB-AMIO in patients surviving index episodes of ventricular tachyarrhythmias.

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)
			(HR = 0.415; 95% CI = 0.202-0.852; p = 0.017).	
Huang CH, et al. Acute hospital administration of amiodarone and/or lidocaine in shockable patients presenting with out-of-hospital cardiac arrest: A nationwide cohort study. Int J Cardiol 2017:227:292-298.	Retrospective, observational, and nationwide population-based cohort study, Nationwide registry analysis (Taiwan National Health Insurance Research Database (NHIRD))	P: patients with shockable cardiac arrest I: amiodarone (n=6,459), lidocaine (n=1,077), amiodarone with lidocaine (n= 1,487) C: placebo (non-treatment., n=18,440) O: 1-year survival; survival to intensive care unit (ICU) admission; survival to discharge T: from 2004 until 2011	Odds ratios for 1-year survival via multiple regression analysis were 1.84 (95% CI: 1.58-2.13; p<0.0001) for amiodarone, 1.88 (95% CI: 1.40-2.53; p<0.0001) for lidocaine, and 2.18 (95% CI: 1.71-2.77; p<0.0001) for dual agent use. The dual treatment group also surpassed the other groups in terms of survival to ICU admission (34.10%) and survival to discharge (12.25%) administration of anti-arrhythmic agents during resuscitation increased chances of survival to ICU admission and survival to discharge compared with non-treatment, with the highest ORs seen in the dual-agent (amiodarone and lidocaine) group.	In patients with shockable cardiac arrest, 1-year survival rates were improved with association of using amiodarone and/or lidocaine, as opposed to non-treatment. Outcomes of patients given one or both medications did not differ significantly in intergroup comparisons.

Reviewer Comments:

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

Specifically:

1. Review of interim evidence does not provide new data that would alter previous recommendations regarding use of lidocaine and amiodarone in shock-refractory VF/Pulseless VT.
2. Confidence in effect estimates remain low to support an ALS Task Force recommendation about the use of bretylium, nifekalant, or sotalol in the treatment of adults in cardiac arrest with shock-refractory VF/pVT.
3. Use of beta blockers (esmolol, propranolol, metoprolol) for this indication was not included in the 2018 treatment recommendations and this issue warrants a more detailed systematic review.
4. While bretylium has recently re-entered the market following its discontinuation in 1999, no new evidence has since emerged from earlier studies that would change prior guideline recommendations. Those recommendations previously indicated that bretylium should not be used as a first-line antiarrhythmic agent because of a high occurrence of side effects and the availability of safer agents at least as efficacious. More study of the drug is required. (Thind M. Bretylium, a class III antiarrhythmic, returns to the market. Am J Cardiol 2020;133:77-80.)
5. Three observational studies have specifically addressed the prophylactic use of lidocaine and amiodarone following out-of-hospital cardiac arrest, and do not provide sufficient evidence to alter previous recommendations (those indicated there was insufficient evidence to support any specific recommendations).
6. There are limited data on the use of combination drugs (amiodarone and lidocaine) as compared with amiodarone or lidocaine used singly for the treatment of VF/pVT, and these do not provide sufficient evidence to support any recommendations.
7. Use of drugs such as quinidine for unique ventricular rhythm presentations and associated genetic conditions remains mainly anecdotal or based on limited case series in selected patients with insufficient evidence to support any specific recommendations.
8. Procainamide is used in some EMS systems and was not addressed in our 2018 review – this could be part of a formal systematic review.

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2025 Evidence Update
ALS 3202 – Steroids for Cardiac Arrest

Worksheet Author(s): Tonia Nicholson
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / 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)?

Year of last full review: 2010 (but similar literature search done to address 2015 PICOST 433, and EvURs done in 2019, 2021 and 2023).

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
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."*
Consensus on Science: There were no human or animal studies that directly addressed the use of the estrogen, progesterone, insulin, or insulin-like growth factor in cardiac arrest. Early observational studies of the use of corticosteroids during cardiac arrest suggested possible benefit (LOE 4). One complex randomized pilot study (LOE 1) and 1 non-randomized human study (LOE 2) suggested benefit with corticosteroids, whereas 1 small, older, human prehospital controlled clinical trial suggested no benefit (LOE 1). One animal study of corticosteroids suggested possible benefit (LOE 5).

Search strategy for 2025
Databases searched: Pubmed / Cochrane Reviews**/**National Clinical Trails database
This search was time-limited from Sept 2022 (when last search for this PICO was done) to May 7th 2024 .

PubMed:
(heart arrest[MH] OR cardiopulmonary resuscitation[MH] OR heart massage[MH] OR advanced cardiac life support[MH] OR ventricular fibrillation[MH] OR heart massage[TW] OR heart arrest*[TW] OR cardiac arrest*[TW] OR OHCA[TW] OR IHCA[TW] OR CPR[TW] OR advanced cardiac life support[TW] OR ACLS[TW] OR asystole[TW] OR pulseless electrical activity[TW] OR pulseless ventricular tachycardia[TW] OR ventricular fibrillation[TW] OR chest compression*[TW] OR cardiopulmonary resuscitation[TW]) AND (adrenal cortex hormones[MH] OR adrenal cortex hormone*[TW] OR corticosteroid*[TW] OR glucocorticoid*[TW] OR methylprednisolone[TW] OR dexamethasone[TW] OR hydrocortisone[TW] OR prednisolone[TW] OR prednisone[TW] OR solu-medrol[TW] OR fludrocortisone[TW] OR florinef[TW])

Cochrane Central Register of Controlled Trials:
("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]).

International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.Gov:
The ICTRP was searched for *cardiac arrest AND glucocorticoids OR cardiac arrest AND corticosteroids OR cardiac arrest AND methylprednisolone OR cardiac arrest AND vasopressin*. To optimize sensitivity, an additional search was performed for the condition *cardiac arrest* and other terms *corticosteroids OR glucocorticoids OR methylprednisolone OR vasopressin* (filters: recruiting, not yet recruiting, active not recruiting, interventional study type) on ClinicalTrials.Gov.
Search Results (Number of articles identified / number identified as relevant):

PubMed	2,088	(3)[1-3]
Cochrane	21	(2)[2,3]

Trials Registry 15 (2)[4,5]
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.

Summary of Evidence Update:
Relevant Guidelines or Systematic Reviews – None

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

RCTs:

Study Acronym; Author; Yr 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
STEROHCA ;[2] Obling LER, Beske RP, Meyer MAS, Grand J, Wiberg S et al; 2023	To investigate the anti-inflammatory & neuroprotective effect of pre-hospital administration of a high-dose glucocorticoid following OHCA. Randomized, blinded, placebo-controlled, phase II prehospital multicentre clinical trial. N = 137 (68 in the intervention group, 69 in the placebo group)	Eligible patients were adults (≥18yrs) with OHCA of suspected cardiac aetiology, who remained unconscious(GCS≤ 8) following ROSC, & achieved ROSC for ≥ 5 min. Exclusion criteria were: ALS termination-of-resuscitation exclusion criteria, asystole as 1st monitored rhythm, women of childbearing age, previous decision of no resuscitation, known allergy to methylprednisolone, known pre-arrest modified Rankin Scale (mRS) score ranging from 4 to 5, temperature <	68 patients were randomized to receive a bolus injection of methyl-prednisolone 250 mg IV (2×125 mg/2ml) & 69 were randomised to receive placebo (4 mL isotonic NaCl) both administered over 5 min.	The co-primary outcome consisted of daily measurements of IL-6 and NSE from admission until 72 h from admission. The first IL-6 level was almost identical in the 2 groups (15 pg/mL [95% CI 10.4;21.6) vs 15pg/mL (10.4; 21.7), *p*=1), subsequently a reduction in IL-6 levels was seen in the intervention group with a significant treatment-by-time interaction, *p*< 0.0001. The intervention group exhibited significantly lower IL-6 levels at 24hrs compared to the placebo group 2.1pg/mL (1.3; 3.2) vs. 29.8 pg/mL (18.9;46.8) *p*<0.0001, but by 72hrs levels were similar (4.3 pg/mL (2.7;6.6) vs 3.4 pg/mL (2.2; 5.4),	Secondary outcomes included survival & neurological function at hospital d/c & after 180 days. Neurological function was defined by CPC score (range 1–5, with 3/4=severe disability, coma/vegetative state & 5=death) and mRS score (range 0–6; 0= no disability or dependence in daily activities & 6 = death) CPC and mRS at discharge were determined by retrospective chart review & at 180 days through telephone interview. After 180 days, 51 (75%) patients in the intervention

		30 °C upon randomization, or > 30 min to ROSC.		p= 0.51) There was no difference in NSE levels over time, *p*=0.22	group vs. 44 (64%) patients in the placebo group were alive (unadjusted hazard ratio 0.65 (0.35–1.2), *p* = 0.17, adjusted hazard ratio 0.35 (0.18-0.67), p=0.002 CPC & mRS-scores, evaluated at ≥ 180 days following OHCA, were similar in the two groups.

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**
A sub-study of STEROHCA ;[3] Obling LER, Beske RP, Meyer MAS, Grand J, Wiberg S et al; 2024	To investigate the haemodynamic effects of pre-hospital administration of a high-dose glucocorticoid in resuscitated comatose patients post OHCA. Randomized, blinded, placebo-controlled, phase II prehospital multicentre clinical trial. N = 114 (56 in the intervention group, 58 in the placebo group)	Eligible patients were adults (≥18 yrs), with OHCA of suspected cardiac aetiology, who remained unconscious (GCS ≤ 8) following ROSC, & survived until ICU admission. The exclusion criteria were: ALS termination-of-resuscitation exclusion criteria, asystole as 1st monitored rhythm, women of childbearing age, previous decision of no resuscitation, known allergy to methylprednisolone, known pre-arrest modified Rankin Scale (mRS) score ranging from 4 to	56 patients had been randomized to receive a bolus injection of methyl-prednisolone 250 mg IV (2×125 mg/2ml) & 58 had been randomised to receive placebo(4 mL isotonic NaCl), both administered over 5 min.	The primary outcome was cumulated norepinephrine use from ICU admission until 48 h reported as mcg/kg/min. From ICU admission up to 48 h post-admission, patients in the glucocorticoid group cumulated a lower norepinephrine use (mean difference - 0.04 mcg/kg/min, 95% CI - 0.07 to - 0.01, p = 0.02).	Secondary outcomes included hemodynamic status characterized by MAP, heart rate, vasoactive-inotropic score (VIS), the VIS/MAP-ratio, & cardiac function assessed by pulmonary artery catheter measurements . After 12-24 h post-admission, the treatment group had a higher MAP, mean differences from 6 to 7 mmHg (95% CIs from 1 to 12), a lower VIS (mean differences from - 4.2 to - 3.8, 95% CIs from - 8.1 to 0.3), and a lower

		5, temperature < 30 °C upon randomization, or > 30 min to ROSC.			VIS/MAP ratio (mean differences from - 0.10 to - 0.07, 95% CIs from - 0.16 to - 0.01), while there were no major differences in heart rate (mean differences from - 4 to - 3, 95% CIs from - 11 to 3). These treatment differences between groups were also present 30-48hr post-admission, but to a smaller extent with increased statistical uncertainty.

Nonrandomized Trials, Observational Studies - *None*

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:	

Clinical trials registry:

The search of International Clinical Trials Registry identified 2 trials actively recruiting patients, that may provide evidence relevant to this PICOST:

1) **NCT05139849 (VAST-A)**[4]

This is an in-hospital, randomized, placebo controlled, double blind, superiority, multi-centre clinical trial based in Gothenberg in Sweden, led by S. Forsberg & P. Lundgren. It commenced in 2021 (with a pilot phase), and is currently estimated for completion in 2027. Patients eligible for inclusion are those with IHCA arrest meeting criteria(s) for adrenaline administration according to current ERC guidelines. In addition to receiving adrenaline during the arrest, patients are randomized to treatment with either vasopressin and steroids (intervention) or sodium chloride (placebo) (control).

Subsequently, for those achieving ROSC and admitted to ICU, the intervention arm are given Hydrocortisone 3 mg/ml At 4hrs post ROSC, and then once daily. Surviving patients with post-resuscitation shock receive an infusion of 100 ml (300 mg hydrocortisone/ d) for ≤ 7 days. From day 8 post ROSC or when vasopressors are not needed the hydrocortisone dose is reduced daily to 67 ml (200 mg) and 33 ml (100 mg) and then discontinued). Patients with evidence of acute myocardial infarction receive an infusion of 100 ml (300mg hydrocortisone/d) for maximum 3 days to prevent retardation of infarct healing. The patients in the placebo group post-ROSC are given sodium chloride in the same manner.

Based on preliminary assumptions, to confirm or reject an increase in survival with the addition of the intervention from 9% to 14%, the aim is to enrol about 1400 patients in the study. The primary outcome is survival at 30 days.

2) **NCT05895838 (DOHCA Study)**[5]

This is a phase III trial, aiming to randomize 1000 patients at Danish cardiac arrest centres who are comatose post OHCA. Estimated for completion in 2027.
The aim is to evaluate 4 interventions in a factorial design addressing each in a randomized clinical trial:

1. Systemic inflammation: Anti-inflammatory treatment with high dose steroids (dexamethasone) or placebo.
2. Cerebral perfusion: Backrest elevation during sedation at 5 or 35 degrees.
3. Duration of sedation: Early wakeup call and potential extubation at ≤6 hours after admission or later as current standard practice at 28-36 hours.
4. Delirium: Prophylactic treatment with anti-psychotic medication (olanzapine) or placebo

The primary endpoint is 90 days all-cause mortality for the interventions targeting systemic inflammation and cerebral perfusion. (It is days alive outside of hospital within 30 days for the interventions concerning duration of sedation and delirium)

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
Evidence update reviews in 2020, 2021 and 2023 did not identify sufficient new evidence to suggest that a new scoping or systematic review regarding post-ROSC administration of steroids was indicated. This EvUR has identified one new RCT and a sub-study of it, comparing the effects of the administration of methylprednisolone and saline to resuscitated comatose patients post OHCA. There was no statistically significant difference in either survival or neurological outcome between the intervention and placebo groups.
Two further RCTs have been identified in the International Trials Registry which may provide further evidence on the effects of administration of post-ROSC steroids in resuscitated comatose patients post OHCA, but not until at least 2027.
It would therefore seem prudent to avoid doing another scoping or systematic review on this topic until the trails in the International Trials Registry have been completed.

Reference list:
1) Obling LER, Beske RP, Wiberg S, Folke F, Moeller JE, Kjaergaard J, Hassager C. Steroid treatment as anti-inflammatory and neuroprotective agent following out-of-hospital cardiac arrest: a randomized clinical trial. Trials. 2022 Nov 22;23(1):952. doi: 10.1186/s13063-022-06838-0. PMID: 36414975; PMCID: PMC9682762.

2) Obling LER, Beske RP, Meyer MAS, Grand J, Wiberg S, Nyholm B, Josiassen J, Søndergaard FT, Mohr T, Damm-Hejmdal A, Bjerre M, Frikke-Schmidt R, Folke F, Møller JE, Kjaergaard J, Hassager C. Prehospital high-dose methylprednisolone in resuscitated out-of-hospital cardiac arrest patients (STEROHCA): a randomized clinical trial. Intensive Care Med. 2023 Dec;49(12):1467-1478. doi: 10.1007/s00134-023-07247-w. Epub 2023 Nov 9. PMID: 37943300; PMCID: PMC10709228.

3) Obling LER, Beske RP, Meyer MAS, Grand J, Wiberg S, Nyholm B, Josiassen J, Søndergaard FT, Mohr T, Damm-Hejmdal A, Bjerre M, Frikke-Schmidt R, Folke F, Møller JE, Kjaergaard J, Hassager C. Effect of prehospital high-dose glucocorticoid on hemodynamics in patients resuscitated from out-of-hospital cardiac arrest: a sub-study of the STEROHCA trial. *Critical Care (2024) 28:28.* doi.org/10.1186/s13054-024-04808-3

5) VAsopressin and STeroids in Addition to Adrenaline in Cardiac Arrest - a Randomized Clinical Trial. https://clinicaltrials.gov/show/NCT05139849.

6) Steroid Treatment as Anti-inflammatory and Neuroprotective Agent Following Out-of-Hospital Cardiac Arrest. A Randomized Trial.
https://clinicaltrials.gov/show/NCT04624776.

2025 Evidence Update
ALS 3404 – Drugs for Torsades De Pointes

Worksheet Author(s): Mathias J. Holmberg
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / Research Question:
In adult patients with Torsades De Pointes (P), does the use of any drug or combination of drugs (I) compared with not using drugs or alternative drugs (C), improve outcomes (O) (ROSC, survival, or survival with favorable neurological outcome).

Year of last full review: 2010 (the last Evidence Update was performed in 2021)
Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
Polymorphic wide-complex tachycardia associated with familial long QT may be treated with IV magnesium, pacing, and/or beta blockers; however, isoprenaline should be avoided.
Polymorphic wide-complex tachycardia associated with acquired long QT may be treated with magnesium. Addition of pacing or IV isoprenaline may be considered when polymorphic wide-complex tachycardia is accompanied by bradycardia or appears to be precipitated by pauses in rhythm.

Current Search Strategy:
("torsades de pointes"[MeSH Terms] OR "torsade*"[All Fields] OR ("torsades"[All Fields] AND "de"[All Fields] AND "pointes"[All Fields]) OR "torsades de pointes"[All Fields] OR (("polymorphic"[All Fields] OR "polymorphics"[All Fields] OR "polymorphism s"[All Fields] OR "polymorphism, genetic"[MeSH Terms] OR ("polymorphism"[All Fields] AND "genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields] OR "polymorphisms"[All Fields]) AND ("tachycardia, ventricular"[MeSH Terms] OR ("tachycardia"[All Fields] AND "ventricular"[All Fields]) OR "ventricular tachycardia"[All Fields] OR ("ventricular"[All Fields] AND "tachycardia"[All Fields]))) OR ("catecholaminergic"[All Fields] AND ("tachycardia"[MeSH Terms] OR "tachycardia"[All Fields] OR "tachycardia*"[All Fields]))) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therap*"[All Fields] OR "treatment*"[All Fields])

Observational studies and RCTs in humans were considered.

Database searched: PubMed
Time Frame: May 2, 2021, to February 10, 2024
Date Search Completed: February 10, 2024
Search Results (Number of articles identified and number identified as relevant): 488 identified and 0 included
The search strategy yielded 488 records, 3 full-text articles were reviewed, and 0 articles identified as relevant.
Summary of Evidence Update: No new evidence was identified on this topic.
Relevant Guidelines or Systematic Reviews: Not applicable.
Reviewer Comments: ***(including whether this PICOST should have a systematic or scoping review*****)**
A total of 488 records were screened, 3 full-text articles were reviewed, and 0 articles were included. The 3 full-text articles were anecdotal case reports. Two described the use of isoproterenol to terminate Torsades De Pointes and one described the use of mexiletine to prevent recurrent Torsades De Pointes. None of the studies met the inclusion criteria for this evidence update.

Reference list:
Soar J et al. Adult Advanced Life Support: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation. 2020 Nov; 156: A80-A119. PMID: 33099419

2025 Evidence Update
ALS 3501 – PCI after ROSC without ST-Elevation

Worksheet Author(s): Nikolaos Nikolaou
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / Research Question:

PICOST Short Title: ***PCI post ROSC***	***PICOST: Early Coronary Angiography Post-ROSC***

1. ***Research Question based on PICOST***
   (Population, Intervention, Control, Outcomes, Study design and Timeframe)

PICOST	***Description***
Population	***Unresponsive adults (> 18 years old) with return of spontaneous circulation (ROSC) after cardiac arrest***
Intervention	***Emergent or early coronary angiography (CAG) with percutaneous coronary intervention (PCI) if indicated***
Comparison	***Delayed CAG or no CAG.***
Outcomes	***Any clinical outcome.***
Study Design	***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.***
Timeframe	***All years and all languages are included as long as there is an English abstract***

The full document for the approved PICO is attached.

Year of last full review: (*insert year where this PICOST was most recently reviewed):* April 2024.

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

When coronary angiography is considered for comatose post-arrest patients without ST elevation, we suggest that either an early or delayed approach for angiography is reasonable. (weak recommendation, low-certainty evidence)

We suggest performing early coronary angiography in comatose post-cardiac arrest patients with ST-segment elevation. (good practice statement)

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

#	Searches
1	exp Heart Arrest/
2	((heart or cardiac or cardiovascular) adj1 arrest*).ab,kf,ti.
3	post arrest patient*.ab,kf,ti.
4	asystole.ab,kf,ti.

5	((cardiopulmonary or cardio-pulmonary) adj1 arrest*).ab,kf,ti.
6	code blue.ab,kf,ti.
7	respiratory arrest*.ab,kf,ti.
8	(Cardiac Arrest adj2 Registr*).ab,kf,ti.
9	pulseless electrical activity.ab,kf,ti.
10	(spontaneous circulation or Return of circulation).ab,kf,ti.
11	ROSC.ab,kf,ti.
12	Advanced Cardiac Life Support.ab,kf,ti.
13	ACLS.ab,kf,ti.
14	exp Cardiopulmonary Resuscitation/
15	ventricular fibrillation/
16	resuscitation/
17	((cardiopulmonary or cardio-pulmonary) adj1 resuscitation).ab,kf,ti.
18	CPR.ab,kf,ti.
19	reanimation.ab,kf,ti.
20	(post resuscitation or postresuscitation).ab,kf,ti.
21	or/1-20
22	((early or earlier or earliest or immediate* or emergent or emergency or late or later or delay* or time or timing or timely or hours or prompt or promptly or urgent*) adj1 (Coronary or heart or cardiac) adj1 Angiograph*).ab,kf,ti.
23	((early or earlier or earliest or immediate* or emergent or emergency or late or later or delay* or time or timing or timely or hours or prompt or promptly or urgent*) adj1 (Coronary or heart or cardiac) adj1 intervention*).ab,kf,ti.
24	((early or earlier or earliest or immediate* or emergent or emergency or late or later or delay* or time or timing or timely or hours or prompt or promptly or urgent*) adj1 (Coronary or heart or cardiac) adj1 angiogram*).ab,kf,ti.
25	((early or earlier or earliest or immediate* or emergent or emergency or late or later or delay* or time or timing or timely or hours or prompt or promptly or urgent*) adj1 revasculari?ation).ab,kf,ti.
26	(Percutaneous adj1 (Coronary or Intervention* or revasculari?ation or Stent*)).ab,kf,ti.
27	exp *Percutaneous Coronary Intervention/
28	exp *Cardiac Catheterization/
29	((heart or cardiac or coronary) adj1 (catheteri?ation or intervention*)).ab,kf,ti.
30	Coronary Angiography/
31	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	21 and 31
33	Animals/ not (Animals/ and Humans/)
34	32 not 33
35	(exp Infant/ or exp Pediatrics/ or exp CHILD/) not exp Adult/
36	34 not 35
37	(case reports or comment or editorial).pt.
38	36 not 37
39	case report.m_titl.
40	38 not 39

41	limit 40 to yr="1990 -Current"
42	Extracorporeal Membrane Oxygenation/
43	Extracorporeal Membrane Oxygenation.ab,ti.
44	ECMO.ab,ti.
45	IMPELLA.ab,ti.
46	42 or 43 or 44 or 45
47	41 not 46
48	("20190719" or 2019072* or 2019073* or 201908* or 201909* or 201910* or 201911* or 201912* or 2020*).dt,ez,da.
49	47 and 48

Search Strategy:
Database searched: Medline
Time Frame: (existing PICOST) – updated from end of last search: Jan 8 2022, April 5 2024
Time Frame: (new PICOST) – at the discretion of the Task Force (please specify)
Date Search Completed: April 5 2024
Search Results (Number of articles identified and number identified as relevant): identified 336, relevant 3

Summary of Evidence Update:
Relevant Guidelines or Systematic Reviews

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
ESC; Robert A. Byrne et al; 2023	2023 ESC Guidelines for the management of acute coronary syndromes	OHCA in ACS			Routine immediate angiography after resuscitated cardiac arrest is not recommended in haemodynamically stable patients without persistent ST-segment elevation (or equivalents) (Class III, LOE: A) A PPCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG with persistent ST-segment elevation (or equivalents) (Class I, LOE B)
1. Rashid 2024	Early coronary angioplasty fails to lower all-cause	Effect of early CAG on mortality and neurological	Total:18 studies. RCTs: 6,	Primary Outcome 30-day mortality: early	Performing emergency CAG fails to reduce mortality and improve neurological outcomes in

	mortality in patients with out-of-hospital cardiac arrest without ST-segment elevation: A systematic review and meta-analysis.	outcomes in OHCA patients without ST-elevation	Observational: 12. RCTs: Lemkes 2019, Elfwen 2019, Kern 2020, Desch 2021, Hauw Berlemont 2022, Patterson 2017	CAG (≤2 h) vs. delayed CAG (>2 h) (relative risk [RR]: 1.57, 95% CI: 0.84–2.93 The effect of RCTs:RR: 0.90, 95% CI: 0.71–1.13 30-day mortality: early CAG (within 24 h) of OHCA vs. late CAG (after 24 h), RR: 0.86, 95% CI: 0.62–1.19	patients with OHCA without ST elevations on post- ROSC ECG. Therefore, in this cohort of patients, early CAG should not be a preferred approach while evaluating and managing the cause of OHCA, and nonemergent delayed CAG should be performed to look for a cardiac cause of OHCA.
2.Hamidi 2024	Early versus delayed coronary angiography in patients with out-of-hospital cardiac arrest and no ST-segment elevation: a systematic review and meta-analysis of randomized controlled trials.	To pull data from all RCTs that compared an early/immediate vs. a delayed/ selective strategy in OHCA patients without ST-segment elevation	5 RCTs, 1512 patients, follow-up of at least 30 days Lemkes 2019, Kern 2020, Desch 2021, Hauw Berlemont 2022, Viana Tejedor 2022	Primary outcome of interest: all-cause death Early/immediate 48.3% vs. delayed/selective CAG 45.6% OR 1.12 [95%-CI 0.91-1.38] All cause death or neurologic injury: OR 1.1 [95% CI 0.89-1.36] No significant differences in safety events including bleeding OR 0.94 [95%CI 0.52-1.70]and kidney events OR 1.13 [95%CI 0.75-1.70]	No significant difference between immediate/early CAG vs. delayed/selective CAG regarding all-cause mortality or neurologic impairment
3.Costa 2024	Coronary angiography after out-of-hospital cardiac arrest without ST-segment	To compare an early CAG versus delayed CAG strategy in OHCA patients	7 RCTs,1625 patients Patterson 2017, Lemkes 2019, Elfwen	Primary endpoints: All-cause mortality for an early CAG vs. delayed CAG group (pooled	In patients experiencing OHCA without ST elevation, early CAG was not associ- ated with reduced mortality or an improved neurological status.

	elevation: a systematic review and meta-analysis of randomised trials.	without ST elevation.	2019, Kern 2020, Desch 2021, Hauw Berlemont 2022, Viana Tejedor 2022	OR, 1.22 95% CI [0.99–1.50], P = 0.06; I2 = 0%) *Subgroup analysis* 180-day survival: pooled OR, 1.15; 95% CI [0.77–1.72] 30-day survival: OR 1.21 [95% CI 0.90–1.62] Secondary Outcomes: Neurologic Status: pooled OR 0.94 [0.74–1.21], *P* = 0.65, need for RRT (pooled OR 1.11 [0.78–1.74], *P* = 0.47), major bleeding events (pooled OR 0.97 [0.56–1.69], *P* = 0.92,) and primary coronary intervention (pooled OR 1.51 [0.95–2.40], *P* = 0.08).	
4.Al Lawati 2023	Early Versus Delayed Coronary Angiography After Out-of-Hospital Cardiac Arrest Without ST-Segment Elevation-A Systematic Review and Meta-Analysis of Randomized Controlled Trials.	To evaluate the efficacy and safety of early angiography versus delayed angiography following OHCA without ST elevation	Six RCTs, 1.590 patients Lemkes 2019, Elfwen 2019, Kern 2020, Desch 2021, Hauw Berlemont 2022, Viana Tejedor 2022	Mortality at the longest follow-up: RR 1.04; 95% CI 0.94–1.15; moderate certainty Survival with good neurologic outcome (CPC score) :RR 0.97 (95% CI 0.87–1.07) ICU LOS (MD 0.41 d fewer; 95% CI –1.3 to 0.5 d; duration of mechanical ventilation (MD 0.29 d fewer; 95% CI –1.2 to	Early angiography probably has no effect on mortality. Early an-giography may have no effect on survival with good neurologic outcome, hospital LOS, and ICU LOS and has an uncertain effect on most adverse events.

				0.6 d; hospital LOS (MD 0.82 d fewer; 95% CI –3.9 to 2.3 d , major bleeding (RR 0.95, 95% CI 0.55–1.62; acute kidney injury (RR 1.18, 95% CI 0.33–4.20; need for RRT RR 1.10 [95% CI 0.78–1.57], ventricular arrhythmia RR 0.75, [95% CI 0.30–1.90]	
5.Goel 2023	Early versus deferred coronary angiography following cardiac arrest. A systematic review and meta-analysis.	to assess the impact of early versus deferred CAG on mortality and neurological outcomes in patients with OHCA and no STE.	5 RCTs, 1524 patients Lemkes 2019, Elfwen 2019, Kern 2020, Desch 2021, Hauw Berlemont 2022	Primary endpoint: 30-day mortality Early versus deferred CAG: OR 1.17, (CI 0.91 - 1.49) Secondary outcomes: Early versus deferred CAG Mortality at hospital discharge: OR 1.11, [CI 0.87 – 1.42]; good neurological outcome (CPC score of 1 or 2) at 30 days: OR 0.88, [CI 0.52 – 1.49]; major bleeding : OR 0.97, [CI 0.34 – 2.77] renal failure requiring RRT OR 1.14, CI 0.77 – 1.69	There is no significant difference in 30-day mortality and neurological outcomes in patients with OHCA and no STE treated with an early CAG strategy compared with a deferred strategy. These findings do not support an early invasive strategy for hemodynamically stable OHCA patients without STE
6.Gupta 2023	Early Coronary Angiography in Patients With Out-of-Hospital	This study aimed to compare early and nonearly CAG in this population, in	16 studies (7 RCTs) including 5234 cases	In-hospital mortality Early vs. late CAG: RR, 0.79; 95% [CI, 0.65-0.97; P = 0.02]; however,	The study concluded that in patients with OHCA without STEMI, early CAG might be beneficial in terms of in-hospital and mid-term mortality.

	Cardiac Arrest Without ST-Segment Elevation: A Systematic Review, Meta-Analysis, and Comparative Analysis of Studies	addition to the identification of differences between randomized controlled trials (RCTs) and observational studies conducted in this regard.	RCTs: Patterson 2017, Lemkes 2019, Elfwen 2019, Kern 2020, Desch 2021, Hauw Berlemont 2022, Viana Tejedor 2022	RCT studies did not find a statistical difference in this outcome RR, 1.01; [95% CI, 0.83-1.23; P = 0.91]. Mid-term mortality rates were lower in the early-CAG group (RR, 0.87; 95% CI, 0.78-0.98; P = 0.02), mostly due to observational studies.	However, these findings were not repeated in a subgroup of RCTs. There were several differences between RCTs and registry studies (comorbidities, bleeding). Current evidence from RCTs may not be representative of real-world patients and should be interpreted within its limitation.
7.Shoaib 2023	Effectiveness of Emergency versus Nonemergent Coronary Angiography After Out-of-Hospital Cardiac Arrest without ST-Segment Elevation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.	To investigate the effectiveness of emergency CAG versus delayed CAG in OHCA patients with a non-ST-segment elevated rhythm	Nine RCTs, 2,569 patients Patterson 2017, Lemkes 2019, Elfwen 2019, Kern 2020, Lemkes 2020, Desch 2021, Hauw Berlemont 2022, Viana Tejedor 2022, Lemkes 2021	Primary end point: survival with a good neurological outcome Emergency CAG versus delayed CAG: RR 0.96, [95% Confidence Interval 0.87, 1.06], p=0.52 No benefit in terms of secondary outcomes: short term survival (RR = 0.98, 95% CI = 0.89, 1.08; p = 0.29 mid-term survival (RR = 0.98, 95% CI = 0.87, 1.10; p = 0.86), recurrence of arrhythmias (RR = 1.02, [95% CI = 0.50, 2.06; p = 0.96)], MI: RR = 0.66, [95% CI = 0.13, 3.30; p = 0.46]; Major bleeding RR=0.96,[95%CI	In the NSTEMI OHCA, an emergency CAG strategy offers no significant improvement in the overall prognosis of the patients

				=0.55,1.69;p=0.42], AKI RR = 1.20, [95% CI = 0.32, 4.49; p = 0.18]	
8.Kundu, 2023	Immediate vs Delayed Coronary Angiography for Out-of-Hospital Cardiac Arrest A Meta-Analysis of Randomized controlled trials	Filling knowledge gaps regarding CAG post ROSC in patients without ST-segment elevation	Four RCTs, 1,446 patients, that assessed short-term (#180 days) outcomes with immediate vs delayed angiography for OHCA survivors who did not have evidence of STEMI on presentation	All-cause mortality: Immediate CAG: 54.5%, Delayed CAG: 51%.4, OR: 1.14; [95% CI: 0.91-1.44] Favourable Neurologic Outcome: Immediate CAG: 56.6%, Delayed CAG: 58% OR: 0.97 (95% CI 0.75-1.25) Frequency of PCI (OR: 1.02; 95% CI: 0.71-1.45). Major bleeding (OR: 0.98; 95% CI: 0.38-2.53; I2 1⁄4 43%)	There is no established benefit in short-term outcomes with im-mediate CAG for OHCA survivors who present without evidence of STEMI on postresuscitation electrocardiography.
9.Heyne, 2023	Coronary angiography after cardiac arrest without ST-elevation myocardial infarction: a network meta-analysis	To assess the effect of early coronary angiography (CAG) compared with selective CAG (late and no CAG) for patients after out-of-hospital cardiac arrest without ST-elevation myocardial infarction	16 studies (6 RCTs, 10 NRS) comparing the effect of early CAG to selective CAG after NSTE-OHCA on survival and/or neurological outcomes were included. Patterson 2017, Patterson 2017, Lemkes 2019, Elfwen 2019, Kern 2020, Desch 2021, Hauw	Overall analysis: early CAG vs. selective CAG [OR: 1.40, 95% confidence interval (CI): (1.12–1.76), P < 0.01. This effect was lost in the subgroup analysis of RCTs [OR: 0.89, 95% CI: (0.73–1.10), P = 0.29, I2 = 0%] Random effects model network meta-analysis of NRS based on a Bayesian method showed statistically sig-nificant increased	Randomized controlled trials did not show a prognostic benefit regard- ing survival and neurological outcome after early CAG compared with selective late CAG in NSTE-OHCA patients. In summary, the results of this meta-analysis do not support routinely performing early CAG in survivors of NSTE-OHCA. Whether selected patients might still benefit from early CAG remains unclear and needs to be evaluated in future RCTs.

			Berlemont 2022, Viana-Tejedor 2022	survival after late compared with early CAG [OR: 4.20, 95% CI: (1.22, 20.91)].	
10.Bavishi 2022	Meta-Analysis of Early Versus Delayed or Selective Coronary Angiography in Patients With Out-of-Hospital Cardiac Arrest Without ST-Elevation Myocardial Infarction	To perform a meta-analysis of all randomized con- trolled trials (RCTs) on the role of early coronary angiography in patients with OHCA, without ST-segment elevation.	5 RCTs, 1281 patients Patterson 2017, Lemkes 2019, Elfwen 2019, Kern 2020, Desch 2021,	Early CAG was associated with similar short-term mortality (pooled OR 1.18, 95% CI 0.94 to 1.48), 6-month or 1-year all- cause mortality (OR 1.05, 95% CI 0.76 to 1.44), neurological recovery (OR 0.91, 95% CI 0.68 to 1.21), bleeding (OR 0.99, 95% CI 0.57 to 1.74), and need for RRT (OR 1.10, 95% 0.73 to 1.66)	Evaluating early versus delayed/ selective coronary angiography in patients with OHCA without STEMI, we found no difference in all-cause mortality or neuro- logic recovery between the 2 strategies. Early coronary angiography in patients with OHCA and no STEMI does not confer any meaningful benefit and can be delayed on the basis of the overall clinical or neurologic recovery.
11.Hamed , 2022	Meta-Analysis on Early Versus Delayed Coronary Angiography for Patients With Out-of-Hospital Cardiac Arrest Without ST-Elevation Myocardial Infarction	Meta-analysis of ran-domized controlled trials (RCTs) to evaluate the role of early coronary angiography in patients with OHCA without STEMI.	6 RCTs, 1544 patients Patterson 2017, Lemkes 2019, Elfwen 2019, Kern 2020, Desch 2021, Hauw Berlemont 2022, Lemkes 2020	Short-term all-cause mortality between early and delayed CAG groups (42.6% vs 38.9%; risk ratio [RR] 1.10; 95% confidence interval [CI] 0.97 to 1.26) Early CAG group and delayed angiography group,long-term all-cause mortality (48.4% vs 48.5%; RR 0.98; 95% CI 0.87 to 1.11), coronary revascularizatio n (RR 1.00; 95%	Our study highlights the small number of available trials, and further studies are warranted with larger sample size to better address that clinical question.

				CI 0.76 to 1.31), neurologic recovery (RR 1.00; 95% CI 0.89 to 1.12), bleeding (RR 0.92; 95% CI 0.53 to 1.61), AKI requiring RRT (RR 1.19; 95% CI 0.81 to 1.73), and incidence of stroke (RR 0.80; 95% CI 0.26 to 2.46)	
12.Kiyohara 2022	Immediate coronary angiography in patients with out-of-hospital cardiac arrest without ST-segment elevation: a meta-analysis of randomized trials	To investigate the benefit of immediate coronary angiography in patients without STE following OHCA.	6RCTs, 1589 patients Patterson 2017, Lemkes 2019, Elfwen 2019, Kern 2020, Desch 2021, Hauw Berlemont 2022	Immediate CAG had similar all-cause mortality compared with those with delayed CAG, [RR (95% CI): 1.04 (0.94 – 1.15]. No significant improvement in patients that had immediate CAG neurological outcomes [RR (95% CI): 1.04 (0.94 – 1.15]. No significant difference in the number of patients who underwent PCI between the two groups, RR (95% CI): 1.27 [0.92 – 1.75]	This analysis demonstrated no significant difference between patients with immediate and delayed angiography in mortality, neurological outcomes, or the rate of PCI
13.Alves 2022	Impact of emergent coronary angiography after out-of-the-hospital cardiac arrest without ST-segment	To assess the impact of emergent CAG(<2h) vs standard of care (ie CAG >2 h after OHCA or not performed) in	Five studies (1278 patients) Patterson 2017, Lemkes 2019, Elfwen 2019, Kern	Primary end point: Short-term survival (57 vs 61%; OR 0.85, [95% CI 0.68-1.07] No significant differences for	Routine emergent CAG did not improve survival in comatose survivors of OHCA with shockable rhythm and no-STE.

	elevation - A systematic review and meta-analysis.	no-STE OHCA patients	2020, Desch 2021	any of the secondary endpoints: survival with good neurological outcome (OR 0.84 [95%CI 0.67-1.07], mid-term survival OR 0.89 [95% CI 0.63-1.25], normal left ventricle EF OR 0.88 [95%CI 0.54-1.44], acute kidney injury OR 0.85 [95%CI 0.49-1.47], need for RRT OR 1.1 [95%CI 0.73-1.65], (recurrence of) ventricular arrhythmias OR 1.23 [95%CI 0.64-2.23]and major bleeding OR 0.60 [95%CI [0.25-1.44]	

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**
EMERGE; Hauw-Berlemont;2022	Study Aim: To assess the 180-day survival rate with CPC 1 or 2 of patients who experience an OHCA without ST-segment elevation on ECG and	279 patients included Inclusion Criteria: patients >18 years with ROSC after OHCA, without an obvious noncardiac cause of arrest, admitted to a	Intervention: Patients allocated to the emergency CAG group were transferred directly to the catheterization laboratory. Comparison:	1° endpoint: Primary study outcome: 180-day survival rate with no or minimal neurologic sequelae. 180-day survival rates with CPC 1 or 2: emergency CAG group 34.1% (47 of 141);	**Study Limitations:** Preplanned sample size was not achieved, and thus, the EMERGE study was underpowered to adequately assess the primary and secondary end points.

	undergo emergency CAG vs delayed CAG Study Type: A national, multicenter, randomized open-label parallel-group trial. Patients were randomly assigned (1:1) to either emergency CAG or delayed CAG (within 48 to 96 hours).	center withan intensive care unit and a 24/7 interventional cardiology department. Exclusion criteria: age< 18 years, in-hospital cardiac arrest, no ROSC, ST-segment elevation, 15 suspected noncardiac etiology, comorbidities with life expectancy of <1 year, pregnancy, adults subject to a legal protection measure (guardianship or curatorship), and participation in another interventional trial	Patients randomly assigned to the delayed CAG group were admitted to the intensive care unit, and a CAG was planned 48 to 96 hours after admission	delayed CAG group 30.7% (42 of 138) in the (HR, 0.87; 95% CI, 0.65- 1.15; P =.32) Overall survival rate at 180 days: emergency CAG, 36.2% [51 of 141] vs delayed CAG, 33.3% [46 of 138]; HR, 0.86; 95% CI, 0.64-1.15; P = .31) No differences in all secondary end points: CPC 1,2 at 90 days [HR 0.64 (95%CI 0.64-1.14), p=0.29], Occurrence of shock [1.03 (95% CI 0.76-1.39), p=0.86], Occurrence of VT/VF in<48 h [HR 0.51 (95%CI 0.18-1.40), p=0.21], LVEF at 180 d [emergency CAG median EF 60% IQR (50-63); delayed CAG median EF 57.5 IQR (51-60), p=0.26], Evolution of LVEF from baseline to 180 d [emergency CAG median dEF 10.5 IQR (0-24); delayed CAG median dEF 9.5 IQR (1.5-18), p=0.94] , length of hospital stay emergency CAG median 7 days IQR (2-13 days); delayed CAG	The physicians were not blinded to randomized treatment allocation but were not involved in the research process. Determination of culprit lesions is subjective, and the angiograms were not analyzed by a core laboratory. The echocardiograms and the follow-up visits, including neurologic assessment, were not evaluated by a core laboratory.

				median 5 days IQR(1-11 days), p=0.75], withdrawal of care OR 1.19 [95% CI (0.91-1.55)], p=0.22	
COUPE; Viana-Tejedor; 2023	Study Aim: to assess whether emergency CAG and PCI would improve survival with good neurological outcome following out-of-hospital cardiac arrest (OHCA) in patients without ST-segment elevation myocardial infarction (STEMI) Study Type: A prospective, multicenter, randomized open-label, investigator-initiated clinical trial comparing the efficacy of emergency vs deferred CAG in survivors of an OHCA without STEMI	69 patients were included Inclusion Criteria: Patients were eligible if they had ROSC within 60 minutes, remained in coma,and had an electrocardiogram without STEMI or LBBB. Both shockable and nonshockable rhythms were included. Obvious noncoronary etiology of the cardiac arrest was ruled out prior to randomization. Cranial computed tomography and echocardiography were performed for this purpose Exclusion Criteria Age < 18 y, Pregnant women, women of childbearing age unless they have a negative pregnancy test.	Intervention: In the immediate CAG group, coronary angiography was performed as soon as possible within 2 hours after hospital admission and randomization. Comparison In the delayed CAG group, coronary angiography was performed after neurological recovery, when the patient was extubated, in general before being discharged from the intensive cardiac care unit.	1° endpoint: In-hospital survival free of severe dependence: immediate angiography group: 59.4%; delayed angiography group 52.9% (HR, 1.29; 95%CI, 0.60-2.73; P = .4986). In-hospital survival was 62.5% in the immediate angiography group and 58.8% in the delayed angiography group (HR, 0.96; 95%CI, 0.45-2.09; P = .9262). There were also no differences related to in-hospital major adverse cardiac events including death, reinfarction, bleeding and ventricular arrhythmias (primary safety endpoint) between the 2 groups. No differences were found in any of the other secondary endpoints except for the incidence	Study Limitations: The target sample size was not reached, statistical power was 63.3% and therefore all results should be considered as exploratory. The physicians were not blinded to randomized treatment allocation, but they were not involved in the analysis process. The results do not apply to patients with in-hospital cardiac arrest, ST-segment elevation, left bundle branch block or hemodynamic instability

		Time to ROSC > 60 min. Noncardiac etiology of the comatose state: drug overdose, head injury, or stroke Signs of STEMI or LBBB on the ECG, Hemodynamic instability (refractory cardiogenic shock despite vasoactive drugs or refractory arrhythmias) Known coagulopathy or bleeding Refusal to participate in the study by the next of kin		of acute kidney failure, which was more frequent in the immediate CAG group (15.6% vs 0%, P = .002) and infections, which were higher in the delayed CAG group (46.9% vs 73.5%, P = .003).	
TOMAHAWK 1-year; Desch 2023	Study Aim: To compare the clinical outcomes of early unselective angiography with the clinical outcomes of a delayed or selective approach for successfully resuscitated patients with OHCA of presumed cardiac origin without ST-segment	Patient Population 554 patients Included: Age ³ 30 years, OHCA, Possible cardiac origin, No ST-segment elevation, shockable and nonshockable arrest rhythms, Informed consent Excluded: ST-segment elevation or LBBB, No ROSC upon hospital admission,	Intervention: Immediate-angiography Group: patients were transferred to the catheterization laboratory as soon as possible after hospital admission. Comparison Delayed-angiography group: patients were first transferred to the intensive care unit (ICU)	All-cause mortality: immediate angiography group 60.8% (161of 265); delayed or selective angiography group 54.3% (144 of 265) (hazard ratio, 1.25; 95% CI, 0.99-1.57; log-rank *P* = .05) For the surviving patients, the rates of severe neurologic deficit (relative risk, 1.47; 95% CI, 0.66-3.26), myocardial	Although prespecified, outcomes at 1 year are exploratory only. Physi- cians and intensive care unit staff members were not blinded to treatment randomization. Management of OHCA involves complex clinical decision-making; thus, residual bias cannot be ruled out. The end points analyzed might not comprehensively

	elevation at 1-year follow-up. Study Type: investigator-initiated, randomized, inter national, multicenter, open-label clinical trial	Severe hemodynamic or electrical instability requiring immediate CAG/intervention (delay clinically not acceptable), Life-threatening arrhythmia possibly caused by acute myocardial ischemia, Cardiogenic shock, Obvious extra-cardiac etiology such as traumatic brain injury, primary metabolic or electrolyte disorders, intoxication, overt hemorrhage, respiratory failure due to known lung disease, suffocation, drowning In-hospital cardiac arrest Known or likely pregnancy, Participation in another intervention study interfering with the research questions of the TOMAHAWK trial	for further evaluation of the cause of the cardiac arrest and for treatment. If the likelihood of an acute coronary trigger for the cardiac arrest was deemed to be high, the treating physician could proceed to coronary angiography after a minimum delay of 24 hours after cardiac arrest.	infarction (relative risk, 0.00; 95% CI, 0.00-1.47), and rehospitalization for congestive heart failure (relative risk, 0.92; 95% CI, 0.27-3.08) were similar at 1 year. There was no difference in all-cause mortality between the treatment groups in the period between 30 days and 1 year (relative risk, 0.95; 95% CI, 0.54-1.67)	cover the complete spectrum of clinical outcomes; Data on medical treatment in the surviving patients were not assessed during long-term follow-up. Psychosocial impact will be reported separately. The results do not apply to patients with ST-segment elevation or cardiogenic shock after OHCA, for whom immediate angiography is still strongly recommended.

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 this PICOST should have a systematic or scoping review*)
Guidelines, SRs:
The ESC has given a Class III recommendation for routine immediate angiography after resuscitated cardiac arrest in patients without ST-segment elevation on post-ROSC ECG (Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful-intervention not recommended)

Thirteen SRs and meta-analyses were conducted since our last update of the CoSTR. Ten included only RCTs and only three included both Non-RCTs and RCTs. Combined effects from non-RCTs showed some benefit with early CAG. Despite differences in the number of included studies and strategy for the combination of data across outcomes, all SRs meta-analyses of RCTs failed to show benefit with early CAG.

RCTs:
Two RCTs were published, The EMERGE trial in 2022, including 279 patients and the COUPE trial in 2023, including 69 patients. Both trials were stopped early due to slow recruitment.

None showed any difference in terms of efficacy outcomes. The Coupe trial showed increased acute kidney failure rates in the immediate CAG group and higher infection rates in the delayed CAG group.

There was also a report of 1-year outcomes from the Tomahawk trial. All-cause mortality was higher in the immediate angiography group 60.8% vs. 54.3% in the delayed or selective angiography group (HR 1.25 [95% CI, 0.99-1.57]; This effect was of borderline significance (log-rank *P* = .05). There was no difference in all-cause mortality between the treatment groups in the period between 30 days and 1 year (relative risk, 0.95; 95% CI, 0.54-1.67). The observed difference can thus be attributed to the corresponding difference observed in the 30-day all-cause mortality [OR 0.73 (95% CI 0.52-1.08, p=0,07].
Combining 1-year Tomahawk data with those from COACT 1-year the overall effect size is OR 0.83 995% CI 0.65-1.06, p=0.13)

In our previous CoSTR, the effect size observed for all-cause mortality at 1 month in the Tomahawk was partially offset when combined with data from Kern 2020 [Combined OR 0.81 (95% CI 0.59-1.11 p=0.19). Now they are further offset when data for the COUPE trial are added [Combined OR 0.86 (95% CI 0.64-1,16 p=0.31]

The increased number of AKI with emergency CAG and increased infections with late/selective CAG in the small COUPE trial were not observed in larger trials.

For efficacy outcomes, there is no statistically significant effect either in favour or against early CAG post-ROSC in comatose patients after OHCA without ST-segment elevation on post-ROSC ECG. There is also no substantial evidence of difference between the intervention and control groups for safety outcomes.
I suggest that we keep the existing TRs. We can go on for an update of our SR and CoSTR when data from the ongoing DISCO trial with >1000 patients will be available.

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2025 Evidence Update
ALS 3504 – Steroids Post-Resuscitation

Worksheet Author(s): Tonia Nicholson
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / 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)?

Year of last full review:
2010 (but similar literature search done to address 2015 PICOST 433, and EvURs done in 2019, 2021 and 2023).

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
Consensus on Science: There were no human or animal studies that directly addressed the use of the estrogen, progesterone, insulin, or insulin-like growth factor in cardiac arrest. Early observational studies of the use of corticosteroids during cardiac arrest suggested possible benefit (LOE 4). One complex randomized pilot study (LOE 1) and 1 non-randomized human study (LOE 2) suggested benefit with corticosteroids, whereas 1 small, older, human prehospital controlled clinical trial suggested no benefit (LOE 1). One animal study of corticosteroids suggested possible benefit (LOE 5).

Search strategy for 2025

Databases searched: Pubmed / Cochrane Reviews**/**National Clinical Trails database
This search was time-limited from Sept 2022 (when last search for this PICO was done) to May 7th 2024 .

Pubmed:
(heart arrest[MH] OR cardiopulmonary resuscitation[MH] OR heart massage[MH] OR advanced cardiac life support[MH] OR ventricular fibrillation[MH] OR heart massage[TW] OR heart arrest*[TW] OR cardiac arrest*[TW] OR OHCA[TW] OR IHCA[TW] OR CPR[TW] OR advanced cardiac life support[TW] OR ACLS[TW] OR asystole[TW] OR pulseless electrical activity[TW] OR pulseless ventricular tachycardia[TW] OR ventricular fibrillation[TW] OR chest compression*[TW] OR cardiopulmonary resuscitation[TW]) AND (adrenal cortex hormones[MH] OR adrenal cortex hormone*[TW] OR corticosteroid*[TW] OR glucocorticoid*[TW] OR methylprednisolone[TW] OR dexamethasone[TW] OR hydrocortisone[TW] OR prednisolone[TW] OR prednisone[TW] OR solu-medrol[TW] OR fludrocortisone[TW] OR florinef[TW])

Cochrane Central Register of Controlled Trials:
("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]).

International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.Gov:
The ICTRP was searched for *cardiac arrest AND glucocorticoids OR cardiac arrest AND corticosteroids OR cardiac arrest AND methylprednisolone OR cardiac arrest AND vasopressin*. To optimize sensitivity, an additional search was performed for the condition *cardiac arrest* and other terms *corticosteroids OR glucocorticoids OR methylprednisolone OR vasopressin* (filters: recruiting, not yet recruiting, active not recruiting, interventional study type) on ClinicalTrials.Gov.
Search Results (Number of articles identified / number identified as relevant):

PubMed 2,088 (3)[1-3]
Cochrane 21 (2)[2,3]
Trials Registry 15 (2)[4,5]
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.

Summary of Evidence Update:
Relevant Guidelines or Systematic Reviews – None

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

RCTs:

Study Acronym; Author; Yr 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
STEROHCA ;[2] Obling LER, Beske RP, Meyer MAS, Grand J, Wiberg S et al; 2023	To investigate the anti-inflammatory & neuroprotective effect of pre-hospital administration of a high-dose glucocorticoid following OHCA. Randomized, blinded, placebo-controlled, phase II prehospital multicentre clinical trial. N = 137 (68 in the intervention group, 69 in the placebo group)	Eligible patients were adults (≥18yrs) with OHCA of suspected cardiac aetiology, who remained unconscious(GCS≤ 8) following ROSC, & achieved ROSC for ≥ 5 min. Exclusion criteria were: ALS termination-of-resuscitation exclusion criteria, asystole as 1st monitored rhythm, women of childbearing age, previous decision of no resuscitation, known allergy to methylprednisolone, known pre-arrest modified Rankin Scale (mRS) score	68 patients were randomized to receive a bolus injection of methyl-prednisolone 250 mg IV (2×125 mg/2ml) & 69 were randomised to receive placebo (4 mL isotonic NaCl) both administered over 5 min.	The co-primary outcome consisted of daily measurements of IL-6 and NSE from admission until 72 h from admission. The first IL-6 level was almost identical in the 2 groups (15 pg/mL [95% CI 10.4;21.6) vs 15pg/mL (10.4; 21.7), *p*=1), subsequently a reduction in IL-6 levels was seen in the intervention group with a significant treatment-by-time interaction, *p*< 0.0001. The intervention group exhibited significantly lower IL-6 levels at 24hrs compared to the placebo group 2.1pg/mL (1.3; 3.2) vs. 29.8 pg/mL (18.9;46.8) *p*<0.0001, but by 72hrs levels were similar (4.3	Secondary outcomes included survival & neurological function at hospital d/c & after 180 days. Neurological function was defined by CPC score (range 1–5, with 3/4=severe disability, coma/vegetative state & 5=death) and mRS score (range 0–6; 0= no disability or dependence in daily activities & 6 = death) CPC and mRS at discharge were determined by retrospective chart review & at 180 days through telephone interview.

		ranging from 4 to 5, temperature < 30 °C upon randomization, or > 30 min to ROSC.		pg/mL (2.7;6.6) vs 3.4 pg/mL (2.2; 5.4), p= 0.51) There was no difference in NSE levels over time, *p*=0.22	After 180 days, 51 (75%) patients in the intervention group vs. 44 (64%) patients in the placebo group were alive (unadjusted hazard ratio 0.65 (0.35–1.2), *p* = 0.17, adjusted hazard ratio 0.35 (0.18-0.67), p=0.002 CPC & mRS-scores, evaluated at ≥ 180 days following OHCA, were similar in the two groups.

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**
A sub-study of STEROHCA ;[3] Obling LER, Beske RP, Meyer MAS, Grand J, Wiberg S et al; 2024	To investigate the haemodynamic effects of pre-hospital administration of a high-dose glucocorticoid in resuscitated comatose patients post OHCA. Randomized, blinded, placebo-controlled, phase II prehospital multicentre clinical trial. N = 114 (56 in the intervention group, 58 in the placebo group)	Eligible patients were adults (≥18 yrs), with OHCA of suspected cardiac aetiology, who remained unconscious (GCS ≤ 8) following ROSC, & survived until ICU admission. The exclusion criteria were: ALS termination-of-resuscitation exclusion criteria, asystole as 1st monitored rhythm, women of childbearing age, previous decision of no resuscitation, known allergy to methylprednisolone, known pre-arrest	56 patients had been randomized to receive a bolus injection of methyl-prednisolone 250 mg IV (2×125 mg/2ml) & 58 had been randomised to receive placebo(4 mL isotonic NaCl), both administered over 5 min.	The primary outcome was cumulated norepinephrine use from ICU admission until 48 h reported as mcg/kg/min. From ICU admission up to 48 h post-admission, patients in the glucocorticoid group cumulated a lower norepinephrine use (mean difference - 0.04 mcg/kg/min, 95% CI - 0.07 to - 0.01, p = 0.02).	Secondary outcomes included hemodynamic status characterized by MAP, heart rate, vasoactive-inotropic score (VIS), the VIS/MAP-ratio, & cardiac function assessed by pulmonary artery catheter measurements . After 12-24 h post-admission, the treatment group had a higher MAP, mean differences from 6 to 7 mmHg (95% CIs from 1 to 12), a lower VIS (mean differences

		modified Rankin Scale (mRS) score ranging from 4 to 5, temperature < 30 °C upon randomization, or > 30 min to ROSC.			from - 4.2 to - 3.8, 95% CIs from - 8.1 to 0.3), and a lower VIS/MAP ratio (mean differences from - 0.10 to - 0.07, 95% CIs from - 0.16 to - 0.01), while there were no major differences in heart rate (mean differences from - 4 to - 3, 95% CIs from - 11 to 3). These treatment differences between groups were also present 30-48hr post-admission, but to a smaller extent with increased statistical uncertainty.

Nonrandomized Trials, Observational Studies - None

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:	

Clinical trials registry:

The search of International Clinical Trials Registry identified 2 trials actively recruiting patients, that may provide evidence relevant to this PICOST:

1) **NCT05139849 (VAST-A)**[4]

This is an in-hospital, randomized, placebo controlled, double blind, superiority, multi-centre clinical trial based in Gothenberg in Sweden, led by S. Forsberg & P. Lundgren. It commenced in 2021 (with a pilot phase), and is currently estimated for completion in 2027. Patients eligible for inclusion are those with IHCA arrest meeting criteria(s) for adrenaline administration according to current ERC guidelines. In addition to receiving adrenaline during the arrest, patients are randomized to treatment with either vasopressin and steroids (intervention) or sodium chloride (placebo) (control).

Subsequently, for those achieving ROSC and admitted to ICU, the intervention arm are given Hydrocortisone 3 mg/ml At 4hrs post ROSC, and then once daily. Surviving patients with post-resuscitation shock receive an infusion of 100 ml (300 mg hydrocortisone/ d) for ≤ 7 days. From day 8 post ROSC or when vasopressors are not needed the hydrocortisone dose is reduced daily to 67 ml (200 mg) and 33 ml (100 mg) and then discontinued). Patients with evidence of acute myocardial infarction receive an infusion of 100 ml (300mg hydrocortisone/d) for maximum 3 days to prevent retardation of infarct healing. The patients in the placebo group post-ROSC are given sodium chloride in the same manner.

Based on preliminary assumptions, to confirm or reject an increase in survival with the addition of the intervention from 9% to 14%, the aim is to enrol about 1400 patients in the study. The primary outcome is survival at 30 days.

2) **NCT05895838 (DOHCA Study)**[5]
This is a phase III trial, aiming to randomize 1000 patients at Danish cardiac arrest centres who are comatose post OHCA. Estimated for completion in 2027.
The aim is to evaluate 4 interventions in a factorial design addressing each in a randomized clinical trial:

1. Systemic inflammation: Anti-inflammatory treatment with high dose steroids (dexamethasone) or placebo.
2. Cerebral perfusion: Backrest elevation during sedation at 5 or 35 degrees.
3. Duration of sedation: Early wakeup call and potential extubation at ≤6 hours after admission or later as current standard practice at 28-36 hours.
4. Delirium: Prophylactic treatment with anti-psychotic medication (olanzapine) or placebo

The primary endpoint is 90 days all-cause mortality for the interventions targeting systemic inflammation and cerebral perfusion. (It is days alive outside of hospital within 30 days for the interventions concerning duration of sedation and delirium)

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping 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."*

Evidence update reviews in 2020, 2021 and 2023 did not identify sufficient new evidence to suggest that a new scoping or systematic review regarding post-ROSC administration of steroids was indicated. This EvUR has identified one new RCT and a sub-study of it, comparing the effects of the administration of methylprednisolone and saline to resuscitated comatose patients post OHCA. There was no statistically significant difference in either survival or neurological outcome between the intervention and placebo groups.
Two further RCTs have been identified in the International Trials Registry which may provide further evidence on the effects of administration of post-ROSC steroids in resuscitated comatose patients post OHCA, but not until at least 2027.
It would therefore seem prudent to avoid doing another scoping or systematic review on this topic until the trails in the International Trials Registry have been completed.

Reference list:
1) Obling LER, Beske RP, Wiberg S, Folke F, Moeller JE, Kjaergaard J, Hassager C. Steroid treatment as anti-inflammatory and neuroprotective agent following out-of-hospital cardiac arrest: a randomized clinical trial. Trials. 2022 Nov 22;23(1):952. doi: 10.1186/s13063-022-06838-0. PMID: 36414975; PMCID: PMC9682762.

2) Obling LER, Beske RP, Meyer MAS, Grand J, Wiberg S, Nyholm B, Josiassen J, Søndergaard FT, Mohr T, Damm-Hejmdal A, Bjerre M, Frikke-Schmidt R, Folke F, Møller JE, Kjaergaard J, Hassager C. Prehospital high-dose methylprednisolone in resuscitated out-of-hospital cardiac arrest patients (STEROHCA): a randomized clinical trial. Intensive Care Med. 2023 Dec;49(12):1467-1478. doi: 10.1007/s00134-023-07247-w. Epub 2023 Nov 9. PMID: 37943300; PMCID: PMC10709228.
3) Obling LER, Beske RP, Meyer MAS, Grand J, Wiberg S, Nyholm B, Josiassen J, Søndergaard FT, Mohr T, Damm-Hejmdal A, Bjerre M, Frikke-Schmidt R, Folke F, Møller JE, Kjaergaard J, Hassager C. Effect of prehospital high-dose glucocorticoid on hemodynamics in patients resuscitated from out-of-hospital cardiac arrest: a sub-study of the STEROHCA trial. Critical Care (2024) 28:28. doi.org/10.1186/s13054-024-04808-3

5) VAsopressin and STeroids in Addition to Adrenaline in Cardiac Arrest - a Randomized Clinical Trial. https://clinicaltrials.gov/show/NCT05139849.
6) Steroid Treatment as Anti-inflammatory and Neuroprotective Agent Following Out-of-Hospital Cardiac Arrest. A Randomized Trial.
https://clinicaltrials.gov/show/NCT04624776.

2025 Evidence Update
ALS 3510 – CT Imaging for prognostication

Worksheet Author(s): Claudio Sandroni, Sonia D'Arrigo; external collaborator (data extraction and management) Sofia Cacciola
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Interventions: index test based on imaging: brain Computed Tomography (CT**)**
Comparison: the accuracy of the index test was assessed by comparing the predicted outcome with the final outcome.
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.

Year of last full review: 2020
Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: COSTR 2020
We suggest using GWR on brain CT for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence). However, no GWR threshold for 100% specificity can be recommended.

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
"Cardiac arrest [all fields]" AND "Coma" [all fields] AND "Prognosis" [all fields].

New Search strategy: (for a new PICOST should be outlined here as per Evidence Update Process)
Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) – updated from end of last search (please specify): From April 2020 to Jun 2024
Time Frame: (new PICOST) – at the discretion of the Task Force (please specify)
Date Search Completed: Jun 30, 2024
Search Results (Number of articles identified, and number identified as relevant): 88 articles were evaluated in full-text, and 9 were included as relevant.

Inclusion/Exclusion Criteria:
- Inclusion: adult (≥16 years); resuscitated from cardiac arrest (either in-hospital or out-of-hospital). Comatose (unconscious, unresponsive, and/or having a Glasgow Coma Score (GCS)≤8 at the time of study enrolment). Predictor assessed within 7 days from CA. We included only studies where sensitivity and FPR could be calculated, i.e., those where the 2×2 contingency table of true/false negatives and positives for prediction of poor outcome was reported or could be calculated from reported data. We included only studies with neurological outcome assessed at hospital discharge/1 month or later.
- Exclusion: Studies including non-comatose patients or patients in hypoxic coma from causes other than cardiac arrest (e.g., respiratory arrest, carbon monoxide intoxication, drowning, and hanging) were excluded. Studies with neurological outcome assessed at ICU discharge were excluded.

Summary of Evidence Update:

Nine studies evaluated the ability of the grey matter/white matter ratio (GWR) on brain CT within 7 days after ROSC to predict poor neurological outcome in comatose survivors after CA (da Silva Pereira 2024, In 2022, Kenda 2021, Kim 2020, Kirsch 2021, Lang 2024, Wang 2022, Yeh 2020, Yoon 2023,)

Four studies (da Silva Pereira 2024, In 2022, Yeh 2020, Yoon 2023) in 789 patients investigated GWR-basal ganglia <24 h after ROSC. In these studies, GWR-basal ganglia with threshold values between 1.06 and 1.16 predicted poor neurological outcome at hospital discharge to 6 months with 100% specificity and sensitivity ranging from 10[7-14]% to 28[22-34]%.

Two studies (In 2022, Wang 2022) in 148 patients investigated GWR basal ganglia from 24 h to 7 days after ROSC. In these studies, GWR-basal ganglia with threshold values of 1.04 and 1.16 predicted poor neurological outcome at hospital discharge to 6 months with 100% specificity and sensitivity of 46[28-66]% and 75[65-83]%, respectively.

One study (Yeh 2020)in 228 patients investigated GWR-cerebrum <24h after ROSC. A GWR value of 1.11 predicted poor neurological outcome at hospital discharge with 100[98-100]% specificity and 14[10-20]% sensitivity.

Two studies (Kim 2020, Yeh 2020) in 337 patients evaluated the GWR-average <24 h after ROSC. In these studies, a GWR value below 1.12 and 1.14 predicted poor neurological outcome with 100% specificity and 12[7-20]% and 21[16-27%] sensitivity, respectively.

Two studies (Kenda 2021, Lang 2024) in 334 patients assessed the ability of a simplified GWR automatically calculated simplified GWR (GWR_si) between <24 h and 7 days after ROSC. In these studies, an automated GWR_si of 1.10 and 1.13 predicted poor outcome with 100% specificity and sensitivity ranging from 19[14-25]% to 59[50-68]%.
One study (Kirsch 2021) in 55 patients evaluated a modified simplified method (GWR_si_mod). In that study, a GWR_si_mod <1.17 at 12-86h after ROSC predicted poor neurological outcome with 100% specificity and 67[53-79]% sensitivity.

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**
Sandroni C et al., *Intensive Care Med,* 2020; 46:1803–1851.	Systematic review	Same as this Evidence Update	94 studies were included, of which 24 were about imaging findings.	Quantitative estimates of cerebral oedema on a brain CT at 1–2 h or later after ROSC and reduced diffusion on brain MRI at 2–5 days or later after ROSC are both specific predictors, but with very variable cutoff values for 0% FPR, presumably because of variation in measurement techniques used in studies.	

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
	Study Aim: **Study Type:**	**Inclusion Criteria:**	**Intervention:** **Comparison:**	**1° endpoint:**	**Study Limitations:**

Nonrandomized Trials, Observational Studies published April 1, 2020 to Jun 30, 2024

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)
GWR-basal ganglia				
da Silva Pereira, 2024	Study Type: retrospective observational multicentre study. 354 patients were included. Brain CT scan was performed in all patients.	Inclusion Criteria: comatose OHCA survivors who underwent a brain CT scan within 2 h after ROSC Exclusion criteria: Brain CT scan performed >2 h after ROSC<, traumatic cardiac arrest; CT images with substantial artifacts; ECMO treatment; missing data on CA characteristics, laboratory results and motor score on the GCS at the time of ROSC	1° endpoint: to investigate the association between GWR values, measured using early HCT (within 2 h after ROSC), and neurologic outcomes based on HIBI severity in OHCA survivors. Results: GWR-basal ganglia <1.06 on brain CT scan performed at ≤2h from ROSC predicted poor neurological outcome at 6 months with 100 [99-100]% specificity and 10 [7-14]% sensitivity.	In comatose survivors after OHCA, GWR-basal ganglia <1.06 on an early brain CT predicted poor neurological outcome at 6 months with 100% specificity and low sensitivity.

		that could determine HIBI severity.		
In, 2022	Study Type: retrospective observational monocentric study. 78 patients were included. Brain CT scan was performed in 76 patients at ≤ 6 h from ROSC and in 54 patients at 72-96h from ROSC.	Inclusion Criteria: adult comatose OHCA survivors treated with TTM underwent neuroimaging scan. Exclusion criteria: traumatic CA; interrupted TTM due to hemodynamic instability; large artefacts on HCT or MRI scans; first CT scan 6 h after ROSC; second CT or MRI scans outside the window of 72–96 h after ROSC; ECMO.	1° endpoint: to compare the neurological outcome predictive performance of CT and MRI performed after TTM (72-96 h) to CT performed early after ROSC (≤ 6 h) Results: GWR-basal ganglia <1.14 on brain CT scan performed at ≤6 h from ROSC predicted poor neurological outcome at 6 months with 100 [89-100]% specificity and 16 [7-30]% sensitivity. GWR-basal ganglia <1.04 on brain CT scan performed at 72-96 h from ROSC predicted poor neurological outcome at 6 months with 100 [87-100]% specificity and 46 [27-66]% sensitivity.	In comatose survivors after OHCA, GWR-basal ganglia <1.14 on an early brain CT predicted poor neurological outcome at 6 months with 100 % specificity and low sensitivity. GWR-basal ganglia on brain CT scan recorded at 72-96 h showed higher sensitivity.
Wang, 2022	Study Type: Retrospective observational study. 94 patients were included. Brain CT scan was performed in all patients.	Inclusion Criteria: Adult comatose CA survivors who underwent brain CT. Exclusion criteria: age< 18 years, terminal malignancy, baseline neurological disorders, unavailable CT images.	1° endpoint: to assess the association between GWR at different time and neurological prognosis. Results: GWR-basal ganglia <1.12 on brain CT scan performed at 24 h predicted poor neurological outcome at hospital discharge with 100 [95-100]% specificity and 32 [23-43]% sensitivity. GWR-basal ganglia <1.16 on brain CT scan performed at 24 h-7 days predicted poor	In comatose survivors after CA, GWR-basal ganglia <1.12 on brain CT at 24 from ROSC predicted poor neurological outcome at 6 months with 100 % specificity and low sensitivity. GWR-basal ganglia <1.04 on brain CT scan performed between 24h -7 days from ROSC predicted poor outcome with 100% specificity and higher sensitivity than at 24h.

			neurological outcome at hospital discharge with 100 [95-100]% and 75 [65-83]% sensitivity.	
Yeh, 2020	Study Type: Retrospective monocentre observational study. 228 patients were included. Brain CT scan was performed in all patients.	Inclusion Criteria: Adult comatose non-traumatic OHCA with sustained ROSC (≥ 20 minutes). Exclusion criteria: no brain CT within 24 h following ROSC; the presence of intracranial hemorrhage, severe old insult, brain tumor, ventriculoperitoneal shunt, and severe image artifact.	1° endpoint: to investigate the association between post-arrest GWR and neurological outcome. Results: GWR-basal ganglia <1.16 on brain CT scan performed at <24 h predicted poor neurological outcome at hospital discharge with 100 [98-100]% specificity and 28 [22-34]% sensitivity.	In comatose survivors after OHCA, GWR-basal ganglia <1.16, on brain CT scan performed at <24 h predicted poor neurological outcome at hospital discharge with 100 % specificity and low sensitivity.
Yoon, 2023	Study Type: Retrospective single-centre observational study. 131 patients were included. Brain CT scan was performed in all patients	Inclusion Criteria: Comatose adult OHCA survivors treated with TTM underwent MRI within 6 h after ROSC. Exclusion criteria: traumatic CA; evidence of severe brain atrophy or a sequela of a previous injury on MRI; poor neurological status before the OHCA; extracorporeal	1° endpoint: to investigate the association between ADC values based on voxel quantification in DW-MRI and poor neurological outcomes at 6 months post-ROSC. 2° endpoint: to identify the optimal MRI-based ADC metrics (ADC value and thresholds) and compare their predictive performance with CT-based GWR values. Results: GWR-basal ganglia <1.11 on brain CT scan performed at ≤6 h predicted poor	In comatose survivors after OHCA, GWR-basal ganglia <1.11 on brain CT performed at <6h after ROSC predicted poor neurological outcome at 6 months with 100% specificity and low sensitivity.

		membrane oxygenation (ECMO); MRI scan time exceeded 6 h after ROSC.	neurological outcome at 6 months with 100 [96-100]% specificity and 16 [11-24]% sensitivity.	
GWR-average				
Kim, 2020	Study Type: retrospective observational cohort study. 109 patients were included. Brain CT scan was performed in all patients.	Inclusion Criteria: Adult comatose OHCA treated with TTM, who underwent at least one NSE value measurement at 48- 72 h after ROSC and received both a brain CT scan within 24 h and MRI within 7 days after ROSC. Exclusion criteria: age<18 years, CA due to trauma or intracranial hemorrhage, a previous history of neurological disease and CT or DW-MRI with a poor image quality.	1° endpoint: to test whether the combination of NSE, a quantitative analysis GWR-average on brain CT and a quantitative analysis of brain MRI could improve diagnostic performance for predicting outcomes after CA. Results: GWR-average <1.12 on brain CT scan performed at <24h after ROSC predicted poor neurological outcome at 6 months with 100 [96-100]% specificity and 12 [7-20]% sensitivity.	In comatose survivors after OHCA, GWR-average <1.12 on an early brain CT predicted poor neurological outcome at 6 months with 100% specificity and low sensitivity.
Yeh, 2020	Study Type: Retrospective monocentre observational study. 228 patients were included. Brain CT scan was performed in all patients.	Inclusion Criteria: Adult comatose non-traumatic OHCA with sustained ROSC (≥ 20 minutes). Exclusion criteria:	1° endpoint: to investigate the association between post-arrest GWR and neurological outcome. Results: GWR-average <1.14 on brain CT scan performed at <24 h predicted poor neurological outcome at	In comatose survivors after OHCA, GWR-average <1.14 on brain CT scan performed at <24 h predicted poor neurological outcome at hospital discharge with 100 % specificity and low sensitivity.

		no brain CT within 24 h following ROSC; the presence of intracranial hemorrhage, severe old insult, brain tumor, ventriculoperitoneal shunt, and severe image artifact.	hospital discharge with 100 [98-100]% specificity and 21 [16-27]% sensitivity.	
GWR-cerebrum				
Yeh, 2020	Study Type: Retrospective monocentre observational study. 228 patients were included. Brain CT scan was performed in all patients.	Inclusion Criteria: Adult comatose non-traumatic OHCA with sustained ROSC (≥ 20 minutes). Exclusion criteria: no brain CT within 24 h following ROSC; the presence of intracranial hemorrhage, severe old insult, brain tumor, ventriculoperitoneal shunt, and severe image artifact.	1° endpoint: to investigate the association between post-arrest GWR and neurological outcome. Results: GWR-Cerebrum <1.107 on brain CT scan performed at <24 h predicted poor neurological outcome at hospital discharge with 100 [98-100]% specificity and 14 [10-20]% sensitivity.	In comatose survivors after OHCA, GWR-Cerebrum <1.107 on brain CT scan performed at <24 h predicted poor neurological outcome at hospital discharge with 100 % specificity and low sensitivity.
Simplified GWR automatically calculated (GWR-si)				
Kenda, 2021	Study Type: Observational, derivation/validation cohort study design. Brain CT was performed in 194 patients <24 h from ROSC and in 115 patients at >24 h from ROSC.	Inclusion Criteria: Non-traumatic CA treated with TTM: Exclusion criteria: DICOM files unretrievable from database, severe motion	1° endpoint: to test the hypothesis that a simplified GWR automatically calculated (GWR_si) determination can accurately predict poor neurologic outcome, and to investigate whether this prediction depends on CT timing.	In comatose survivors after OHCA, GWR_si <1.10 on brain CT performed ≤24h predicted poor neurological outcome at hospital discharge with 100 % specificity and 19% sensitivity. GWR_si on brain CT scan performed >24 h from RSOC showed higher

		artifacts, intracerebral hemorrhage, large old ischemic lesion, massive calcification of the basal ganglia.	Results: GWR_si <1.10 on brain CT scan performed at <24h predicted poor neurological outcome (CPC 4-5) at hospital discharge with 100 [98-100]% specificity and 19 [14-25]% sensitivity. GWR_si <1.13 on brain CT scan performed at >24h predicted poor neurological outcome (CPC 4-5) at hospital discharge with 100 [96-100]% specificity and 59 [50-68]% sensitivity.	sensitivity than within 24h from ROSC.
Lang, 2024	Study Type: prospective multicenter observational study (substudy of TTM2 trial). 140 patients were included. Brain CT scan was performed in all patients.	Inclusion Criteria: Consecutive unconscious patients ≥18 years admitted to hospital after OHCA of a presumed cardiac or unknown cause. Exclusion criteria: unmet technical requirements; the presence of other intracranial pathologies.	1° endpoint: to determine if an automatically obtained GWR <1.10, would predict poor neurological outcome without false positives in brain CTs performed at 48h –7 days after CA. Results: Automated GWR <1.10 on brain CT scan performed at 48h - 7 days after ROSC predicted poor neurological outcome at 6 months with 100 [97-100]% specificity and 41 [33-50]% sensitivity.	In comatose survivors after OHCA, an automated GWR <1.10 on brain CT at 48h – 7 days predicted poor neurological outcome at 6 months with 100 % specificity and low sensitivity.
Kirsch, 2021	Study Type: retrospective monocentre observational study. 91 patients were included.	Inclusion Criteria: Adult comatose survivors after ROSC who underwent non-contrast enhanced brain CT within 3	1° endpoint: to investigate the prognostic value of a variation of the simplified method (GWR_si var) on brain CT imaging within the first three days after CA. Results:	In comatose survivors after OHCA, GWR_si var <1.17 on an early brain CT predicted poor neurological outcome at 1 month with 100 % specificity and low sensitivity. GWR_si var <1.17 on brain CT scan performed >12 h showed higher sensitivity.

	Brain CT was performed ≤12 h from ROSC in 36 patients and >12 h from ROSC in 55 patients.	days after admission. Exclusion criteria: Age <18 years old, neuroimaging not available.	GWR_si var <1.17 on brain CT scan performed at ≤12 h and 12-85 h after ROSC predicted poor neurological outcome (CPC 4-5) at 1 month or hospital discharge with 100 [88-100]% specificity and 17 [7-34]% and 67 [53-79]% sensitivity, respectively.	

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

The evidence found does not justify a new systematic review at present.
We found no evidence suggesting a need to change the 2024 ILCOR recommendations.

Note on the interpretation of test results
Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as "positive," and a normal response as "negative," or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should also ideally offer a reasonably high sensitivity when "negative" (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.
In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treatment decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome. This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2020 Consensus for this PICOST is that the decision to limit the treatment of comatose post–cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that in patients who remain comatose in the absence of confounders (e.g., sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.
For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

Notes on the interpretation of neuroprognostic tests based on GWR
The grey matter / white matter ratio on brain CT is calculated by measuring the density of specific regions of interest (ROIs) in the grey matter (most often, the caudate nucleus and the putamen) and dividing it by the density of ROIs in the white matter (most often, corpus callosum and the posterior limb of the internal capsule). Unlike the results of other neuroprognostic tests (e.g., clinical examination), GWR is a continuous rather than dichotomous (categorical) variable. Results are dichotomized to calculate the sensitivity and specificity of GWR by establishing a

threshold that divides positive from negative results. Consequently, test sensitivity and specificity depend on the threshold chosen: a high threshold increases the test's specificity and decreases the sensitivity, and vice versa. A source of heterogeneity for neuroprognostication based on GWR is the presence of different calculation methods. They depend on which and how many regions of the grey or the white matter are sampled. This may create different results across measuring methods. Another potential source of heterogeneity is the use of different equipment and different acquisition techniques.

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2025 Evidence Update
ALS 3510 – Imaging Brain MRI

Worksheet Author(s): Claudio Sandroni, Sonia D'Arrigo; external collaborator (data extraction and management) Sofia Cacciola
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Interventions: index test based on imaging: Magnetic Resonance Imaging (MRI)
Comparison: the accuracy of the index test was assessed by comparing the predicted outcome with the final outcome.
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.

Year of last full review: 2020

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: COSTR 2020
We suggest using diffusion-weighted brain MRI for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).
We suggest using ADC on brain MRI for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
"Cardiac arrest [all fields]" AND "Coma" [all fields] AND "Prognosis" [all fields].

New Search strategy: (for a new PICOST should be outlined here as per Evidence Update Process)
Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) – updated from end of last search (please specify): From April 2020 to Jun 2024
Time Frame: (new PICOST) – at the discretion of the Task Force (please specify)
Date Search Completed: Jun 30, 2024
Search Results (Number of articles identified, and number identified as relevant): 88 articles were evaluated in full-text, and 10 were included as relevant.

Inclusion/Exclusion Criteria:
- Inclusion: adult (≥16 years); resuscitated from cardiac arrest (either in-hospital or out-of-hospital). Comatose (unconscious, unresponsive, and/or having a Glasgow Coma Score (GCS)≤8 at the time of study enrolment). Predictor assessed within 7 days from CA. We included only studies where sensitivity and FPR could be calculated, i.e., those where the 2×2 contingency table of true/false negatives and positives for prediction of poor outcome was reported or could be calculated from reported data. We included only studies with neurological outcome assessed at hospital discharge/1 month or later.
- Exclusion: Studies including non-comatose patients or patients in hypoxic coma from causes other than cardiac arrest (e.g., respiratory arrest, carbon monoxide intoxication, drowning, and hanging) were excluded. Studies with neurological outcome assessed at ICU discharge were excluded.

Summary of Evidence Update:

Ten studies evaluated the ability of the Magnetic Resonance Imaging (MRI) within seven days after ROSC to predict poor neurological outcome in comatose patients after CA (An 2020, Barth 2020, Calabrese 2023, Iten 2024, Keijzer 2022, Kim 2020, Vanden Berghe 2020, Wouters 2021, Yoon 2023, Yoon 2024).

Three studies (Keijzer 2022, Yoon 2023, Kim 2020) in a total of 290 patients assessed the mean apparent diffusion coefficient (ADC) of the whole brain between <6h and seven days after ROSC. In these studies, a mean ADC less than 760, 739 and 610 x 10^{-6} mm^2/s on brain MRI predicted poor neurological outcome with 100% specificity and 50%, 50% and 36% sensitivity, respectively.

Six studies (Calabrese 2023, Keijzer 2022, Kim 2020, Wouters 2021, Yoon 2023, Yoon 2024) in a total of 898 patients assessed the volume of brain tissue (percentage of voxels) with low ADC as a predictor of poor neurological outcome after cardiac arrest.

Two studies (Yoon 2023, Kim 2020) in a total of 240 patients showed that a percentage of brain voxels with ADC <400 x 10^{-6} mm^2/s greater than 3.4% within 6 h and greater than 6.5% within 7 days after ROSC predicted poor neurological outcome with 100[96-100]% specificity and 34 [26-43]% and 63[53-72]% sensitivity, respectively.

Two studies (Keijzer 2022,Yoon 2023) in a total of 181 patients showed that a percentage of brain voxels with ADC <450 x 10^{-6} mm^2/s greater than 5.2% within 6 h and greater than 3.2% at 2-4 days after ROSC predicted poor neurological outcome with 100[96-100]% specificity and 36 [28-45]% and 55[40-69]% sensitivity, respectively. In the same studies, a percentage of brain voxels with ADC <550 x 10^{-6} mm^2/s greater than 11.7 % within 6 h and greater than 8% at 2-4 days after ROSC predicted poor neurological outcome with 100[91-100]% specificity and 43 [35-52]% and 55[40-69]% sensitivity, respectively.

Four studies (Calabrese 2023, Keijzer 2022, Wouters 2021, Yoon 2024) in a total of 658 patients showed that a percentage of brain voxels with ADC <650 x 10^{-6} mm^2/s ranging from 5% to 41% at 3-6 days after ROSC predicted poor neurological outcome with a specificity ranging from 37[32-42]% to 100% and sensitivity ranging from 38[28-50]% to 76[72-80]%.

Two studies from the same group (Barth 2020, Iten 2024) in a total of 136 patients assessed the accuracy of MR lesion pattern (MLP) for predicting poor neurological outcome. MRI lesion patterns were dichotomized into severe hypoxic brain injury (MLP 3–4) and no or minimal hypoxic brain injury (MLP 1–2). An MLP 3-4 at 36-72 h from ROSC predicted poor neurological outcome with a specificity ranging from 83 [69-82]% to 100[95-100]% and sensitivity ranging from 33[23-44]% to 94[82-99]%.

Two studies (An 2020, Vanden Berghe 2020) in a total of 145 patients investigated two different diffusion weighted imaging (DWI) scores for qualitative MRI assessment. They showed that a DWI score ³52 on MRI performed at 72-96 h after ROSC predicted poor neurological outcome at 6 months with 100 [93-100]% specificity and 81 [70-89]% sensitivity (An 2020) and a simplified DWI score ³6 on MRI performed at 5±2 days after ROSC predicted poor neurological outcome at 6 months with 94 [85-98]% specificity and 93 [84-97]% sensitivity (Vanden Berghe 2020).

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**
Sandroni C et al., *Intensive Care Med,* 2020;	Systematic review	Same as this Evidence Update	94 studies were included, of which 24	Quantitative estimates of cerebral oedema on a brain CT at 1–2 h or later after ROSC and	

46:1803–1851.			were about imaging findings.	reduced diffusion on brain MRI at 2–5 days or later after ROSC are both specific predictors, but with very variable cutoff values for 0% FPR, presumably because of variation in measurement techniques used in studies.	

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**
	Study Aim: Study Type:	Inclusion Criteria:	Intervention: Comparison:	1° endpoint:	Study Limitations:

Nonrandomized Trials, Observational Studies published April 1, 2020 to Jun 30, 2024

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)**
Whole-brain apparent diffusion coefficient (ADC)				
Keijzer, 2022	Study Type: prospective multicenter cohort study. 50 patients were included. MRI was performed in all patients.	Inclusion Criteria: Consecutive comatose adult CA on the basis of a cardiac cause and admission to the ICU. Exclusion criteria: Pregnancy; life expectancy < 24 h post cardiac arrest; any known	1° endpoint: to estimate the additional value of MRI-DWI and FLAIR on day 2–4 after resuscitation, in addition to continuous, early EEG, for prediction of neurological outcome. Results: Mean ADC whole brain <760 x 10^{-6} mm^2/s on MRI performed at 3±1 days after ROSC predicted poor neurological at 3 months with 100 [91-100]%	Mean ADC whole brain <760 x 10^{-6} mm^2/s on MRI performed at 3±1 days after ROSC predicted poor neurological at 3 months with 100% specificity and moderate sensitivity.

		progressive brain illness—such as a brain tumor or neurodegenerative disease; preexisting dependency in daily living; contraindication to undergo MRI examination.	specificity and 50 [36-64]% sensitivity.	
Kim, 2020	Study Type: retrospective observational cohort study. 109 patients were included. MRI was performed in all patients.	Inclusion Criteria: Adult comatose OHCA treated with TTM, who underwent at least one NSE value measurement at 48- 72 h after ROSC and received both a brain CT scan within 24 h and MRI within 7 days after ROSC. Exclusion criteria: age<18 years, CA due to trauma or intracranial hemorrhage, a previous history of neurological disease and CT or DW-MRI with a poor image quality.	1° endpoint: to assess whether the combination of NSE, a quantitative analysis GWR-average on brain CT and a quantitative analysis of brain MRI could improve diagnostic performance for predicting outcomes after CA. Results: Mean ADC whole brain <610 x 10^{-6} mm^2/s on MRI performed within 7 days after ROSC predicted poor neurological at 6 months with 100 [96-100]% specificity and 36 [27-46]% sensitivity.	Mean ADC whole brain <610 x 10^{-6} mm^2/s on MRI performed within 7 days after ROSC predicted poor neurological at 6 months with 100% specificity and low sensitivity.
Yoon, 2023	Study Type: Retrospective monocentre observational study.	Inclusion Criteria: Comatose adult OHCA survivors treated with	1° endpoint: to investigate the association between ADC values based on voxel quantification in DW-	Mean ADC whole brain <739 x 10^{-6} mm^2/s on MRI performed on an early MRI predicted poor neurological

	131 patients were included. MRI was performed in all patients.	TTM underwent MRI within 6 h after ROSC. Exclusion criteria: traumatic CA; evidence of severe brain atrophy or a sequela of a previous injury on MRI; poor neurological status before the OHCA; extracorporeal membrane oxygenation (ECMO); MRI scan time exceeded 6 h after ROSC.	MRI and poor neurological outcomes at 6 months post-ROSC. Results: Mean ADC whole brain <739 x 10^{-6} mm^2/s on MRI performed at ≤6 h predicted poor neurological outcome with 100 [96-100]% specificity and 50 [41-59]% sensitivity.	outcome with 100% specificity and moderate sensitivity.
Percentage of brain tissue with low ADC				
Calabrese, 2023	Study Type: Retrospective single-centre study. 81 patients were included. MRI was performed in all patients.	Inclusion Criteria: Adult comatose CA patients treated with TTM. Exclusion criteria: missing MR imaging sequences; TTM not completed; significant unrelated abnormality on brain MR imaging such as hemorrhage or large-territory encephalomalacia; or MR imaging acquired >7 days post-CA.	1° endpoint: to quantitatively describe the regional neuroanatomic distribution of brain injury post-CA using DWI. Results: A percentage of brain volume with ADC <650 x 10^{-6} mm^2/s greater than 10% on MRI performed at 4-6 days after ROSC predicted poor neurological outcome at hospital discharge with 94 [86-98]% specificity, and 59 [48-70]% sensitivity.	A percentage of brain volume with ADC <650 x 10^{-6} mm^2/s greater than 10% on MRI performed at 4-6 days after ROSC predicted poor neurological at hospital discharge with high specificity and moderate sensitivity.

Keijzer, 2022	Study Type: prospective multicenter cohort study. 50 patients were included. MRI was performed in all patients.	Inclusion Criteria: Consecutive comatose adult CA on the basis of a cardiac cause and admission to the ICU. Exclusion criteria: Pregnancy; life expectancy < 24 h post cardiac arrest; any known progressive brain illness—such as a brain tumor or neurodegenerative disease; preexisting dependency in daily living; contraindication to undergo MRI examination.	1° endpoint: to estimate the additional value of MRI-DWI and FLAIR on day 2–4 after resuscitation, in addition to continuous, early EEG, for prediction of neurological outcome. Results: A percentage of brain volume with ADC <450 x 10^{-6} mm^2/s greater than 3.2%, or ADC<550 x 10^{-6} mm^2/s greater than 8% or ADC<650 x 10^{-6} mm^2/s greater than 21.8% on MRI performed at 3±1 days after ROSC predicted poor neurological outcome at 3 months with 100 [91-100]% specificity and sensitivity ranging from 50% to 55%.	A percentage of brain volume with low ADC above different thresholds on MRI performed at 3±1 days after ROSC predicted poor neurological outcome at 3 months with 100% specificity and moderate sensitivity.
Kim, 2020	Study Type: retrospective observational cohort study. 109 patients were included. MRI was performed in all patients.	Inclusion Criteria: Adult comatose OHCA treated with TTM, who underwent at least one NSE value measurement at 48- 72 h after ROSC and received both a brain CT scan within 24 h and MRI within 7 days after ROSC. Exclusion criteria:	1° endpoint: to test whether the combination of NSE, a quantitative analysis GWR-average on brain CT and a quantitative analysis of brain MRI could improve diagnostic performance for predicting outcomes after CA. Results: A percentage of brain volume with ADC <400 x 10^{-6} mm^2/s greater than 6.5% on MRI performed within 7 days (median 68 [54-81]h) after ROSC predicted poor	A percentage of brain volume with ADC <400 x 10^{-6} mm^2/s greater than 6.5% on MRI performed within 7 days after ROSC predicted poor neurological at 6 months with 100% specificity and moderate sensitivity.

		age<18 years, CA due to trauma or intracranial hemorrhage, a previous history of neurological disease and CT or DW-MRI with a poor image quality.	neurological at 6 months with 100 [96-100]% specificity and 63 [53-72]% sensitivity.	
Wouters, 2021	Study Type: prospective randomized controlled trial. 102 patients were included. MRI was performed in 79 patients.	Inclusion Criteria: Adult patients resuscitated after OHCA of a presumed cardiac cause who remained unconscious at hospital admission. Exclusion criteria: devices incompatible with MRI, suspected stroke, refractory shock, and immediate need for mechanical cardiac support.	1° endpoint: to explore the prediction of neurological outcome based on brain volume with low ADC values. Results: A percentage of brain volume with ADC < 650 x 10^{-6} mm^2/s greater than 41% on MRI performed at 4-6 days after ROSC predicted poor neurological outcome at 6 months with 100[94-100]% specificity and 38[28-50]% sensitivity.	A percentage of brain volume with ADC <650 x 10^{-6} mm^2/s greater than 41% on MRI performed at 4-6 days after ROSC predicted poor neurological at 6 months with 100% specificity and low sensitivity.
Yoon, 2023	Study Type: Retrospective monocentre observational study. 131 patients were included. MRI was performed in all patients.	Inclusion Criteria: Comatose adult OHCA survivors treated with TTM underwent MRI within 6 h after ROSC. Exclusion criteria:	1° endpoint: to investigate the association between ADC values based on voxel quantification in DW-MRI and poor neurological outcomes at 6 months. Results: A percentage of brain volume with low ADC	Different percentages of brain volume with low ADC on MRI performed within 6 h after ROSC predicted poor neurological outcome at 6 months with 100% specificity and low to moderate sensitivity.

		traumatic CA; evidence of severe brain atrophy or a sequela of a previous injury on MRI; poor neurological status before the OHCA; extracorporeal membrane oxygenation (ECMO); MRI scan time exceeded 6 h after ROSC.	ranging from greater than 2.2% with ADC<350 x 10^{-6} mm^2/s to greater than 17.2% with ADC <600 x 10^{-6} mm^2/s on MRI performed within 6 h after ROSC predicted poor neurological outcome at 6 months with 100% [96-100]% specificity and sensitivity ranging from 31[33-40]% to 51[43-60]%.	
Yoon, 2024	Study Type: retrospective multicentric observational study from a prospectively collected cohort registry. 448 patients were included. MRI was performed in all patients.	Inclusion Criteria: comatose adults non-traumatic OHCA treated with TTM and underwent MRI scan between 72 and 96 h after ROSC. Exclusion criteria: evidence of severe brain atrophy or previous brain injury on MRI; traumatic cardiac arrest; MRI not performed between 72 and 96 h after ROSC; serious intracranial metastases and other diseases that could affect the ADC analysis.	1° endpoint: to validate ADC values and thresholds to predict poor neurological outcomes at 6 months. Results: A percentage of brain volume with ADC <650 x 10^{-6} mm^s/s greater than 20.5% on MRI performed at 72-96 h after ROSC predicted poor neurological outcome at 6 months with 99 [98-100]% specificity and 76 [72-80]% sensitivity.	A percentage of brain volume with ADC <650 x 10^{-6} mm^2/s greater than 20.5% on MRI performed at 72-96 h after ROSC predicted poor neurological at 6 months with high specificity and sensitivity.
Imaging lesion patterns and scores				

Barth, 2020	Study Type: retrospective analysis of prospective single-centre registry. 89 patients were included. MRI was performed in all patients.	Inclusion Criteria: Adult comatose CA who underwent a brain MRI and at least one EEG. Exclusion criteria: CA of non-cardiac origin, previous structural brain lesions such as stroke, neurodegenerative disorders or tumor.	1° endpoint: To correlate the presence and topography of MRI lesion patterns (MLPs) based on DWI/ADC restriction with standardized EEG patterns in comatose patients in the early phase after CA. Results: The presence of MLP 3 (basal ganglia lesions without involvement of other subcortical grey matter, with or without cortical lesions) and the presence of MLP 4 (lesions of the thalami and/or hippocampi and/or brain stem, with or without cortical or basal ganglia lesion) on MRI performed at 47.7 ± 16 h after ROSC predicted poor neurological outcome with 100 [95-100%] and 96 [89-99]% specificity, respectively, and 33 [23-44]% and 39 [29-50%] sensitivity, respectively.	The presence of MRI lesion patterns 3 or 4 on MRI performed at 47.7±16 hours after ROSC predicted poor neurological outcome at 6 months with high specificity and low sensitivity.
Iten, 2024	Study Type: retrospective single-centre cohort study. 52 patients were included. MRI was performed in 48 patients.	Inclusion Criteria: Adult comatose OHCA patients. Exclusion criteria: regained consciousness within the first 24 h; brain death; absence of consent for the registry; explicitly stated advanced directives not fully aligned	1° endpoint: To validate an MRI lesion patterns (MLPs) score to predict poor neurological outcome at 6 months. Results: The presence of MLP 3 or MLP 4 on MRI performed at 54 [48-72] h after ROSC predicted a poor neurological outcome at 6 months with 83 [69-92]% specificity and 94 [82-98]% sensitivity.	The presence of MRI lesion patterns 3 or 4 on MRI performed at 54 [48-72] h after ROSC predicted poor neurological outcome at 6 months with moderate specificity and high sensitivity.

		with comprehensive ICU care.		
An, 2020	Study Type: prospective single-centre observational cohort study. 70 patients were included. MRI was performed in all patients.	Inclusion Criteria: Adult comatose OHCA patients treated with TTM. Exclusion criteria: Age <18 years; traumatic CA or interrupted TTM; not eligible for TTM; apparent previous brain parenchymal disease; DWI that was not obtained 72-96 h after ROSC; ECMO; further treatment refusal by the next of kin.	1° endpoint: to assess a cut-off value for the DWI scoring system at 72-96h after ROSC to predict poor neurologic outcome at 6 months. Results: A DWI score ³52 on MRI performed at 72-96 h after ROSC predicted poor neurological outcome at 6 months with 100 [93-100]% specificity and 81 [70-89]% sensitivity.	A DWI score ³52 on MRI performed at 72-96 h after ROSC predicted poor neurological outcome at 6 months with 100% specificity and high sensitivity.
Vanden Berghe, 2020	Study Type: retrospective analysis of NEUROPROTECT , a prospective multi-center, randomized clinical trial. 75 patients were included. MRI was performed in all patients.	Inclusion Criteria: comatose adult CA patients Exclusion criteria: refuse signing informed consent, asphyxia as the cause of CA, MR imaging not available or without good quality.	1° endpoint: to compare a qualitative and a quantitative assessment of brain DWI in predicting poor neurological outcome at 6 months. Results: A simplified DWI score ³6 on MRI performed at 5 ± 2 days after ROSC predicted poor neurological outcome at 6 months with 94 [85-98]% specificity and 93 [84-97]% sensitivity.	A simplified DWI score ³6 on MRI performed at 5 ± 2 days after ROSC predicted poor neurological outcome at 6 months with high specificity and sensitivity.
Keijzer, 2022	Study Type: prospective multicenter cohort study.	Inclusion Criteria: Consecutive comatose adult	1° endpoint: to estimate the additional value of MRI-DWI and FLAIR on day 2–	A DWI score >16.7 and a FLAIR score >10.7 on MRI performed at 3±1 days after ROSC predicted poor

	50 patients were included. MRI was performed in all patients.	CA on the basis of a cardiac cause and admission to the ICU. Exclusion criteria: Pregnancy; life expectancy < 24 h post cardiac arrest; any known progressive brain illness—such as a brain tumor or neurodegenerative disease; preexisting dependency in daily living; contraindication to undergo MRI examination.	4 after resuscitation, in addition to continuous, early EEG, for prediction of neurological outcome. Results: A DWI score >16.7 and a FLAIR score >10.7 on MRI performed at 3±1 days after ROSC predicted poor neurological outcome a 3 months with 100 [91-100]% specificity and sensitivity ranging from 35% to 55%.	neurological outcome a 3 months with 100% specificity and moderate sensitivity.

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
The evidence found does not justify a new systematic review at present.
We found no evidence suggesting a need to change the 2024 ILCOR recommendations.

Note on the interpretation of test results
Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as "positive," and a normal response as "negative," or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should also ideally offer a reasonably high sensitivity when "negative" (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.
In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treating decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome. This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2020 Consensus for this PICOST is that the decision to limit treatment of comatose post–cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was

that in patients who remain comatose in the absence of confounders (eg, sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.

Notes on the interpretation of MRI

In patients with hypoxic-ischaemic brain injury (HIBI), diffusion-weighted Imaging (DWI) on brain MRI detects reduced water diffusion in the brain tissue due to cellular swelling. The assessment of DWI changes is qualitative. To semi-quantitatively assess DWI changes, MRI scores have been developed. However, scoring methods differ. The apparent diffusion coefficient (ADC) is used to assess the impedance of water molecules' diffusion quantitatively, and it is measured in mm^2/sec. ADC values less than 1000-1100 x 10^{-6} mm^2/s are generally acknowledged in adults as indicating restriction. In neuroprognostication studies, ADC is calculated as a whole-brain ADC, or as the percentage of brain volume below an ADC threshold.

Unlike the results of other neuroprognostic tests (e.g., clinical examination), ADC is a continuous rather than dichotomous (categorical) variable. Results are dichotomised to calculate the sensitivity and specificity by establishing a threshold that divides positive from negative results. Consequently, test sensitivity and specificity depend on the threshold chosen: a high threshold increases the specificity of the test and decreases the sensitivity, and vice versa.

A source of heterogeneity for neuroprognostic tests based on MRI is the presence of different calculation methods, which may create different results across measuring methods. Another potential source of heterogeneity is the use of different equipment and different acquisition techniques.

For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

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2025 Evidence Update
ALS 3511 – EEG Post-Resuscitation EEG

Worksheet Author(s): Claudio Sandroni, Sonia D'Arrigo; external collaborator (data extraction and management) Sofia Cacciola
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Interventions: index test based on electrophysiology: electroencephalogram (EEG)
Comparison: the accuracy of the index test was assessed by comparing the predicted outcome with the final outcome.
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.

Year of last full review: 2020

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: COSTR 2020
We recommend that neuroprognostication always be undertaken by using a multimodal approach because no single test has sufficient specificity to eliminate false positives (strong recommendation, very low-certainty evidence).
We suggest using highly malignant EEG patterns to predict poor outcome in adult patients who are comatose and who are off sedation after cardiac arrest (weak recommendation, very low-certainty evidence).
We suggest against EEG background reactivity alone to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
"Cardiac arrest [all fields]" AND "Coma" [all fields] AND "Prognosis" [all fields].

New Search strategy: (for a new PICOST should be outlined here as per Evidence Update Process)
Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) – updated from end of last search (please specify): From April 2020 to April 2024
Time Frame: (new PICOST) – at the discretion of the Task Force (please specify)
Date Search Completed: April 30, 2024
Search Results (Number of articles identified, and number identified as relevant): 88 articles were evaluated in full-text, and 9 were included as relevant.

Inclusion/Exclusion Criteria:

- Inclusion: adult (≥16 years); resuscitated from cardiac arrest (either in-hospital or out-of-hospital). Comatose (unconscious, unresponsive, and/or having a Glasgow Coma Score (GCS)≤8 at the time of study enrolment). Predictor assessed within 7 days from CA. We included only studies where sensitivity and FPR could be calculated, i.e., those where the 2×2 contingency table of true/false negatives and positives for prediction of poor outcome was reported or could be calculated from reported data. We included only studies with neurological outcome assessed at hospital discharge/1 month or later.

- Exclusion: Studies including non-comatose patients or patients in hypoxic coma from causes other than cardiac arrest (e.g., respiratory arrest, carbon monoxide intoxication, drowning, and hanging) were excluded. Studies with neurological outcome assessed at ICU discharge were excluded.

Summary of Evidence Update:
Nine studies evaluated the presence of highly malignant patterns on EEG in 1794 patients (Arctaedius 2024, Barth 2020, Benghanem 2022, Keijzer 2022, Kim 2021, Lilja 2021, Misirocchi 2023, Pouplet 2022, Turella 2024) between 12h and 7 days after ROSC.
In one study (Misirocchi 2023) in 43 patients the presence of highly malignant patterns on early EEG at 12-24h after ROSC predicted poor neurological outcome at 6 months with 35[22-51]% sensitivity and 91 [78-97]% specificity. At 24-72 h instead in 54 patients, its presence predicted poor neurological outcome with 100 [92-100]% specificity and 40 [27-54]% sensitivity.
In one study (Pouplet 2022) in 28 patients the presence of highly malignant patterns on EEG at >24h after ROSC predicted poor neurological outcome at 3 months with 47 [29-67]% sensitivity and 100 [85-100]% specificity.
In one study (Turella 2024) in 822 patients the presence of highly malignant patterns on EEG between 24h and 7 days after ROSC predicted poor neurological outcome at 6 months with 50 [47-54]% sensitivity and 93[91-95]% specificity.
In one study (Arctaedius 2024) the presence of highly malignant EEG patterns at >48 h after CA predicted poor neurological outcome at 2-6 months with 100 [98-100]% specificity and 47 [40-53]% sensitivity.
In five studies (Barth 2020, Benghanem 2022, Keijzer 2022, Kim 2021, Lilja 2021) in 636 patients the presence of highly malignant patterns on EEG between 36h and 72h after ROSC predicted poor neurological outcome at hospital discharge to 6 months with 100% specificity and sensitivity ranging from 15[7-29]% (Keijzer 2022) to 59 [54-64]% (Kim 2021).

Only one study (Turella 2024) in 801 patients evaluated the additional value of the absence of reactivity on EEG at 24h to 14 days showing that it predicted poor neurological outcome at 6 months with 60 [57-64]% specificity and 79 [76-82]% sensitivity. FPR was about 40%.

In all studies, highly malignant EEG patterns were suppression (with or without superimposed discharges) or burst-suppression, defined according to the American Clinical Neurophysiology Society (ACNS) terminology (Hirsch LJ et al, 2012 and 2021). Further details are provided in the note at the end of this document.

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
Sandroni C et al., *Intensive Care Med,* 2020; 46:1803–1851.	Systematic review	Same as this Evidence Update	94 studies were included, of which 19 were about EEG pattern. The presence of highly malignant EEG patterns was evaluated in 10 studies.	Most “highly malignant” patterns included suppression with or without superimposed periodic discharges and burst-suppression. FPR for these combined patterns was low. Results showed that a pattern including isoelectric or low-voltage background or	In comatose resuscitated patients, the presence of highly malignant patterns on EEG recorded 24h or more after ROSC predict poor neurological outcome with high specificity.

				burst-suppression with identical bursts had 0% FPR for poor outcome at 24 and 48 h from ROSC.	

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**
	Study Aim: Study Type:	Inclusion Criteria:	Intervention: Comparison:	1° endpoint:	Study Limitations:

Nonrandomized Trials, Observational Studies published April 1, 2020 to April 30, 2024

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)**
Arctaedius et al, 2024	Study Type: retrospective multi-center observational study. Seven-hundred-nine-four patients were included. EEG was performed on 254 patients.	Inclusion Criteria: adult patients resuscitated from OHCA and IHCA with any presenting rhythm. Exclusion criteria: Not reported	The prognostic accuracy of highly malignant EEG patterns values was not the primary endpoint of the study. 1° endpoint: to evaluate the performance of the 2021 ERC/ESICM algorithm and individual prognostic markers in a mixed cohort of OHC and IHCA patients admitted to in- tensive care. Results: the presence of highly malignant EEG patterns at >48 h after CA predicted poor neurological outcome at 2-6 months with 100 [98-100]% specificity and 47 [40-53]% sensitivity.	In comatose patients after CA, the presence of highly malignant patterns on EEG >48h after ROSC predicts poor outcomes with 100% specificity and low sensitivity.
Barth et al, 2020	Study Type:	Inclusion Criteria:	The prognostic accuracy of highly malignant EEG	In comatose patients after CA, the presence of

	prospective single-centre study. Eighty-nine patients were included. EEG was performed on all patients.	Comatose adult patients resuscitated from CA who underwent brain magnetic resonance imaging (MRI) and at least one EEG. Exclusion criteria: CA of non-cardiac origin, previous structural brain lesions such as stroke, neurodegenerative disorders or tumor.	patterns was not the primary endpoint of the study. 1° endpoint: to correlate the presence and topography of MRI lesions with standardized EEG patterns. Results: the presence of highly malignant EEG patterns at 50.8 ± 22 h after CA predicted poor neurological outcome at 3 months with 100 [95-100]% specificity and 44 [33-55]% sensitivity.	highly malignant patterns on EEG 2-4 days after ROSC predicts poor outcomes with 100% specificity.
Benghanem et al, 2022	Study Type: prospective single-centre study. Eighty-two patients were included. EEG was performed on all patients.	Inclusion Criteria: Consecutive comatose adult patients after resuscitation from CA, regardless of initial rhythm, with somatosensory evoked potentials (SSEPs) performed. Exclusion criteria: brain death, patients awake before SSEP, and patients who died within 48 h post-CA, before a reliable neurological examination could be performed.	The prognostic accuracy of highly malignant EEG patterns was not the primary endpoint of the study. 1° endpoint: to assess if amplitudes of N20-baseline (N20-b) and N20–P25 on SSEP predict neurological outcome at 3 months. Results: the presence of highly malignant EEG patterns at 72 h after CA predicted poor neurological outcome at 3 months with 100 [94-100]% specificity and 36 [26-47]% sensitivity.	In comatose patients after CA, the presence of highly malignant patterns on EEG 72h after ROSC predicts poor outcomes with 100% specificity and low sensitivity.

Keijzer et al, 2022	Study Type: prospective two-centre cohort study. Fifty patients were included. EEG was performed on all patients.	Inclusion Criteria: comatose adult patients after resuscitation from CA. Exclusion criteria: pregnancy, life expectancy < 24 h post-CA, any known progressive brain illness, preexisting dependency in daily living, or a contraindication to undergo an MRI examination (e.g., pacemaker, neurostimulator, foreign metal objects).	1° endpoint: to investigate the additional values of a combination of MRI to EEG to predict neurological outcome at 3 months. Results: the presence of highly malignant EEG patterns at ³24 h predicted poor neurological outcome at 3 months with 100 [91-100]% specificity and 15 [7-29]% sensitivity.	In comatose patients after CA, the presence of highly malignant patterns on EEG at 24h or later after ROSC predicts poor outcome with 100% specificity and low sensitivity.
Kim et al, 2021	Study Type: prospective, multicenter, observational, cohort study. Four-hundred-eighty-nine patients were included. Patients with early EEG ≤72 h (n=353). Patients with late EEG (more than 72h to 7 days) (n=136)	Inclusion Criteria: Comatose adult patients resuscitated from non-traumatic OHCA treated with TTM, who underwent standard intermittent EEG within 7 days after return of ROSC. Exclusion criteria: patients with terminal illness, under hospice care, with a pre-documented	1° endpoint: to assess the prognostic performance of the three standardized EEG pattern categories (highly malignant, malignant and benign) according to the EEG timing (early vs. late) to predict poor neurological outcome at 1 month. Results: the presence of highly malignant EEG patterns at ≤72h or >72h from ROSC predicted poor neurological outcome at 1 months with 100 [97-100]% specificity and 59 [54-64]% and 56 [47-65]% sensitivity, respectively.	In comatose patients after CA, the presence of highly malignant patterns on EEG within 7 days from ROSC predicts poor outcomes with 100% specificity and moderate sensitivity.

		"Do Not Resuscitate" order, with intracranial bleeding or acute stroke, and with pre-arrest CPC score 3 or 4, EEG data within 7 days after ROSC not available or with poor-quality.		
Lilja et al, 2021	Study Type: retrospective analysis of a local cohort. Sixty-two patients were included. EEG was performed on all patients.	Inclusion Criteria: Comatose adult patients resuscitated from OHCA of presumed cardiac or unknown cause, who had an EEG examination at least 7 days after ROSC. Exclusion criteria: Not reported	1° endpoint: to study the prognostic accuracy and the interrater agreement when standardized EEG patterns were analysed and compare them to neurological outcome at hospital discharge. Results: the presence of highly malignant EEG patterns at 59 (42-91) h predicted poor neurological outcome at hospital discharge with 100 [93-100]% specificity and 42 [30-55]% sensitivity.	In comatose patients after CA, the presence of highly malignant patterns on EEG at 2-4 days after ROSC predicts poor outcomes with 100% specificity and low sensitivity.
Misirocchi et al, 2023	Study Type: retrospective analysis of a local cohort. Fifty-eight patients were included. EEG was performed on all patients.	Inclusion Criteria: Comatose adult patients resuscitated from CA, who underwent at least two EEG recordings, one during TTM (12-36 h) and one after progressive rewarming (36-72 h). Exclusion criteria:	1° endpoint: to evaluate the prognostic accuracy of an early (12-36 h) or late (36-72 h after CA) onset of highly malignant EEG patterns to predict poor neurological outcome at 6 months. We asked the authors to provide the data on the accuracy of EEG recorded between 12-24h and 24-72h from ROSC. Results: the presence of early highly malignant EEG patterns at 12-24h after ROSC predicted poor	In comatose patients after CA, the presence of highly malignant patterns on EEG predicts poor outcome with 91% specificity if recorded between 12h and 24h after ROSC and with 100% specificity if recorded between 24h and 72h after ROSC. The sensitivity is low at both time points.

		Not reported	neurological outcome at 6 months with 91 [78-97]% specificity and 35 [22-51]% sensitivity. At 24-72 h highly malignant patterns predicted poor neurological outcome with 100 [92-100]% specificity and 40 [27-54]% sensitivity.	
Pouplet et al, 2022	Study Type: Prospective randomized trial (ISOCRATE trial). Forty-nine patients included. NSE was measured in 48 patients.	Inclusion Criteria: comatose shockable cardiac arrest patients treated with targeted temperature management at 33 °C. Exclusion criteria: Presence of confounders at 72h, non-neurological cause of death or withdrawal.	The prognostic accuracy of EEG was not the primary endpoint of the study. 1° endpoint: to assess the predictive value of NF-L in patients with a shockable rhythm who received cardiopulmonary resuscitation and assess its added value to the ESICM guideline algorithms. Results: the presence of highly malignant EEG patterns at >24h predicted poor neurological outcome at 3 months with 100 [85-100]% specificity and 47 [29-67]% sensitivity.	In comatose patients after CA, the presence of highly malignant patterns on EEG recorded >24 from ROSC predicts poor outcomes with 100% specificity and low sensitivity.
Turella et al, 2024	Study Type: pre-planned sub-study of the TTM trial. Eighty-hundred-forty-five patients were included. EEG was performed on 822 patients.	Inclusion Criteria: comatose adult patients after resuscitation from OHCA of presumed cardiac cause. Exclusion criteria: Unwitnessed CA with an initial rhythm of	1° endpoint: to evaluate the prognostic ability of highly malignant EEG patterns and the additional value of the combination of absence of reactivity to predict poor neurological outcome at 6 months. Results: the presence of highly malignant EEG patterns at 24h to 7 days predicted poor neurological outcome at	In comatose patients after CA, the presence of highly malignant patterns on EEG between 24h and 7 days after ROSC predicts poor outcome with high specificity.

		asystole, temperature on admission <30°C, on ECMO prior to ROSC, obvious or suspect pregnancy, intracranial bleeding, severe COPD with long-term home oxygen therapy.	hospital discharge with 93 [91-95]% specificity and 50 [47-54]% sensitivity.	
Absence of reactivity on EEG				
Turella et al, 2024	Study Type: pre-planned sub-study of the TTM trial. Eighty-hundred-forty-five patients were included. EEG reactivity was evaluated on 801 patients.	Inclusion Criteria: comatose adult patients after resuscitation from OHCA of presumed cardiac cause. Exclusion criteria: Unwitnessed CA with an initial rhythm of asystole, temperature on admission <30°C, on ECMO prior to ROSC, obvious or suspect pregnancy, intracranial bleeding, severe COPD with long-term home oxygen therapy.	1° endpoint: to evaluate the prognostic ability of highly malignant EEG patterns and the additional value of the combination of absence of reactivity to predict poor neurological outcome at 6 months. Results: the additional value of the absence of reactivity on EEG at 24h to 14 days predicted poor neurological outcome at 6 months with 60 [57-64]% specificity and 79 [76-82]% sensitivity.	In comatose patients after CA, the absence of reactivity on EEG recorded between 24h and 14 days after ROSC predicts poor outcome with low specificity.

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
The evidence found does not justify a new systematic review at present.

Note: definition of highly malignant EEG patterns and EEG reactivity
In all studies included in this Evidence Update, highly malignant patterns included suppression or burst-suppression, defined according to the Standardized Critical Care EEG Terminology of the American Clinical Neurophysiology Society's (ACNS). The ACNS terminology was published in 2012 and 2021 (Hirsch LJ et al, J Clin

Neurophysiol 30(1): 1-27; https://pubmed.ncbi.nlm.nih.gov/23377439/ Hirsch LJ et al., J Clin Neurophysiol 2021 Jan 1;38(1):1-29; https://pubmed.ncbi.nlm.nih.gov/33475321/]. Based on the ACNS terminology, suppression occurs when the background voltage in the entire record is below 10 μV, and burst suppression occurs when >50% of the record consists of suppression, alternated with bursts. This definition was consistent with that used in the ILCOR 2020 CoSTR.
EEG background reactivity is defined by ACNS as "change in cerebral EEG activity to intense auditory and/or noxious stimuli. This may include change in amplitude or frequency, including attenuation of activity". This definition was used in the paper by Turella et al. included in the present Evidence Update.

Note on the interpretation of test results
Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as "positive," and a normal response as "negative," or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should also ideally offer a reasonably high sensitivity when "negative" (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.
In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treating decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome. This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2020 Consensus for this PICOST is that the decision to limit treatment of comatose post–cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that in patients who remain comatose in the absence of confounders (eg, sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.
For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

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2025 Evidence Update
ALS 3511 – EEG Post-Resuscitation SSEP

Worksheet Author(s): Claudio Sandroni, Sofia Cacciola, Sonia D'Arrigo
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Interventions: index test based on electrophysiology: short-latency somatosensory evoked potentials (SSEP)
Comparison: the accuracy of the index test was assessed by comparing the predicted outcome with the final outcome.
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.

Year of last full review: 2020
Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: COSTR 2020
We suggest using a bilaterally absent N20 wave of SSEP in combination with other indices to predict poor outcome in adult patients who are comatose after cardiac arrest (weak recommendation, very low–certainty evidence).

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
"Cardiac arrest [all fields]" AND "Coma" [all fields] AND "Prognosis" [all fields].

New Search strategy: (for a new PICOST should be outlined here as per Evidence Update Process)
Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) – updated from end of last search (please specify): From April 2020 to April 2024
Time Frame: (new PICOST) – at the discretion of the Task Force (please specify)
Date Search Completed: April 30, 2024
Search Results (Number of articles identified, and number identified as relevant): 88 articles were evaluated in full-text, and 6 were included as relevant.

Inclusion/Exclusion Criteria:

- Inclusion: adult (≥16 years); resuscitated from cardiac arrest (either in-hospital or out-of-hospital). Comatose (unconscious, unresponsive, and/or having a Glasgow Coma Score (GCS)≤8 at the time of study enrolment). Predictor assessed within 7 days from CA. We included only studies where sensitivity and FPR could be calculated, i.e., those where the 2×2 contingency table of true/false negatives and positives for prediction of poor outcome was reported or could be calculated from reported data. We included only studies with neurological outcome assessed at hospital discharge/1 month or later.
- Exclusion: Studies including non-comatose patients or patients in hypoxic coma from causes other than cardiac arrest (e.g., respiratory arrest, carbon monoxide intoxication, drowning, and hanging) were excluded. Studies with neurological outcome assessed at ICU discharge were excluded.

Summary of Evidence Update:
Six studies evaluated the absent N20 wave on SSEP (Arciniegas-Villanueva 2022, Benghanem 2022, Caroyer 2021, Keijzer 2022, Scarpino 2021, Qing 2024) between 24h after ROSC until ³72 h. They found that the absence of N20 wave on SSEP predicted poor neurological outcome at hospital discharge to 6-12 months with 100% specificity and a sensitivity ranging from 20% (Keijzer 2022) to 53 % (Arciniegas-Villanueva 2022, Scarpino 2021).

One study (Arciniegas-Villanueva 2022) showed that the combination of absent N20 and absent N70 increased sensitivity up to 88%.
Two studies (Benghanem 2022 and Scarpino 2021) evaluated low SSEP amplitude and its threshold for predicting poor neurological outcome.
In one study (Benghanem 2022) an N20 wave amplitude <0,35 µV at 72 h predicted poor neurological outcome at 3 months with 100% specificity and 35% sensitivity. In another study (Scarpino, 2021) a an N20 wave amplitude ≤0.38 mV, ≤0.73 mV and ≤1.01 mV at 12 h, 24 h, and 72 h, respectively, had 0%FPR for predicting poor neurological outcome, with sensitivity ranging from 61[51-69]% to 82[76-88]%.

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
Sandroni C et al., *Intensive Care Med,* 2020; 46:1803–1851.	Systematic review	Same as this Evidence Update	94 studies were included, of which 18 were about short-latency somatosensory evoked potentials (SSEP).	A bilaterally absent N20 wave on SSEP from ROSC up to 5 days after ROSC predicted poor neurological outcome with 100% specificity. However, 2 studies reported a FPR rate of 50% and 75%. In both of these studies, only a few patients were assessed which may have amplified the observed false positive rate index. Sensitivity ranged from 18% to 69%.	In comatose resuscitated patients, a bilaterally absent N20 SSEP wave within the first week after ROSC has 0% FPR for predicting poor neurological outcome (CPC 3–5) at hospital discharge/1 month or later in almost all studies.

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
	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)
Arciniegas-Villanueva et al, 2022	Study Type: retrospective analysis of prospective single center study. Sixty patients were included. SSEPs were performed on all patients	Inclusion Criteria: Consecutive comatose adult patients resuscitated from CA. Exclusion criteria: Less than 18 years-old, those who did not live in the hospital area (to avoid problems in follow-up), previous neurodegenerative disease.	1° endpoint: to evaluate the utility of SSEP (N20 and N70 waves) as an early indicator of neurological outcome at 6-12 months. Results: the absence of N20 at 24-72 h after ROSC predicted poor neurological outcome at 6-12 months with 100% specificity and 53.6 [40.4-66.4]% sensitivity.	In comatose patient after CA, the bilateral absence of the N20 SSEP wave predicts poor outcomes with high specificity and moderate sensitivity.
Benghanem et al, 2022	Study Type: prospective single-center study. Eighty-two patients were included. SSEPs were performed on all patients.	Inclusion Criteria: Consecutive comatose adult patients after resuscitation from CA, regardless of initial rhythm, with SSEP performed. Exclusion criteria: brain death, patients awake before SSEP, and patients who died within 48 h post CA, before a reliable neurological examination	1° endpoint: to assess if amplitudes of N20-baseline (N20-b) and N20–P25 on SSEP predict neurological outcome at 3 months. Results: the bilateral absence of the N20 SSEP wave at 72 h predicted poor neurological outcome at 3 months with 100% specificity and 30 [20-41]% sensitivity.	The bilateral absence of the N20 SSEP wave predicts poor outcomes with high specificity and moderate sensitivity.

		could be performed.		
Caroyer et al, 2021	Study Type: prospective single center cohort study. One-hundred-fifteen patients were included. SSEPs were performed on 48/115 patients.	Inclusion Criteria: Comatose adult resuscitated CA patients receiving continuous EEG monitoring (cEEG). Exclusion criteria: clear signs of consciousness on admission or high risk of death within 24 h after admission.	The prognostic accuracy of absent N20-wave on SSEP was not the primary endpoint of the study. 1° endpoint: to determine and compare the effectiveness, inter-rater reliability and prognostic value of different types of stimulus for EEG reactivity testing, using a standardized stimulation protocol and standardized definitions. Results: the bilateral absence of the N20 SSEP wave at 48-72 h predicted poor neurological outcome at hospital discharge with 100% specificity and 38 [24-53]% sensitivity.	The bilateral absence of the N20 SSEP wave predicts poor outcomes with high specificity and moderate sensitivity.
Keijzer et al, 2022	Study Type: prospective multicenter (two) cohort study. Fifty patients were included. SSEPs were performed on all patients.	Inclusion Criteria: comatose adult patients after resuscitation from CA. Exclusion criteria: pregnancy, life expectancy < 24 h post CA, any known progressive brain illness, preexisting dependency in daily living, or a contraindicatio n to undergo MRI examination	The prognostic accuracy of absent N20-wave on SSEP was not the primary endpoint of the study. 1° endpoint: to investigate the additional values of combination of MRI to EEG to predict neurological outcome at 6 months. Results: the bilateral absence of the N20 SSEP wave at >72 h predicted poor neurological outcome at 6 months with 100% specificity and 20 [10-34]% sensitivity.	In comatose patient after CA, the bilateral absence of the N20 SSEP wave predicts poor outcomes with high specificity and low sensitivity.

		(e.g., pacemaker, neurostimulator, foreign metal objects).		
Qing et al, 2024	Study Type: prospective single center study. Seventy-two patients were included. SSEPs were performed on 29 patients.	Inclusion Criteria: Consecutive comatose adult patients resuscitated from CA. Exclusion criteria: Not reported	The prognostic accuracy of absent N20-wave on SSEP was not the primary endpoint of the study. 1° endpoint: to investigate the prognostic value of a simple stratification system of EEG patterns and spectral types for patients after CA. Results: the bilateral absence of the N20 SSEP wave at 72 h predicted poor neurological outcome at hospital discharge with 100% specificity and 32 [17-52]% sensitivity.	The bilateral absence of the N20 SSEP wave predicts poor outcomes with high specificity and moderate sensitivity.
SSEP amplitude				
Benghanem et al, 2022	Study Type: prospective single center study. Eighty-two patients were included. SSEPs were performed on all patients.	Inclusion Criteria: Consecutive comatose adult patients after resuscitation from CA, regardless of initial rhythm, with SSEP performed. Exclusion criteria: brain death, patients awake before SSEP, and patients who died within 48 h post CA, before a reliable	1° endpoint: to assess if the amplitudes of N20-baseline (N20-b) and N20–P25 on SSEP predict neurological outcome at 3 months. Results: a low voltage N20 <0.35 µV and N20–P25 < 0.56 µV at 72 h predicted poor outcome at 3 months with 100% specificity and a moderate sensitivity (35% and 50%, respectively).	In comatose patients after CA, both N20-b and N20–P25 low amplitudes predict poor outcomes with high specificity and moderate sensitivity.

		neurological examination could be performed.		
Scarpino et al, 2021	Study Type: retrospective analysis of the ProNeCA multicentre prognostication study dataset. Four hundred-three patients were included. SSEPs were performed on 218 patients (12 h), 260 patients (24h) and 240 patients (72 h).	Inclusion Criteria: adult comatose CA survivors whose SSEPs were recorded at 12h, 24 h and 72 h after ROSC. Exclusion criteria: not reported	1° endpoint: to assess high-amplitude SSEP N20 wave recorded at 12 h after CA accurately predicts good neurological outcome at six months. 2° endpoint: to investigate the accuracy of a low SSEP amplitude as a predictor of poor outcome at 12 h, 24 h, and 72 h after CA. Results: an N20 amplitude 0.38 mV, 0.73 mV and 1.01 mV at 12 h, 24 h, and 72 h, respectively, had 0% FPR with sensitivity ranging from 61[51-69]% and 82[76-88]%.	In comatose resuscitated patients, the amplitude of the N20 wave of SSEP can predict 6-months neurological outcome.
Combination of bilaterally absent N20 with absent N70				
Arciniegas-Villanueva et al, 2022	Study Type: retrospective analysis of prospective single center study. Sixty patients included. SSEPs were performed on all patients.	Inclusion Criteria: Consecutive comatose adult patients resuscitated from CA. Exclusion criteria: Less than 18 years-old, those who did not live in the hospital area (to avoid problems in follow-up), previous	1° endpoint: to evaluate the utility of SSEP (N20 and N70 waves) as an early indicator of neurological outcome at 6-12 months. Results: The combination of absent N20 with the absence of N70 wave at 24-72 h after CA increased sensitivity from 53.7[38.7-67.9]% to 88[70-95.8]%, maintaining 100% specificity.	In comatose patients after CA, the absence of bilaterally N20 in combination with absent N70 increases the accuracy of SSEP to predict poor neurological outcomes.

		neurodegenerative disease.		

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
The six studies included in this evidence update largely confirmed the results of both the ILCOR 2020 evidence review and the 2020 systematic review on bilateral absent N20 on SSEP.
Two studies on the SSEP N20 wave amplitude showed that low amplitudes may also predict poor neurological outcome with 100% specificity. In both studies, using a low-amplitude threshold for the N20 SSEP wave yielded higher sensitivity than the absence of the N20 SSEP wave. However, this amplitude was not consistent across these studies.

The evidence found does not justify a new systematic review at present.

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2025 Evidence Update
ALS 3512 – Blood Biomarkers (GFAP and Tau)

Worksheet Author(s): Claudio Sandroni, Sonia D'Arrigo; external collaborator (data extraction and management) Sofia Cacciola
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Interventions: index test based on biomarkers: glial fibrillary acidic protein (GFAP), tau protein
Comparison: the accuracy of the index test was assessed by comparing the predicted outcome with the final outcome.
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.

Year of last full review: 2020
Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: COSTR 2020
We suggest against using serum levels of glial fibrillary acidic protein, serum tau protein, or neurofilament light chain for predicting poor neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
"Cardiac arrest [all fields]" AND "Coma" [all fields] AND "Prognosis" [all fields].

New Search strategy: (for a new PICOST should be outlined here as per Evidence Update Process)
Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) – updated from end of last search (please specify): From April 2020 to April 2024
Time Frame: (new PICOST) – at the discretion of the Task Force (please specify)
Date Search Completed: April 30, 2024
Search Results (Number of articles identified, and number identified as relevant): 88 articles were evaluated in full-text, and 5 were included as relevant.

Inclusion/Exclusion Criteria:

- Inclusion: adult (≥16 years); resuscitated from cardiac arrest (either in-hospital or out-of-hospital). Comatose (unconscious, unresponsive, and/or having a Glasgow Coma Score (GCS)≤8 at the time of study enrolment). Predictor assessed within 7 days from CA. We included only studies where sensitivity and FPR could be calculated, i.e., those where the 2×2 contingency table of true/false negatives and positives for prediction of poor outcome was reported or could be calculated from reported data. We included only studies with neurological outcome assessed at hospital discharge/1 month or later.
- Exclusion: Studies including non-comatose patients or patients in hypoxic coma from causes other than cardiac arrest (e.g., respiratory arrest, carbon monoxide intoxication, drowning, and hanging) were excluded. Studies with neurological outcome assessed at ICU discharge were excluded.

Summary of Evidence Update:
This update identified 5 relevant studies not included in the 2020 ILCOR evidence review.
Five studies (Arctaedius 2024, Ebner 2020, Humaloja 2022, Klitholm 2023, Song 2023) evaluated the ability of the blood levels of Glial Fibrillary Acidic Protein (GFAP) measured between 12h and 72h after ROSC to predict poor neurological outcome in comatose patients after CA.
In one study (Arctaedius 2024) including 300 patients, a GFAP level of 1626 pg/ml at 12 h from ROSC predicted poor neurological outcome at 2-6 months with 99[97-100]% specificity and 42[36-48]% sensitivity. In that study, the GFAP level for 100% specificity (with 7[4-10]% sensitivity) was 33,465 pg/ml.
In three studies (Ebner 2020, Humaloja 2022, Song 2023) including 899 patients, a GFAP level of ranging from 1970 to 8018 pg/ml at 24 h from ROSC predicted a poor neurological outcome at 6 months with specificity ranging from 99% to 100[95-100]% and sensitivity ranging from 13 [2-24]% to 44 [35-55]%.
In five studies (Arctaedius 2024, Ebner 2020, Humaloja 2022, Klitholm 2023, Song 2023) including 1139 patients, GFAP levels ranging from 2591 to 15,000 pg/ml at 48 h from ROSC predicted poor neurological outcome at 2-6 months with specificity ranging from 98[91-100]% to 100% and sensitivity ranging from 8[3-18]% to 44[34-55]%.
In four studies (Ebner 2020, Humaloja 2022, Klitholm 2023, Song 2023) including 877 patients, GFAP levels ranging from 1118 to 8617 pg/ml at 72 h from ROSC predicted poor neurological outcome at 6 months with specificity ranging from 98% to 100% and sensitivity ranging from 8 [4-18]% to 56 [45-65]%.

Three studies (Arctaedius 2024,Humaloja 2022, Song 2023) evaluated the ability of the blood levels of tau protein measured between 12h and 72h after ROSC to predict poor neurological outcome in comatose patients after CA.
In one study (Arctaedius 2024) including 300 patients, a tau protein level of 502.5 pg/ml at 12 h from ROSC predicted poor neurological outcome at 2-6 months with 100[98-100]% specificity and 24[19-29]% sensitivity.
In two studies (Humaloja 2022, Song 2023) including 211 patients, a tau protein level of 40 and 131 pg/ml at 24 h from ROSC predicted poor neurological outcome at 6 months with 99% and 100[95-100]% specificity and 20[13-30]% and 21[10-37]% sensitivity, respectively.
In three studies (Arctaedius 2024, Humaloja 2022, Song 2023) including 419 patients, tau protein levels ranging from 16 to 406 pg/ml at 48 h from ROSC predicted poor neurological outcome at 2-6 months with specificity ranging from 99% to 100% and sensitivity ranging from 19% to 75%.
Two studies (Humaloja 2022, Song 2023) assessed a tau protein levels at 72 h from ROSC. In these studies, tau protein levels of 10 pg/ml and 698 pg/ml predicted poor neurological outcome at 6 months with 99% and 100[92-100]% specificity and 88[77-99]% and 7[3-15]% sensitivity, respectively.

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
Sandroni C et al., *Intensive Care Med,* 2020; 46:1803–1851.	Systematic review	Same as this Evidence Update	94 studies were included, of which 21 were about biomarkers. NSE thresholds were evaluated in 16 studies.	In the present review, we included limited evidence regarding three biomarkers, not included in our previous reviews. These include glial fibrillary acidic protein (GFAP), serum tau protein, and neurofilament light chain (NFL). GFAP has been investigated only in one study (Helwig	

				2017) and serum tau protein only in another (Mattsson 2017).	

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**
	Study Aim: Study Type:	Inclusion Criteria:	Intervention: Comparison:	1° endpoint:	Study Limitations:

Nonrandomized Trials, Observational Studies published April 1, 2020 to April 30, 2024

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)**
Glial Fibrillary Acidic Protein (GFAP)				
Arctaedius, 2024	Study Type: Multicentre retrospective data analysis from three hospitals as part of the SWECRIT biobank project. Among 617 patients from the SWECRIT biobank, 428 were included. GFAP was measured in 300 patients at 12h, in 210 patients at 48 h.	Inclusion Criteria: Adult comatose OHCA, irrespective of rhythm and witnessed status. Exclusion criteria: Patients with only an admission sample (drawn < 6 h after cardiac arrest) were excluded.	1° endpoint: the accuracy of GFAP and tau for predicting poor neurological outcome at 2-6 months after cardiac arrest. Results: GFAP blood levels >33465 pg/ml at 12h after ROSC, or >2591 at 48h after ROSC predicted poor neurological outcome with 100[98-100]% specificity and 7[4-10]% and 41 [34-48]% sensitivity, respectively.	In comatose patients after CA, GFAP at 12h and 48h after ROSC predicts poor outcomes with 100% specificity. At 12h the threshold for 100% specificity was very high, resulting in low sensitivity.
Ebner, 2020	Study Type: explorative analysis of serum	Inclusion Criteria: Comatose adult OHCA patients of presumed	1° endpoint: to evaluate the prognostic accuracy of the serum biomarkers GFAP and UCH-L1 for	In comatose patients after CA, GFAP blood levels at 24h, 48h and 72h after ROSC predict poor outcomes with 100%

	biomarkers in the international multicentre TTM trial. Among 819 patients from the 29 participating centres in the biobank, 717 were included. GFAP was measured in 689 patients at 24h, in 654 patients at 48h, in 598 at 72h.	cardiac cause, irrespective of the initial rhythm. Exclusion criteria: ROSC more than 240 minutes, unwitnessed CA, suspected or known acute intracranial haemorrhage or stroke, and a body temperature of less than 30°C.	neurological outcome after CA. Results: GFAP blood levels >3425 pg/ml at 24h after ROSC, or >2952 at 48h or > 3581 at 72 h predicted poor neurological outcome with 100[99-100]% specificity and 17 [14-20]%, 19[16-23]% and 12 [10-15]% sensitivity, respectively.	specificity and low sensitivity.
Humaloja, 2022	Study Type: Post hoc analysis of COMACARE trial (prospective multicenter study). One-hundred-twelve patients were included. GFAP was measured in 110 patients at 24h, in 108 patients at 48h and 104 patients at 72h.	Inclusion Criteria: Comatose adult OHCA with shockable rhythm, confirmed or suspected cardiac origin treated with TTM. Exclusion criteria: IHCA; CA with non-shockable initial rhythm; arrest with a confirmed or presumed non-cardiac etiology; conscious patient, pre-existing cerebral disease, age<18 or>80 years; pregnancy; severe oxygenation	1° endpoint: To determine the ability of GFAP and tau protein to predict neurological outcome after OHCA. Results: GFAP blood levels >8018 pg/ml at 24h after ROSC predicted poor neurological outcome at 6 months with 99% specificity and 13 [2-24]% sensitivity. GFAP blood levels >6262 pg/ml at 48h after ROSC predicted poor neurological outcome at 6 months with 99% specificity, and 19 [7-31]% sensitivity, GFAP blood levels >4235 pg/ml at 72h after ROSC predicted poor neurological outcome at 6 months with 99% specificity, and 29 [14-45]% sensitivity.	In comatose patients after CA, GFAP blood levels at 24h, 48h and 72h after ROSC predict poor outcomes with 99% specificity and low sensitivity.

		disorder (PaO2/FiO2 < 100 mmHg); severe chronic obstructive pulmonary disease (COPD).		
Klitholm, 2023	Study Type: prospective single-centre cohort study (substudy of the TTH48 trial). 82 patients were included. GFAP was measured in 77 patients at 48h and 75 patients at 72h.	Inclusion Criteria: Adult comatose OHCA with a presumed cardiac origin. Exclusion criteria: unwitnessed asystole, terminal disease, severe coagulopathy, pregnancy, known neurological disease with cognitive impairment, death before randomization.	1° endpoint: To evaluate the neuroprognostic performance at 6 months of NfL and GFAP and to compare it with that of NSE. Results: GFAP blood levels >15,000 ng/L at 48h after ROSC, or >8617.1 ng/L at 72h after ROSC predicted poor outcome at 6 months with 100% [98-100] specificity and 8 [3-17]%, and 8 [4-18]% sensitivity, respectively.	In comatose patients after CA, GFAP blood levels at 48h and 72h after ROSC predict poor outcomes with 100% specificity and low sensitivity.
Song, 2023	Study Type: prospective, observational in two centres in South Korea. One-hundred patients were included. GFAP was measured in all patients.	Inclusion Criteria: Comatose adult OHCA regardless of etiology of cardiac arrest, treated with TTM. Exclusion criteria: history of cerebrovascular disease, active intracranial bleeding, acute stroke, known severe	1° endpoint: NfL, GFAP, tau protein, and UCH-L1 accuracy for predicting poor outcome at 6 months. Results: GFAP blood levels >1970 pg/L at 24h after ROSC, or >9520 pg/L at 48h after ROSC, or >1180 pg/L at 72h after ROSC predicted poor outcome at 6 months with 100[92-100]% specificity and 44[27-62]%, 44[26-62]% and 55[36-72]% sensitivity, respectively.	In comatose patients after CA, GFAP blood levels at 24h, 48h and 72h after ROSC predict poor outcomes with 100% specificity and moderate sensitivity.

		coagulopathy or terminal disease, CA due to trauma or drugs, do-not-attempt resuscitation order.		
Tau protein				
Arctaedius, 2024	Study Type: Multicentre retrospective data analysis from three hospitals as part of the SWECRIT biobank project. Among 617 patients from the SWECRIT biobank, 428 were included. Tau protein was measured in 300 patients at 12h, in 210 patients at 48 h.	Inclusion Criteria: Adult comatose OHCA, irrespective of rhythm and witnessed status. Exclusion criteria: Patients with only an admission sample (drawn < 6 h after cardiac arrest) were excluded	1° endpoint: the accuracy of GFAP and tau for predicting poor neurological outcome at 2-6 months after cardiac arrest. Results: Tau blood levels >502.5 pg/ml at 12h after ROSC, or >104.5 at 48h after ROSC predicted poor neurological outcome at 2-6 months with 100[98-100]% specificity and 24[19-29]% and 56[49-63]% sensitivity, respectively.	In comatose patients after CA, tau blood levels at 12h and 48h after ROSC predict poor outcomes with 100% specificity and low to moderate sensitivity, respectively.
Humaloja, 2022	Study Type: Post hoc analysis of COMACARE trial (prospective multicenter study). One-hundred-twelve patients were included. Tau was measured in 111 patients at 24h, in 109 patients at 48h and 105 patients at 72h.	Inclusion Criteria: Comatose adult OHCA with shockable rhythm, confirmed or suspected cardiac origin treated with TTM. Exclusion criteria: IHCA; CA with non-shockable initial rhythm; arrest with a confirmed or presumed non-cardiac	1° endpoint: To determine the ability of GFAP and tau protein to predict neurological outcome after OHCA. Results: Tau protein blood levels >40 pg/ml at 24h after ROSC predicted poor neurological outcome at 6 months with 99% specificity and 21 [8-34]% sensitivity. Tau protein blood levels >16 pg/ml at 48h after ROSC predicted poor neurological outcome at 6 months with 99% specificity and 75 [61-89]% sensitivity.	In comatose patients after CA, tau protein blood levels at 24h, 48h and 72h after ROSC predict poor outcomes with 99% specificity, low sensitivity at 24h and high sensitivity at 48h and 72h.

		etiology; conscious patient, pre-existing cerebral disease, age<18 or>80 years; pregnancy; severe oxygenation disorder (PaO2/FiO2 < 100 mmHg); severe chronic obstructive pulmonary disease (COPD).	Tau protein blood levels >10 pg/ml at 72h after ROSC predicted poor neurological outcome at 6 months with 99% specificity and 88 [77-99]% sensitivity.	
Song, 2023	Study Type: prospective, observational in two centres in South Korea. One hundred patients were included. Tau protein was measured in all patients.	Inclusion Criteria: Comatose adult OHCA regardless of etiology of cardiac arrest, treated with TTM. Exclusion criteria: history of cerebrovascular disease, active intracranial bleeding, acute stroke, known severe coagulopathy or terminal disease, CA due to trauma or drugs, do-not-attempt resuscitation order.	1° endpoint: to assess NfL, GFAP, tau protein, and UCH-L1 accuracy for predicting poor outcome at 6 months. Results: Tau blood levels >131 pg/L 24h after ROSC, or >406 pg/L 48h after ROSC, or >698 pg/L 72h after ROSC predicted poor outcome at 6 months with 100[92-100]% specificity and 21[10–37]%, 19[8–35]% and 8[2–23]% sensitivity, respectively.	In comatose patients after CA, tau blood levels at 24h, 48h and 72h after ROSC predict poor outcomes with 100% specificity and low sensitivity.

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
The evidence found does not justify a new systematic review at present.

Note on the interpretation of test results

Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as "positive," and a normal response as "negative," or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should also ideally offer a reasonably high sensitivity when "negative" (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.
In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treating decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome. This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2020 Consensus for this PICOST is that the decision to limit treatment of comatose post–cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that in patients who remain comatose in the absence of confounders (eg, sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.

Notes on the interpretation of biomarkers
Unlike the results of other neuroprognostic tests (e.g., clinical examination), biomarker blood levels are continuous rather than dichotomous (categorical) variables. Results are dichotomized to calculate the sensitivity and specificity of these biomarkers by establishing a threshold that divides positive from negative results. Consequently, test sensitivity and specificity depend on the threshold chosen: a high threshold increases the specificity of the test and decreases the sensitivity, and vice versa.
Biomarkers are released with different latency and speed following acute brain injury, although their kinetics has not been investigated in detail in post-cardiac arrest patients. Limited evidence shows that GFAP blood levels increase earlier than NSE after cardiac arrest (Gul SS et al., Med Hypotheses 2017; 105:34-47). In the study from Ebner et al included in this Evidence Update (Ebner, 2020) GFAP was significantly more accurate than NSE in predicting poor outcome at 24h after cardiac arrest, but the difference decreased at 48h and 72h. The blood levels of GFAP after cardiac arrest are in the range of picograms and require ultrasensitive immuonassays for their measurement. Most of the studies we included in this Evidence Update used the single molecular array (SIMOA™) assay. However, this technique is not widely available yet.
An important advantage of biomarkers is that – unlike other outcome predictors after cardiac arrest – they can be easily assessed in a blinded fashion, therefore reducing the risk of a self-fulfilling prophecy bias.
For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

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2025 Evidence Update
ALS 3512 – Blood Biomarkers (NfL)

Worksheet Author(s): Claudio Sandroni, Sonia D'Arrigo; external collaborator (data extraction and management) Sofia Cacciola
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Interventions: index test based on biomarkers: neurofilament light chain (NfL)
Comparison: the accuracy of the index test was assessed by comparing the predicted outcome with the final outcome.
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.

Year of last full review: 2020
Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: COSTR 2020
We suggest against using serum levels of glial fibrillary acidic protein, serum tau protein, or neurofilament light chain for predicting poor neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
"Cardiac arrest [all fields]" AND "Coma" [all fields] AND "Prognosis" [all fields].

New Search strategy:
Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) – updated from end of last search (please specify): From April 2020 to April 2024
Time Frame: (new PICOST) – at the discretion of the Task Force (please specify)
Date Search Completed: April 30, 2024
Search Results (Number of articles identified, and number identified as relevant): 88 articles were evaluated in full-text, and 7 were included as relevant.

Inclusion/Exclusion Criteria:
- Inclusion: adult (≥16 years); resuscitated from cardiac arrest (either in-hospital or out-of-hospital). Comatose (unconscious, unresponsive, and/or having a Glasgow Coma Score (GCS)≤8 at the time of study enrolment). Predictor assessed within 7 days from CA. We included only studies where sensitivity and FPR could be calculated, i.e., those where the 2×2 contingency table of true/false negatives and positives for prediction of poor outcome was reported or could be calculated from reported data. We included only studies with neurological outcome assessed at hospital discharge/1 month or later.
- Exclusion: Studies including non-comatose patients or patients in hypoxic coma from causes other than cardiac arrest (e.g., respiratory arrest, carbon monoxide intoxication, drowning, and hanging) were excluded. Studies with neurological outcome assessed at ICU discharge were excluded.

Summary of Evidence Update:

Seven studies evaluated the ability of the blood levels of NfL measured between 24h and 72h after ROSC to predict poor neurological outcome in comatose patients after CA (Adler 2022, Klitholm 2023, Levin 2023, Pouplet 2022, Song 2023, Wihersaari 2021, Wihersaari 2022).

One study (Levin 2023) in 300 patients investigated NfL 12 h after ROSC. In this study, NfL levels of 90 pg/mL in OHCA and 207 pg/mL in IHCA predicted poor neurological outcome at 2-6 months with 100% specificity and sensitivity of 53[48-59]% and 29 [20-39]%, respectively.
Five studies (Adler 2022, Klitholm 2023, Song 2023, Wihersaari 2021, Wihersaari 2022) in a total of 572 patients investigated NfL 24h after ROSC. In these studies, NfL levels between 242 and 609 pg/mL predicted poor neurological outcome between hospital discharge and 12 months with 100% specificity and sensitivity ranging from 54[47-61]% and 66[54-76]%.
Seven studies (Adler 2022, Klitholm 2023, Levin 2023, Pouplet 2022, Song 2023, Wihersaari 2021, Wihersaari 2022) in a total of 874 patients investigated NfL 48h after ROSC. In these studies, NfL levels between 330 and 4660 pg/mL predicted poor neurological outcome between hospital discharge and 12 months with 100% specificity and sensitivity ranging from 35 [26-45]% and 83[69-91]%.
Three studies (Klitholm 2023, Song 2023, Whihersaari 2021)in a total of 292 patients investigated NfL 72h after ROSC. In these studies, Nfl levels between 244 and 970,1 pg/mL predicted poor outcome with a specificity ranging from 99% to 100% and a sensitivity ranging from 74 [62-83]% and 85 [76-90]%.

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**
Sandroni C et al., *Intensive Care Med,* 2020; 46:1803–1851.	Systematic review	Same as this Evidence Update	94 studies were included, of which 21 were about biomarkers. NfL thresholds were evaluated only in 2 studies.	In the present review, we included limited evidence regarding three biomarkers, not included in our previous reviews. These include glial fibrillary acidic protein (GFAP), serum tau protein, and neurofilament light chain (NFL). NFL has been evaluated in two studies (Moseby-Knappe 2029 and Rana 2013), one of which included measurements on days 5 and 7 after ROSC (Rana 2013). In both these studies, sensitivity of NFL at each time point was always higher than that reported for GFAP and serum tau protein. The NFL thresholds for 0%	

				FPR were very different between these two studies, possibly reflecting different measurement techniques, or outcome definitions. Its low concentrations, measured in the range of pg/mL, make measure- ment of NFL technically challenging.	

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**
	Study Aim: **Study Type:**	**Inclusion Criteria:**	**Intervention:** **Comparison:**	**1° endpoint:**	**Study Limitations:**

Nonrandomized Trials, Observational Studies published April 1, 2020 to April 30, 2024

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)**
Adler, 2022	Study Type: Retrospective, single-centre study. 73 patients were included. NfL was measured in 53 patients.	Inclusion Criteria: Non-traumatic OHCA patients Exclusion criteria: Not reported	1° endpoint: the accuracy of NfL blood values, or its kinetics, to predict poor neurological outcome after cardiac arrest. Results: NfL blood levels >241.7 pg/ml at 24h after ROSC or >508.6 at 48h after ROSC predicted poor neurological outcome with 100% specificity and 57 [42-70]% and 52 [38-66]% sensitivity, respectively. Patients with poor neurological outcomes had greater NfL changes from day 0 to day 2 than	In comatose patients after CA, NfL at 24h and 48h after ROSC predicts poor outcomes with 100% specificity and sensitivity above 50%.

			patients with good neurological outcome.	
Klitholm, 2023	Study Type: prospective single-centre cohort study (substudy of the TTH48 trial). 82 patients were included. NfL was measured in 80 patients at 24h, 77 patients at 48h, and 74 patients at 72h.	Inclusion Criteria: OHCA with a presumed cardiac origin, sustained ROSC for more than 20 consecutive minutes, GCS<8 at hospital admission and age between 18 and 80 years. Exclusion criteria: unwitnessed asystole, terminal disease, severe coagulopathy, pregnancy, known neurological disease with cognitive impairment, death before randomization.	1° endpoint: To evaluate the neuroprognostic performance of NfL and GFAP and to compare it with that of NSE. Results: NfL blood levels >608.7 ng/L 24hafter ROSC, or >720.9 ng/L 48hafter ROSC, or >970.1 ng/L 72h after ROSC predicted poor outcome at 6 months with 100 [94-100]% specificity and 66 [54-76]%, 80 [69-88]% and 74 [62–89]% sensitivity, respectively.	In comatose patients after CA, NfL at 24h, 48h and 72h after ROSC predicts poor outcomes with 100% specificity and 65-80% sensitivity.
Levin, 2023	Study Type: Multicentre retrospective analysis of data from the INTCAR registry and the SWECRIT biobank. Among 617 patients from the SWECRIT biobank, 428 were included. Data provided by the author.	Inclusion Criteria: All patients 18 years or older admitted to intensive care after CA. Exclusion criteria: Availability of admission samples only.	1° endpoint: To assess the ability of blood levels of NfL during the first 48h after OHCA and IHCA to predict neurological outcomes at 2-6 months after arrest. Results: In patients with OHCA, NfL blood levels >90 ng/L 12h after ROSC, or >330 ng/L 48hafter ROSC, predicted poor outcome at 2-6 months with 100 [98-100]% specificity and 53 [48-59]% and 82 [76-	In comatose patients after CA, NfL at 12h and 48h after ROSC predicts poor outcomes with 100% specificity. In patients resuscitated from IHCA the thresholds for 100% specificity are higher and the sensitivity is lower than in OHCA patients.

			87]% sensitivity, respectively. In patients with IHCA, NfL blood levels to predict poor outcome with 100% specificity at 12h and 48h after ROSC were 207 and 640 ng/L, respectively. Corresponding sensitivities were 29 [20-39]% and 49 [35-62]% respectively.	
Pouplet et al, 2022	Study Type: Prospective randomized trial (ISOCRATE trial). Forty-nine patients were included. NfL was measured in 48 patients.	Inclusion Criteria: comatose shockable cardiac arrest patients treated with targeted temperature management at 33 °C. Exclusion criteria: Presence of confounders at 72h, non-neurological cause of death or withdrawal.	1° endpoint: to assess the predictive value of NfL in patients with a shockable rhythm who received cardiopulmonary resuscitation and assess its added value to the ESICM guideline algorithms. Results: NfL >500 ng/L at 48h after CA predicted poor neurological outcome at 3 months with 100 [91-100]% specificity and 83 [69-91]% sensitivity.	In comatose patients after CA, NfL at 48h predicts poor outcomes with 100% specificity and 83% sensitivity.
Song, 2023	Study Type: prospective, observational in two centres in South Korea. One-hundred patients were included. NFL was measured in all patients.	Inclusion Criteria: OHCA regardless of etiology of cardiac arrest, age >18 years, GCS<8) after ROSC and treatment with TTM. Exclusion criteria: history of cerebrovascular disease, active	1° endpoint: the accuracy of NfL, GFAP, tau protein, and UCH-L1 for predicting poor outcome at 6 months. Results: NfL blood levels >521 ng/L 24h after ROSC, or >4660 ng/L 48h after ROSC, or >690 ng/L 72h after ROSC predicted poor outcome at 6 months with 100 [95-100]% specificity and 57 [47–67], 35 [26–45]%	In comatose patients after CA, NfL at 24h, 48h and 72h after ROSC predicts poor outcomes with 100% specificity and 36-77% sensitivity.

		intracranial bleeding, acute stroke, known severe coagulopathy, cardiac arrest due to trauma or drugs, known limitations in therapy and a do-not-attempt resuscitation order, known prearrest cerebral performance category (CPC) 3 or 4, and known terminal disease.	and 78 [68-85]% sensitivity, respectively.	
Wihersaari, 2021	Study Type: Post hoc analysis of a prospective multicentre study (COMACARE). One-hundred-twelve patients were included.	Inclusion Criteria: Comatose adult OHCA patients Exclusion criteria: No blood samples available for measurement	1° endpoint: To assess the ability of plasma NfL to predict outcome at 6 months. Results: NfL blood levels >127 ng/L 24h or >263 ng/L 48h, or >344 ng/L 72h after ROSC predicted poor outcome at 6 months with 99% specificity and 78 [65-92]%, 83 [71-96]% and 85 [73-97]% sensitivity, respectively.	In comatose patients after CA, NfL at 24h, 48h and 72h after ROSC predicts poor outcomes with 99% specificity and 68-85% sensitivity.
Wihersaari, 2022	Study Type: Post hoc analysis of a prospective multicentre study (FINNRESUSCI). Two-hundred-forty-eight patients were included. NfL was measured in 227	Inclusion Criteria: adult comatose patients after witnessed OHCA, initial shockable rhythm, unconscious at hospital or ICU admission.	1° endpoint: to demonstrate the superiority of NfL to NSE in predicting unfavourable outcome at 12 months. Results: NfL > 598 pg/mL at 24 h and > 1624 pg/mL at 48 h after CA predicted poor neurological outcome at 12 months	In comatose patients after CA, NfL levels at 24h and 48 h after ROSC predict poor outcomes with 100% specificity and 47-54% sensitivity.

	patients at 24h and 180 at 48h. Data provided by the author.	Exclusion criteria: No blood samples available for measurement.	with 100 [97-100]% specificity and 54 [47-61]% and 47 [39-54]% sensitivity, respectively.	

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
The evidence found does not justify a new systematic review at present.

Note on the interpretation of test results
Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as "positive," and a normal response as "negative," or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should also ideally offer a reasonably high sensitivity when "negative" (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.
In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treating decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome. This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2020 Consensus for this PICOST is that the decision to limit treatment of comatose post–cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that in patients who remain comatose in the absence of confounders (eg, sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.

Notes on the interpretation of biomarkers
Unlike the results of other neuroprognostic tests (e.g., clinical examination), biomarker blood levels are continuous rather than dichotomous (categorical) variables. Results are dichotomized to calculate the sensitivity and specificity of these biomarkers by establishing a threshold that divides positive from negative results. Consequently, test sensitivity and specificity depend on the threshold chosen: a high threshold increases the specificity of the test and decreases the sensitivity, and vice versa.
The kinetic of NfL after cardiac arrest is largely unknown. As for NSE, a source of confounding for NfL is the presence of different assays, which may create different results across measuring methods. The blood levels of NfL after cardiac arrest are in the range of picograms and require ultrasensitive immunoassays for their measurement. Most of the studies we included in this Evidence Update used the single molecular array (SIMOA™) assay. However, this technique is not widely available yet. In one of the studies we included (Pouplet, 2022), the Ella ™ microfluidic platform was used. Although these two techniques appear comparable, there is evidence that the Ella ™ platform overestimates NfL blood levels compared to SIMOA ™ Gauthier A et al. Ann Clin Transl Neurol 2021;8:1141–50).
An important advantage of biomarkers is that – unlike other outcome predictors after cardiac arrest – they can be easily assessed in a blinded fashion, therefore reducing the risk of a self-fulfilling prophecy bias.
For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of

Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

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2025 Evidence Update
ALS 3512 – Blood Biomarkers (NSE)

Worksheet Author(s): Claudio Sandroni, Sonia D'Arrigo; external collaborator (data extraction and management) Sofia Cacciola
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Interventions: index test based on biomarkers: neuron-specific enolase (NSE)
Comparison: the accuracy of the index test was assessed by comparing the predicted outcome with the final outcome.
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.

Year of last full review: 2020
Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: COSTR 2020
We suggest using NSE within 72 hours after ROSC, in combination with other tests, for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence). There is no consensus on a threshold value.

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
"Cardiac arrest [all fields]" AND "Coma" [all fields] AND "Prognosis" [all fields].

New Search strategy:
Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) – updated from end of last search (please specify): From April 2020 to April 2024
Time Frame: (new PICOST) – at the discretion of the Task Force (please specify)
Date Search Completed: April 30, 2024
Search Results (Number of articles identified, and number identified as relevant): 88 articles were evaluated in full-text, and 11 were included as relevant.

Inclusion/Exclusion Criteria:
- Inclusion: adult (≥16 years); resuscitated from cardiac arrest (either in-hospital or out-of-hospital). Comatose (unconscious, unresponsive, and/or having a Glasgow Coma Score (GCS)≤8 at the time of study enrolment). Predictor assessed within 7 days from CA. We included only studies where sensitivity and FPR could be calculated, i.e., those where the 2×2 contingency table of true/false negatives and positives for prediction of poor outcome was reported or could be calculated from reported data. We included only studies with neurological outcome assessed at hospital discharge/1 month or later.
- Exclusion: Studies including non-comatose patients or patients in hypoxic coma from causes other than cardiac arrest (e.g., respiratory arrest, carbon monoxide intoxication, drowning, and hanging) were excluded. Studies with neurological outcome assessed at ICU discharge were excluded.

Summary of Evidence Update:
Fifteen studies evaluated the ability of NSE blood levels between admission and 96h after ROSC to predict poor neurological outcome in comatose patients after CA (Akin 2021, Arctaedius 2024, Benghanem 2022, Czimmeck

2023, Kang 2021, Kim 2020, Kim 2023, Lee 2021, Martinez-Losas 2020, Peluso 2021, Peluso 2022, Pouplet 2022, Ryczek 2021, Ryoo 2020, Wihersaari 2022).

Two studies (Kang 2021, Ryczek 2021) in 167 patients investigated NSE in the first 12h after ROSC. In these studies, NSE levels between 47 and 106 mcg/L measured at different time points between ≤1h and 12h after ROSC predicted poor neurological outcome between hospital discharge and 3 months with specificity ranging from 95% to 100% and sensitivity ranging from 13% and 45%.
Three studies (Kang 2021, Martinez-Losas 2020, Ryczek 2021,) in 456 patients investigated NSE at 24h after ROSC. In these studies, NSE levels above 78.3 and 139 mcg/L predicted poor outcome between hospital discharge to 3 months with 95 [88-99]% and 100 [95-100]% specificity and 20 [15-25]% and 49 [38-60]% sensitivity, respectively.

Seven studies (Kim 2023, Lee 2021, Martinez-Losas 2020, Pouplet 2022, Ryczek 2021, Ryoo 2020, Wihersaari 2022) in 1983 patients investigated NSE at 48h from ROSC. In one of these studies (Lee 2021), NSE levels above 42 mcg/L predicted poor outcome with 89% specificity and 79% sensitivity. In six studies (Kim 2023, Martinez-Losas 2020, Pouplet 2022 Ryczek 2021, Ryoo 2020, Wihersaari 2022) NSE levels between 22 and 159.3 mcg/L at 48h from ROSC predicted poor outcome with a specificity ranging from 95% to 100% and a sensitivity ranging from 18% and 69%.

In two studies (Kim 2020, Arctaedius 2024) in 490 patients NSE levels above 62.6 mcg/L and above 60 mcg/L at 48-72h after ROSC predicted poor outcome with 94 [92-96]% and 100 [96-99]% specificity and 58 [53-63]% and 71 [61-79]% sensitivity, respectively.

In one study (Czimmeck, 2023) in 356 patients NSE levels above 60 mcg/L and above 100 mcg/L at 48-96h after ROSC predicted poor outcome with 95 [92-97]% and 99 [97-99]% specificity and 64 [59-69]% and 50 [44-55]% sensitivity, respectively.

Four studies (Benghanem 2022, Martinez-Losas 2020, Peluso 2022, Peluso 2021) in 565 patients investigated NSE within 72h after ROSC. In one study (Martinez-Losas 2020) NSE levels >54.9 mcg/L predicted poor outcome with 100 [97-100]% specificity and 58 [50-66]% sensitivity. In two of these studies (Benghanem 2022, Peluso 2022), NSE levels >60 mcg/L predicted poor outcome with 94 [85-98]% and 93 [89-96]% specificity and 25[15-37]% and 61[54-67]% sensitivity, respectively. In one study (Peluso 2021) NSE levels >75 mcg/L predicted poor outcome with 100[96-100]% specificity and 45[36-54]% sensitivity.

Five studies (Akin 2020, Martinez-Losas 2020, Lee 2021, Pouplet 2022, Ryczek 2021) in 1171 patients investigated NSE at 72h after ROSC. In these studies, NSE levels between 32.5 and 101.2 mcg/L predicted poor outcome with a specificity ranging from 80 [75-85]% to 100 [91-100]% and a sensitivity ranging from 55 [40-69]% and 87 [77-93]%.

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**
Sandroni C et al., *Intensive Care Med,* 2020; 46:1803–1851.	Systematic review	Same as this Evidence Update	94 studies were included, of which 21 were about biomarkers. NSE thresholds were	High blood values of NSE predicted poor outcome with 0% FPR at 24, 48, and 72 h after ROSC in almost all studies. The relevant threshold values ranged from 39.8 and 172 µg/L, from 34 and 120 µg/L, and from 33	In comatose resuscitated patients, high blood levels of NSE within the first week after ROSC predict poor neurological outcome (CPC 3–5) at hospital discharge/1 month or later with high specificity. However, the

			evaluated in 16 studies.	to 79 µg/L, respectively. Sensitivities ranged from 7.6% and 56%, from 24.6% and 60.2%, and from 39.3% and 52.6%, respectively. Two studies documented 0% FPR for NSE at 4 days, two at 5 days, and one at 7 days after ROSC.	thresholds for 0% FPR vary across studies.

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**
	Study Aim: **Study Type:**	**Inclusion Criteria:**	**Intervention:** **Comparison:**	**1° endpoint:**	**Study Limitations:**

Nonrandomized Trials, Observational Studies published April 1, 2020 to April 30, 2024

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)**
Akin et al, 2021	Study Type: Prospective observational registry. Two-hundred-fifty-one patients were included. NSE was measured in all patients.	Inclusion Criteria: OHCA patients treated with therapeutic hypothermia. Exclusion criteria: Not reported	1° endpoint: To identify the cut-off levels to assess neurological damage using NSE and S-100b in patients treated with therapeutic hypothermia. Results: NSE >32.5 mcg/L at 72 h after CA predicted poor neurological outcome at hospital discharge with 80 [75-85]% specificity and 61 [55-67]% sensitivity.	In comatose HOCA patients, NSE >32.5 mcg/L at 72 h after CA predicts poor outcomes with 80% specificity and moderate sensitivity.
Arctaedius et al, 2024	Study Type:	Inclusion Criteria:	The prognostic accuracy of NSE values was not	In comatose CA patients, NSE >60 mcg/L at 48-72h

	Retrospective multicenter observational study. Seven-hundred-ninety-four patients were included. NSE was measured in 381 patients.	Adults (age >18 yrs) OHCA and IHCA patients with any presenting rhythm. Exclusion criteria: no blood samples available.	the primary endpoint of the study. 1° endpoint: to evaluate the performance of the 2021 ERC/ESICM algorithm and individual prognostic markers in a mixed cohort of OHCA and IHCA patients admitted to ICU Results: NSE >60 mcg/L at 48-72 h after CA predicted poor neurological outcome at 2-6 months with 94[92-96]% specificity and 58[53-63]% sensitivity.	after CA predicts poor outcomes with high specificity.
Benghanem et al, 2022	Study Type: prospective single-centre study. Eighty-two patients were included. NSE was measured in 66 patients.	Inclusion Criteria: Consecutive comatose adult patients after resuscitation from CA, regardless of initial rhythm, with somatosensory evoked potentials (SSEPs) performed. Exclusion criteria: brain death, patients awake before SSEP, and patients who died within 48 h post-CA, before a reliable neurological examination could be performed.	The prognostic accuracy of NSE values was not the primary endpoint of the study. 1° endpoint: to assess if the amplitudes of N20-baseline (N20-b) and N20–P25 on SSEP predict neurological outcome at 3 months after CA. Results: NSE peak >60 mcg/L measured within 72 h after CA predicted poor neurological outcome at 3 months with 94 [85-98]% specificity and 25 [15-37]% sensitivity.	In comatose patients after CA, NSE peak >60 mcg/L predicts poor outcomes with high specificity and low sensitivity.

Czimmeck et al, 2023	Study Type: retrospective single-centre study based on a prospective registry. Three-hundred-fifty-six patients were included. NSE was measured in all patients.	Inclusion Criteria: Consecutive adult IHCA and OHCA patients with shockable and non-shockable initial rhythms. Exclusion criteria: Infection with Sars-CoV-19 and missing NSE concentrations and/or h-index values at 48-96 h.	The prognostic accuracy of NSE values was not the primary endpoint of the study. 1° endpoint: to investigate the prevalence of haemolysis and other confounders and their influence on the prognostic accuracy of NSE levels in CA patients treated with TTM. Results: NSE > 100 mcg/L at 48-96 h after CA predicted poor neurological outcome at hospital discharge with 99 [97-100]% specificity and 50 [44-55]% sensitivity. Instead, NSE > 60 mcg/L at 48-96 h after CA predicted poor neurological outcome at hospital discharge with 95 [92-97]% specificity and 64 [59-69]% sensitivity.	In comatose patients after CA, NSE levels >60 mcg/L and 100 mcg/L at 48-96 h after CA predict poor outcomes with high specificity and moderate sensitivity.
Kang et al, 2021	Study Type: prospective observational single-centre cohort study. Eighty-five patients were included. NSE was measured in all patients.	Inclusion Criteria: Comatose adult patients with OHCA who received TTM. Exclusion criteria: Declination for further treatment by patient's next-of-kin and known medical history of end-stage renal disease.	The prognostic accuracy of NSE values was not the primary endpoint of the study. 1° endpoint: to compare the usefulness of serum NGAL for prognostication in patients with OHCA with that of serum NSE during the entire period of TTM after CA. Results: NSE >54.8 mcg/L at 4.5 h after CA predicted poor neurological outcome at 3 months with 100 [95-	In comatose patients after CA, NSE levels >54.8 mcg/L and >85.3 mcg/L at 5.4 h and 24 h after ROSC, respectively, predict poor outcomes at 3 months with 100% specificity.

			100]% specificity and 45 [34-56]% sensitivity. NSE >85.3 mcg/L at 24 h after CA predicted poor neurological outcome at 3 months with 100 [95-100]% specificity and 49 [38-60]% sensitivity.	
Kim et al, 2020	Study Type: Retrospective observational cohort study. 109 patients were included. NSE was measured in all patients.	Inclusion Criteria: Comatose adult CA patients treated with TTM, with at least one NSE value measurement between 48 and 72 h after ROSC and received both a brain CT scan within 24 h and DW-MRI within 7 days after ROSC. Exclusion criteria: age<18 years, CA due to trauma or intracranial hemorrhage, a previous history of neurological disease and CT or DW-MRI with a poor image quality.	1° endpoint: To test if the combination of NSE and neuroimaging could improve the accuracy of the neurological outcome prediction. Results: NSE >62.6 mcg/L at 48-72 h after CA predicted poor neurological outcome at 6 months with 100 [96-100]% specificity and 71 [61-79]% sensitivity.	In comatose patients after CA, NSE >62.6 mcg/L at 48-72 h after ROSC predicted poor neurological outcome at 6 months with 100% specificity and moderate sensitivity.
Kim et al, 2023	Study Type: Prospective multicenter registry-based cohort study.	Inclusion Criteria: Comatose adult patients with non-traumatic OHCA who	1° endpoint: To assess the prognostic performance of NSE measured at 48 h after ROSC and to establish NSE cutoff values for poor neurologic outcome	In comatose patients after CA, NSE levels >86.95 mcg/L predict poor outcome with 99% specificity and moderate sensitivity.

	Sixty-hundred-twenty-three patients were included. NSE was measured in all patients.	were treated with TTM. Exclusion criteria: active intracranial bleeding or acute ischemic stroke, limitations in therapy, a do-not-attempt resuscitation order, cerebral performance category (CPC) 3 or 4 before OHCA, body temperature <30 °C on admission, and unknown out-comes for 6 months after the ROSC.	at 6 months with false positive rate (FPR) < 1%. Results: NSE >86.95 mcg/L at 48 h after ROSC predicted poor neurological outcome at 1 month and 6 months with 99 [98-100]% specificity and 63 [59-67]% and 62 [58-65]% sensitivity, respectively.	
Lee et al, 2021	Study Type: Retrospective analysis of the Korean Hypothermia Network prospective registry (KORHN). Four-hundred-seventy-five patients included. NSE was measured in all patients.	Inclusion Criteria: Comatose patients after OHCA. Exclusion criteria: incomplete NSE-level data at 48 and 72 h after ROSC; incomplete FOUR scores after ROSC; incomplete data concerning neurological outcomes at 6 months; WLST decision; initial GCS score >8.	1° endpoint: to investigate whether the combination of initial neurological examination and the NSE assay using a scorecard method could improve the prediction of neurological outcomes at 6 months. Results: NSE >41.5 mcg/L at 48 h after CA predicted poor neurological outcome at 6 months with 89 [86-92]% specificity and 79 [75-83]% sensitivity. NSE >49.3 mcg/L at 72 h after CA predicted poor neurological outcome at 6 months with 94 [92-96]% specificity and 77 [73-81]% sensitivity.	In comatose patients after CA, NSE levels >41.5 at 48 h after ROSC predict poor outcome with moderate specificity; NSE levels >49.3 mcg/L at 72 h after ROSC predict poor outcome with high specificity.

Martinez-Losas et al, 2020	Study Type: Retrospective analysis of a prospective monocenter database. Three-hundred-twenty patients were included. NSE was measured in 289 patients.	Inclusion Criteria: Consecutive comatose IHCA and OHCA treated with TTM, suspected cardiac-origin CA, irrespective of initial rhythm; at least one serum NSE determination during hospitalization. Exclusion criteria: Missing samples; death within 72 h; lost to follow-up.	1° endpoint: to analyse the NSE kinetics as a prognostic biomarker of neurological outcome at 3 months in CA survivors treated with TTM. Results: NSE >78.3 and >139.3 mcg/L at 24 h after CA predicted poor neurological outcome at 3 months with 95 [92-97]% and 100 [98-100]% specificity, respectively and 37 [31-43]% and 20 [15-25]% sensitivity, respectively. NSE levels >61.5 and >159.3 mcg/L at 48 h after CA predicted poor neurological outcome at 3 months with 95 [91-97]% and 100 [98-100]% specificity and 69 [63-74]% and 32 [27-38]% sensitivity, respectively. NSE levels >57.6 and >101.2 mcg/L at 72 h after CA predicted poor neurological outcome at 3 months with 95 [91-97]% and 100 [98-100]% specificity and 68 [61-74]% and 56 [49-62]% sensitivity, respectively.	In comatose patients after CA, NSE levels above 78.3 mcg/L, 61.5 mcg/L, and 57.6 mcg/L at 24h, 48h, and 72h, respectively, predict poor neurological outcome at 3 months with 95% specificity. The thresholds for 100% specificity at the same time points were 139.3 mcg/L, 159.3 mcg/L, and 101 mcg/L, respectively.
Peluso et al, 2021	Study Type: Retrospective single-centre study. One-hundred-thirty-seven patients included. NSE was measured in 119 patients.	Inclusion Criteria: adult comatose CA survivors admitted into the ICU. Exclusion criteria: early deaths or awakening (<24 h) who did not have at least	The prognostic accuracy of NSE values was not the primary endpoint of the study. 1° endpoint: to evaluate the prognostic value of different predictive tools and their concordance in CA patients; to describe the accuracy of a multimodal approach to	In comatose patients after CA, NSE levels >75 mcg/L within 72 h predict poor outcomes with 100% specificity and low sensitivity.

		two prognostic tools assessed.	predict neurological outcome at 3 months. Results: NSE >75 mcg/L within 72 h after CA predicted poor neurological outcome at 3 months with 100 [96-100]% specificity and 45 [36-54]% sensitivity.	
Peluso et al, 2022	Study Type: post hoc analysis of a prospective, multicentric international prognostic study. Four-hundred-fifty-six patients included. NSE was measured in 228 patients.	Inclusion Criteria: Comatose adult CA patients from all rhythms. Exclusion criteria: Not reported	The prognostic accuracy of NSE values was not the primary endpoint of the study. 1° endpoint: to assess the concordance of NPi with other prognostication tools in unconscious patients after cardiac arrest. Results: NSE >60 mcg/L within 72 h after CA predicted poor neurological outcome at 3 months with 93 [89-96]% specificity and 61 [54-67]% sensitivity.	In comatose patients after CA, NSE levels >60 mcg/L within 72 h predict poor outcomes with high specificity and moderate sensitivity.
Pouplet et al, 2022	Study Type: Prospective randomized trial (ISOCRATE trial). Forty-nine patients were included. NSE was measured in 48 patients.	Inclusion Criteria: comatose shockable cardiac arrest patients treated with TTM at 33 °C. Exclusion criteria: Presence of confounders at 72h, non-neurological cause of death or withdrawal.	The prognostic accuracy of NSE was not the primary endpoint of the study. 1° endpoint: to assess the predictive value of NFL in patients with a shockable rhythm who received cardiopulmonary resuscitation and assess its added value to the ERC-ESICM prognostication algorithm. Results:	In comatose patients after CA, NSE levels >60 mcg/L at 48h and 72h predict poor outcome with 100% specificity and moderate sensitivity.

			NSE >60 mcg/L at 48 and 72 h after CA predicted poor neurological outcome at 3 months with 100 [91-100]% specificity and 57 [42-70]% and 55 [40-69]% sensitivity, respectively.	
Ryczek et al, 2021	Study Type: observational, prospective single-center cohort study. Eighty-two patients included. NSE was measured in 82 patients.	Inclusion Criteria: Consecutive adult comatose patietns after OHCA. Exclusion criteria: Not reported	1° endpoint: to establish the NSE cutoff values for prediction of poor outcome after OHCA. Results: NSE levels >46.6 mcg/L at ≤1 h, >79.7 mcg/L at 1 h, >106.1 mcg/L at 3 h, and >62.5 mcg/L at 12 h after ROSC predicted poor neurological outcome at hospital discharge with 95 [88-99]% specificity and 28 [19-40]%, 17 [10-27]%, 13 [7-23]% and 37 [27-48]% sensitivity, respectively. NSE levels >81.8 mcg/L at 24 h, >78.7 mcg/L at 48 h, and >46.2 at 72 h after ROSC predicted poor neurological outcome at 12 months with 95 [88-99]% specificity and 33 [24-45]%, 53 [41-64]% and 87 [77-93]% sensitivity, respectively.	In patients who are comatose after resuscitation from CA. NSE predicted poor neurological outcome with 95% specificity and low sensitivity within 12h after ROSC. NSE thresholds ranged from 46.6 and 106.1 mcg/L. At 24h, 48h, and 72h after ROSC, the NSE thresholds for 95% specificity were 81.8, 78.8, and 46.2 mcg/L, respectively.
Ryoo et al, 2020	Study Type: Registry-based, retrospective single-centre observational study. One-hundred-sixty patients were included. NSE was measured in all patients.	Inclusion Criteria: Comatose adult OHCA patients treated with TTM. Exclusion criteria: Intracranial haemorrhage; acute stroke; “do not	1° endpoint: To determine the prognostic ability of NSE and lactate in CA survivors treated with TTM. 2° endpoint: To investigate whether a combination of NSE and lactate increase prognostic information.	In comatose patients after CA, NSE levels above 83 mcg/L predict poor neurological outcome at 28 days with high specificity and moderate sensitivity.

		attempt resuscitation" statement; pre-arrest cerebral dysfunction; severe comorbidity hence "expected to die within 180 days".	Results: At 48h after ROSC, NSE levels >83 mcg/L predicted poor neurological outcome at 28 days with 98 [95-100]% specificity and 67 [59-74]% sensitivity. The NSE threshold for 100 [98-100]% specificity was >107 mcg/L.	
Wihersaari et al, 2022	Study Type: Post hoc analysis of a prospective multicentre study. Two-hundred-forty-eight patients were included. NSE was measured in 217 patients.	Inclusion Criteria: Adult comatose patients after witnessed OHCA, with an initial shockable rhythm, unconsciousness at hospital or ICU admission. Exclusion criteria: Not reported	1° endpoint: to demonstrate the superiority of NfL to NSE in predicting unfavourable outcome at 12 months. Results: NSE > 67.5 mcg/L at 48 h after CA predicted poor neurological outcome at 12 months with 100 [98-100]% specificity and 18 [13-23]% sensitivity.	In comatose patients after CA, NSE levels >67.5 mcg/L at 48 h predict poor outcome at 12 months with 100% specificity and low sensitivity.

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

The evidence found does not justify a new systematic review at present.

Note on the interpretation of test results

Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as "positive," and a normal response as "negative," or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should also ideally offer a reasonably high sensitivity when "negative" (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.

In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treating decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome. This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2020 Consensus for this PICOST is that the decision to limit treatment of comatose post–

cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that in patients who remain comatose in the absence of confounders (eg, sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.

Notes on the interpretation of biomarkers

Unlike the results of other neuroprognostic tests (e.g., clinical examination), biomarker blood levels are continuous rather than dichotomous (categorical) variables. Results are dichotomized to calculate the sensitivity and specificity of these biomarkers by establishing a threshold that divides positive from negative results. Consequently, test sensitivity and specificity depend on the threshold chosen: a high threshold increases the specificity of the test and decreases the sensitivity, and vice versa.

Biomarkers are released with different latency and speed following acute brain injury. Although the kinetics of NSE after cardiac arrest is incompletely known, studies have shown that NSE blood levels increase up to 72h in patients with unfavourable outcome and tend to decrease in patients with favourable outcome (Martìnez-Losas P Rev Esp Cardiol (Engl Ed) 73(2): 123-130. https://www.ncbi.nlm.nih.gov/pubmed/30857978). Ryczek R, Kardiol Pol. 2021;79(5):546-553. https://pubmed.ncbi.nlm.nih.gov/34125928/)

NSE is released from red blood cells following haemolysis and from neuroendocrine tumours. Both these conditions may, therefore, cause falsely pessimistic predictions in patients resuscitated from cardiac arrest (Czimmeck C, Resuscitation 2023 Nov; 192:109964. https://pubmed.ncbi.nlm.nih.gov/37683997/). A final source of confounding for biomarkers is the presence of different assays, which may create different results across measuring methods (Rundgren M, BMC Research Notes 2014, 7:726. http://www.ncbi.nlm.nih.gov/pubmed/25319200).

An important advantage of biomarkers is that – unlike other outcome predictors after cardiac arrest – they can be easily assessed in a blinded fashion, reducing the risk of a self-fulfilling prophecy bias.

For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

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2025 Evidence Update
ALS 3513 – Neuroprognostication – Clinical Tests

Worksheet Author(s): Claudio Sandroni, Sonia D'Arrigo; external collaborator (data extraction and management) Sofia Cacciola
Task Force: Advanced Life Support
Date Approved by SAC Representative: 4 July 2024
Conflicts of Interest: none

PICOST / Research Question:
Population: Adults who are comatose after resuscitation from cardiac arrest (either in-hospital or out-of-hospital), regardless of target temperature.
Interventions: index tests based on clinical examination
Comparison: the accuracy of the index test was assessed by comparing the predicted outcome with the outcome at the study endpoint.
Outcomes: poor neurological outcome, defined as Cerebral Performance Categories (CPC) 3-5 or Glasgow Outcome Scale (GOS) 1-3, or modified Rankin Score (mRS) 4-6 at hospital discharge/1 month or later.

Year of last full review: 2020
Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: COSTR 2020
We recommend that neuroprognostication always be undertaken by using a multimodal approach because no single test has sufficient specificity to eliminate false positives (strong recommendation, very low-certainty evidence).
We suggest using PLR at 72 hours or more after ROSC for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).
We suggest using quantitative pupillometry at 72 hours or more after ROSC for predicting neurological outcome of adults who are comatose after cardiac arrest (weak recommendation, low-certainty evidence).
We suggest using bilateral absence of corneal reflex at 72 hours or more after ROSC for predicting poor neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence).
We suggest using presence of myoclonus or status myoclonus within 7 days after ROSC, in combination with other tests, for predicting poor neurological outcome in adults who are comatose after cardiac arrest (weak recommendation, very low-certainty evidence). We also suggest recording EEG in the presence of myoclonic jerks to detect any associated epileptiform activity (weak recommendation, very low-certainty evidence).

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
"Cardiac arrest [all fields]" AND "Coma" [all fields] AND "Prognosis" [all fields].

New Search strategy:
Database searched: PubMed. The references of full-text articles were screened for additional studies.

Time Frame: (existing PICOST) – updated from end of last search (please specify): From April 2020 to April 2024
Time Frame: (new PICOST) – at the discretion of the Task Force (please specify)
Date Search Completed: April 30, 2024
Search Results (Number of articles identified and number identified as relevant): 88 articles were evaluated in full-text, and 8 were included as relevant.

Inclusion/Exclusion Criteria:

- Inclusion: adult (≥16 years); resuscitated from cardiac arrest (either in-hospital or out-of-hospital). Comatose (unconscious, unresponsive, and/or having a Glasgow Coma Score (GCS)≤8 at the time of study enrolment). Predictor assessed within 7 days from CA. We included only studies where sensitivity and FPR could be calculated, i.e., those where the 2×2 contingency table of true/false negatives and positives for

prediction of poor outcome was reported or could be calculated from reported data. We included only studies with neurological outcome assessed at hospital discharge/1 month or later.

- Exclusion: Studies including non-comatose patients or patients in hypoxic coma from causes other than cardiac arrest (e.g., respiratory arrest, carbon monoxide intoxication, drowning, and hanging) were excluded. Studies with neurological outcome assessed at ICU discharge were excluded.

Summary of Evidence Update:
This update identified 8 relevant studies that were not included in the 2020 ILCOR evidence review.

Concerning clinical examination, four studies (Caroyer 2021, Keijzer 2022, Kim 2021, Qing 2024) evaluated the absence of standard pupillary light reflex (PLR) to predict poor neurological outcome at timings ranging from 36 h to 72 h, showing a specificity ranging from 83.3% to 100% and sensitivity ranging from 20 [11-34]% to 67 [62-71]%. None of the included studies was designed to investigate PLR as a neuroprognostic test.

Automated pupillometry showed greater specificity for predicting poor neurological outcomes than standard PLR. Three studies (Macchini 2022, Nyholm 2023, Paramanathan 2021) showed that a low value of the Neurological Pupillary Index (NPi) (≤2.0) on day 1 and day 2 (Macchini 2022) or day 2 and day 3 (Paramanathan, 2021) predicted poor neurological outcome at 3-6 months with 100% specificity. One study (Nyholm 2023) explored the NPi thresholds for 100 [96-100]% specificity on days 1-3 after CA. These varied from NP ≤2.44 (days 1 and 2) and NPi 3.14 (day 3). Sensitivities ranged from 6.0 [0-15]% to 17 [6-31]%.
One study showed that a quantitative PLR (qPLR) £4% on day 1, <4.5% on day 2 and ≤5% on day 3 predicted poor neurological outcome at 3 months with 100 [94-100]% specificity and sensitivity ranging from 18.7 [8-29]% to 28.3 [17-40]%.

Three studies (Caroyer 2021, Keijzer 2022, Kim 2021) showed that the absence of corneal reflex (CR) at > 48h predicted poor neurological outcome with specificity ranging from 81 [77-85]% to 100 [91-100]% and sensitivity ranging from 25 [14-40]% to 84 [80-88]%.

In one study (Benghanem 2022) the presence of status myoclonus within 72 h after CA predicted poor neurological outcome at 3 months with 94 [86-98]% specificity and 56 [45-67]% sensitivity. Another study (Caroyer 2021) showed that myoclonus within 72h after CA predicted poor neurological outcomes at hospital discharge with 100 [96-100]% specificity and 32.6 [24-42]% sensitivity.

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
Sandroni C et al., *Intensive Care Med,* 2020; 46:1803–1851.	Systematic review	Clinical examination, biomarkers, neurophysiology, imaging.	94 studies were included, of which 37 were about clinical examination.	Standard pupillary reflex (PLR) or corneal reflex (CR) are very specific indices of poor neurological outcome, but false positive predictions may occur with a rate up to 6–7% even at 72 h	In comatose resuscitated patients, clinical examination tests have a potential to predict poor neurological outcome.

				from ROSC. The lowest FPR (0%) is achieved after day 4 from ROSC. Automated quantitative pupillometry may provide accurate results earlier than the standard PLR. However, the number of supporting studies is still limited. 0The occurrence of clinical myoclonus early after cardiac arrest is an unfavourable prognostic sign, but it does not rule out neurological recovery.	

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**
	Study Aim: Study Type:	Inclusion Criteria:	Intervention: Comparison:	1° endpoint:	Study Limitations:

Nonrandomized Trials, Observational Studies published April 1, 2020 to April 30, 2024

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)**

Pupillary Light Reflex (PLR)				
Caroyer et al., 2021	Study Type: prospective single-centre cohort study. One-hundred-fifteen patients were included in the study. Ninety-nine patients had PLR tested.	Inclusion Criteria: Comatose adult resuscitated CA patients receiving continuous EEG monitoring (cEEG). Exclusion criteria: clear signs of consciousness on admission or high risk of death within 24 hours after admission.	The PLR accuracy was not the primary endpoint of this study. 1° endpoint: to determine and compare the effectiveness, inter-rater reliability and prognostic value of different stimulus types for EEG reactivity. Results: The absence of PLR 48-72 h after CA predicted a poor neurological outcome at hospital discharge with 100 [95-100]% specificity and 31 [22-41]% sensitivity.	The absence of PLR at 48-72h predicted poor neurological outcome at hospital discharge with high specificity but low sensitivity.
Keijzer et al., 2022	Study Type: prospective two-centre cohort study. Fifty patients were included in the study.	Inclusion Criteria: comatose adult patients after resuscitation from CA. Exclusion criteria: pregnancy, life expectancy < 24 h post CA, any known progressive brain illness, preexisting dependency in daily living, or a contraindicatio n to undergo MRI examination (e.g., pacemaker, neurostimulato r, foreign metal objects).	The PLR accuracy was not the primary endpoint of the study. 1° endpoint: to investigate the additional values of combining MRI and EEG to predict neurological outcome at 3 months. Results: the absence of PLR at ^{3}72 h after CA predicted poor neurological outcome at 3 months with 100 [91-100]% specificity and 20 [11-34]% sensitivity.	The absence of PLR at ^{3}72 h predicted poor neurological outcome at 3 months with high specificity but low sensitivity.

Kim et al., 2021	Study Type: prospective, multicentre, observational, cohort study. Four hundred eighty-nine patients were included and 475 had PLR tested.	Inclusion Criteria: Comatose adult non-traumatic out-of-hospital cardiac arrest (OHCA) patients. Exclusion criteria: OHCA patients with documented terminal illness in medical records, with intracranial bleeding or acute stroke, and with pre-arrest CPC 3 or 4, patients without EEG data within 7 days after ROSC or with poor-quality EEG data.	The PLR accuracy was not the primary endpoint of the study. 1° endpoint: to assess the prognostic accuracy of the EEG patterns ("highly malignant", "malignant," and "benign") according to the EEG timing (early vs. late) and to investigate the EEG features to enhance the predictive power for poor neurologic outcome at 1 month after CA. Results: The absence of PLR at >72 h after CA predicted poor neurological outcome at 1 month with 95 [93-97]% specificity and 67 [62-71]% sensitivity.	The absence of PLR at >72 h predicted poor neurological outcome at 1 month with high specificity and 67% sensitivity.
Qing et al., 2024	Study Type: a single-centre prospective study. Seventy-two patients were included.	Inclusion Criteria: Comatose adult patients resuscitated from CA. Exclusion criteria: Interference on EEG from heavy noise or artefact.	The PLR accuracy was not the primary endpoint of the study. 1° endpoint: to apply a stratification system of EEG patterns and spectral types that may be helpful for standardised interpretation of EEG. Results: the absence of PLR at 36 h predicted poor neurological outcome at hospital discharge with 83 [72-91]% specificity and 20 [12-31]% sensitivity.	The absence of PLR at 36 h predicted poor neurological outcome at hospital discharge with only 83% Specificity. This confirms the inaccuracy of PLR when assessed early after ROSC.
Corneal Reflex (CR)				

Caroyer et al., 2021	Study Type: prospective single-centre cohort study. One-hundred-fifteen patients were included in the study and 76 patients had CR tested.	Inclusion Criteria: Comatose adult resuscitated CA patients receiving continuous EEG monitoring (cEEG). Exclusion criteria: clear signs of consciousness on admission or high risk of death within 24h after admission.	The CR accuracy was not the primary endpoint of the study. 1° endpoint: to determine and compare the effectiveness, inter-rater reliability and prognostic value of different stimulus types for EEG reactivity. Results: the absence of CR at 48-72 h after CA predicted poor neurological outcome at hospital discharge with 94 [86-98]% specificity and 50 [34-62]% sensitivity.	The absence of CR at 48-72 h predicted poor neurological outcome at hospital discharge with high specificity and moderate sensitivity.
Keijzer et al., 2022	Study Type: prospective cohort study in two centres. Fifty patients were included.	Inclusion Criteria: comatose adult patients after resuscitation from CA. Exclusion criteria: pregnancy, life expectancy < 24 h post-CA, any known progressive brain illness, preexisting dependency in daily living, or a contraindicatio n to undergo an MRI examination (e.g., pacemaker, neurostimulato r, foreign metal objects).	The CR accuracy was not the primary endpoint of the study. 1° endpoint: to investigate the additional values of a combining MRI and EEG to predict neurological outcome at 3 months. Results: The absence of CR 72 h after CA predicted a poor neurological outcome at 3 months with 100 [91-100]% specificity and 25 [14-40]% sensitivity.	The absence of CR at ³72 h predicted poor neurological outcome at 3 months with high specificity but low sensitivity.
Kim et al., 2021	Study Type: prospective, multicentre,	Inclusion Criteria:	The CR accuracy was not the primary endpoint of the study.	Absent CR at ≥72 h after CA predicted poor neurological outcome at 1 month with

	observational, cohort study. Four hundred eighty-nine patients were included in the study, and 382 patients had CR tested.	Comatose adult non-traumatic out-of-hospital cardiac arrest (OHCA) patients. Exclusion criteria: OHCA patients with documented terminal illness in medical records, with intracranial bleeding or acute stroke, and with pre-arrest CPC 3 or 4, patients without EEG data within 7 days after ROSC or with poor-quality EEG data.	1° endpoint: to assess the prognostic accuracy of the EEG patterns ("highly malignant", "malignant," and "benign") according to the EEG timing (early vs. late) and to investigate the EEG features to enhance the predictive power for poor neurologic outcome at 1 month after CA. Results: the absence of CR at ³72 h after CA predicted poor neurological outcome at 1 month with 81 [77-85]% specificity and 84 [80-88]% sensitivity.	81% specificity and 84.2% sensitivity
Neurologocal Pupil index (NPi)				
Macchini et al., 2022	Study Type: single centre retrospective observational study. One-hundred-two patients included.	Inclusion Criteria: Comatose adult resuscitated CA patients who survived for at least 24 hours. Exclusion criteria: Patients with pupillary disease, periorbital oedema and recent ocular surgery.	1° endpoint: to examine the prognostic accuracy of the NPI and the Pupillary Pain Index (PPI) in predicting poor outcomes in comatose patients after CA. Results: Patients with poor outcome showed a lower NPi and PPI than patients with favourable outcomes. 2° endpoint: to evaluate the agreement between PPI and NPi to predict poor outcome. Results: An NPi£2 on days 1 and 2 predicted poor neurological	NPi£2 on days 1 and 2 after ROSC predicted a poor neurological outcome at 3 months with 100% specificity but low sensitivity.

			outcome at 3 months with 100 [95-100]% specificity. Sensitivity was 12 [5-22]% and 10 [4-20]%, respectively. The coefficient of agreement between NPi and PPI was 0.42. NPi and PPI values showed a moderate correlation both on day 1 and day 2.	
Nyholm et al., 2023	Study Type: Single-centre, retrospective observational study. One-hundred-thirty-five patients included. Pupillometry was performed in all patients (day 1), 121 patients (day 2) and 75 patients (day 3).	Inclusion Criteria: Comatose adult resuscitated from OHCA. Exclusion criteria: IHCA, recovery of consciousness at admission, quantitative pupillometry not performed.	1° endpoint: prediction of poor outcome at 90 days with zero FPR using quantitative PLR (qPLR), NPi, and other pupillary parameters recorded on the first 3 days after admission. Results: NPi £2.44 at days 1 and 2 after CA predicted poor neurological outcome at 3 months with 100 [96-100]% specificity and 9.4 [2-19] % and 6.2 [0-15] % sensitivity, respectively. NPi £3.14 at day 3 after CA predicted poor neurological outcome at 3 months with 100 [94-100]% specificity and 16.7 [6-31] % sensitivity.	NPi≤2.44 measured on days 1-2 from hospital admission predicted poor outcome at 90 days with 0% FPR. The threshold for 100% specificity was 3.14 on day 3. The sensitivity was low at all time points.
Paramanathan et al., 2021	Study Type: Sub-study of an RCT (TTH48 trial) (Kirkegaard H, 2016) Sixty-five patients included and were randomized to a target temperature of 33±1 °C for 24 or 48h.	Inclusion Criteria: Comatose adults resuscitated from OHCA. Exclusion criteria: In hospital cardiac arrest (IHCA), 'not to be' resuscitated order, severe coagulopathy,	1° endpoint: NPi recordings in patients with good or poor neurological outcome assessed by cerebral performance category score (CPC) 6 months after CA. Results: NPi <2.0 at days 1, 2 and 3 after CA predicted poor neurological outcome at 6 months with specificity of 96.7%, 100% and 100% and sensitivity of 0	NPi<2 on days 1 and 2 after ROSC predicted a poor neurological outcome at 6 months with 100% specificity but sensitivity was negligible on day 1. NPi thresholds of 3.0 or higher were not associated with 100% specificity. However, 3.0 is the lowest boundary of normality for NPi.

	Pupillometry was performed in 60 patients on day 1, in 63 patients on day 2 and in 45 patients on day 3.	unwitnessed OHCA with asystole as first rhythm, pregnancy, previous neurological disease, persistent cardiogenic shock despite vasoactive treatment and/or intra-aortic balloon pump intervention, suspected or confirmed acute intracerebral bleeding/stroke, lack of consent.	[0-23]%, 6.7 [0-30]% and 17.6 [2-45]%, respectively. NPi <3.0 at days 1, 2 and 3 after CA predicted poor neurological outcome at 6 months with specificity of 96.7%, 97% and 96.4% and sensitivity of 0 [0-30]%, 13.3 [2-38]% and 29.4 [9-61]%. NPi <3.8 at days 1, 2 and 3 after CA predicted poor neurological outcome at 6 months with specificity of 63.3%, 75.8% and 89.3% and sensitivity of 56.7 [29-82]%, 50 [25-75]% and 58.8 [29-82]%.	
Quantitative pupillary reflex (qPLR)				
Nyholm et al., 2023	Study Type: Single-centre, retrospective observational study. One-hundred-thirty-five patients were included. Pupillometry was performed in 135 patients on day 1, in 121 patients on day 2 and in 75 patients on day 3.	Inclusion Criteria: Comatose adults resuscitated from OHCA. Exclusion criteria: IHCA; recovery of consciousness at admission or assessment with quantitative pupillometry not performed.	1° endpoint: 3-month poor neurological outcome with zero FPR of quantitative PLR (qPLR) and other pupillary parameters recorded on the first 3 days after admission. Results: qPLR £3.99 at day 1, qPLR £4.49 at day 2, and qPLR £5.0 at day 3 after CA predicted poor neurological outcome at 3 months with 100% specificity and 28.3 [17-40]%, 18.7 [8-29]% and 27.8 [14-44]% sensitivity, respectively.	Different thresholds of qPLR, measured from hospital admission until day 3, predicted poor outcome at 3 months with 0% FPR in comatose patients resuscitated from OHCA. Sensitivity was low. This study also investigated the average constriction velocity (CV, mm/s), and the maximum CV (MCV, mm/s). With both these variables, thresholds for 100% specificity were identified. For all pupillometry variables except NPi, the values from admission to all time points increased.
Status Myoclonus				
Benghanem et al., 2022	Study Type:	Inclusion Criteria:	The accuracy of the status myoclonus was	The presence of status myoclonus at 72h from

	Monocentric prospective study Eighty-two patients included.	Consecutive comatose adult patients after resuscitation from CA, regardless of initial rhythm, with somatosensory evoked potentials (SSEP) performed. Exclusion criteria: brain death diagnosis, patients awake before SSEP, and patients who died within 48 h post CA, before a reliable neurological examination could be performed.	not the study's primary endpoint. 1° endpoint: to assess if SSEP amplitudes predict neurological outcome at 3 months. Results: The presence of status myoclonus at 72 h predicted poor neurological outcome at 3 months with 94 [86-98]% specificity and 56 [45-67]% sensitivity.	ROSC predicted poor neurological outcomes with 94% specificity and 56% sensitivity.
Myoclonus				
Caroyer et al., 2021	Study Type: Prospective single-centre cohort study. One hundred and fifteen patients were included.	Inclusion Criteria: Comatose adult resuscitated CA patients receiving continuous EEG monitoring (cEEG). Exclusion criteria: clear signs of consciousness on admission or high risk of death within 24h after admission.	The assessment of myoclonus was not the primary endpoint of the study. 1° endpoint: to determine and compare the effectiveness, inter-rater reliability and prognostic value of different stimulus types for EEG reactivity testing using a standardized stimulation protocol and standardized definitions. Results: the presence of myoclonus within 72 h predicted poor neurological outcome at hospital discharge with 100 [96-100]% specificity	The presence of myoclonus within 72h predicted poor neurological outcomes with 100% specificity and 33% sensitivity.

			and 32.6 [24-42]% sensitivity.	

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
Nine studies included in this evidence update largely confirmed the results of both the ILCOR 2020 evidence review and the 2020 systematic review. The evidence found does not justify a new systematic review at present.

Note on the interpretation of test results
Neuroprognostic tests used in patients who are comatose after resuscitation from cardiac arrest measure the severity of brain injury. An abnormal response from these tests may be classified as "positive," and a normal response as "negative," or vice versa, depending on the prognostic perspective taken. Usually, as in this evidence review, a positive result of these tests indicates that the outcome of that patient will be poor. If this occurs, the prediction is correct, and the test result is a true positive. Conversely, if the outcome is good, the positive test result is a false positive. In this context, the false-positive rate (FPR) of a test is the proportion of patients with good outcome who are assigned a falsely pessimistic prediction. In other words, the FPR is the number of false positives divided by the total number of patients with a good outcome. FPR is also the complement of specificity, i.e., 100% − specificity. Therefore, a test with 100% specificity has 0% FPR. Ideally, all neuroprognostic tests predicting poor outcome should yield 100% specificity. While neuroprognostic tests predicting outcome should also ideally offer a reasonably high sensitivity when "negative" (in this case indicating that the outcome of the patient will be good), this is less important than their having a high specificity (low FPR), since the latter minimizes the risk of incorrectly predicting (and acting upon) a poor prognosis in a potentially viable patient.
In most neuroprognostic studies, as in prognostic studies in general, the treating team is aware of the results of the prognostic tests under investigation. Consequently, these results may affect their treating decisions, leading to a self-fulfilling prophecy bias that may overestimate the specificity of prognostic tests in predicting poor outcome. This bias contributes to the low certainty of the evidence of most neuroprognostic studies after cardiac arrest. For that reason, the ILCOR 2020 Consensus for this PICOST is that The decision to limit treatment of comatose post–cardiac arrest patients should never rely on a single prognostication element. The consensus of the task force was that in patients who remain comatose in the absence of confounders (eg, sedative drugs), a multimodal approach should be used, with all supplementary tests considered in the context of the clinical examination.
For further details on the methodology and interpretation of prognostic tests see Geocadin RG, Callaway CW, Fink EL, Golan E, Greer DM, Ko NU, Lang E, Licht DJ, Marino BS, McNair ND, Peberdy MA, Perman SM, Sims DB, Soar J, Sandroni C; American Heart Association Emergency Cardiovascular Care Committee. Standards for Studies of Neurological Prognostication in Comatose Survivors of Cardiac Arrest: A Scientific Statement From the American Heart Association. Circulation. 2019 Aug 27;140(9):e517-e542.).

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2025 Evidence Update
ALS 3519 – Glucose Control After Resuscitation

Worksheet Author(s): Shinichiro Ohshimo
Task Force: Advanced Life Support
Date Approved by SAC Representative: 15 October 2024
Conflicts of Interest: none

PICOST / Research Question:
Among adults with ROSC after cardiac arrest in any setting (P), does a specific target range for blood glucose management (eg. strict 4-6 mmol/L, 72-108 mg/dL) (I), compared with any other target range (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)?

Year of last full review: 06 April 2014

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
Consensus on Science:
For the critical outcome of survival to hospital discharge, there was moderate-quality evidence (downgraded for risk of bias due to lack of blinding) from 1 RCT of 90 subjects showing reduced 30-day mortality (RR, 0.94; 95% CI, 0.53–1.68) when subjects were assigned to strict (4–6 mmol/L, 72-108 mg/dL) versus moderate (6–8 mmol/L, 108-144 mg/dL) glucose control.(Oksanen 2007, 2093) One before-and-after observational study of 119 subjects provided very-low-quality evidence (downgraded for multiple potential confounding variables) of reduced in-hospital mortality (RR, 0.46; 95% CI, 0.28–0.76) after implementation of a bundle of care that included defined glucose management (5–8 mmol/L, 90-144 mg/dL).(Sunde 2007, 29) The effect of glucose management cannot be separated from the effects of other parts of the bundle.

Treatment Recommendation:
We suggest no modification of standard glucose management protocols for adults with ROSC after cardiac arrest (weak recommendation, moderate-quality evidence).

In making this recommendation, we considered the lack of evidence that the approach to glucose management chosen for other critical care populations should be modified for the post–cardiac arrest patients. Moreover, we noted that strict glycemic control is labor intensive, and in other populations, implementation of strict glycemic control is associated with increased episodes of hypoglycemia, which might be detrimental. Avoiding hypoglycemia was considered more important than the unproven benefits of treating moderate hyperglycemia.

Search Strategy:
PubMed: (Search Completed: March 4, 2024) (Blood Glucose[Mesh] OR “blood glucose”[TIAB] OR “blood sugar”[TIAB] OR “plasma glucose”[TIAB] OR Hyperglycemia[Mesh] OR Hyperglycem*[TIAB] OR hyperglycaem*[TIAB] OR Hypoglycem*[TIAB] OR Hypoglycaem*[TIAB] OR Hypoglycemia[Mesh] OR Insulin [Mesh] OR Insulin[TIAB] OR Hypoglycemic Agents[Mesh] OR insulinotherapy[TIAB]) AND ((glucose[TIAB] OR Glycemic[TIAB] OR glycaemic[TIAB]) AND (control[TIAB] OR variability[TIAB] OR homeostasis[TIAB] OR Target[TIAB] OR mmol/L[TIAB] OR mg/dL[TIAB] OR concentration[TIAB] OR mean[TIAB] OR average[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 "cardio-pulmonary arrest"[TIAB] OR "cardio-pulmonary arrests"[TIAB] OR "cardiopulmonary resuscitation"[Mesh] OR "cardiopulmonary resuscitation"[TIAB] OR "cardiopulmonary resuscitations"[TIAB] OR "Heart Massage"[Mesh] OR "Advanced Cardiac Life Support"[TIAB] OR "return of spontaneous circulation"[TIAB] OR ROSC[TIAB] OR “spontaneous circulation”[TIAB]) NOT (animals[Mesh] NOT humans[Mesh]) NOT ("letter"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] or Case Reports[Publication Type])

Search limited to RCTs and before and after studies.

Database searched: PubMed
Time Frame: updated from end of last search (April 6 2014)
Date Search Completed: March 4, 2024
Search Results (Number of articles identified and number identified as relevant): 115/0
Summary of Evidence Update:
Escalated to SR (state what type and which PICO): No
Impact on CoS or TR: No

Relevant Guidelines or Systematic Reviews: none

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

RCT: 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
	Study Aim: Study Type:	Inclusion Criteria:	Intervention: Comparison:	1° endpoint:	Study Limitations:

Nonrandomized Trials, Observational Studies: none

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 this PICOST should have a systematic or scoping review*)
Our main interest was not to determine the association between hyperglycemia and disease severity or prognosis, but the possibility that intensive blood glucose control using insulin may affect patient outcome.
Given the lack of new evidence, there appears to be no need for a systematic review on blood glucose management in patients after cardiac arrest.

In the absence of new RCTs or before-and-after studies specific to post-cardiac arrest patients, we concluded that there was no reason to target anything other than the treatment of general ICU patients

Reference list:

1. Callaway CW, et al. Part 4: Advanced Life Support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 2015;132(16 Suppl 1):S84-145. doi: 10.1161/CIR.0000000000000273. PMID: 26472860
2. Borgquist O, et al. Dysglycemia, Glycemic Variability, and Outcome After Cardiac Arrest and Temperature Management at 33°C and 36°C. Crit Care Med. 2017;45:1337-1343. doi: 10.1097/CCM.0000000000002367. PMID: 28708678. https://pubmed.ncbi.nlm.nih.gov/28708678/
3. Daviaud F, et al. Blood glucose level and outcome after cardiac arrest: insights from a large registry in the hypothermia era. Intensive Care Med. 2014;40:855-62. doi: 10.1007/s00134-014-3269-9. PMID: 24664154. https://pubmed.ncbi.nlm.nih.gov/24664154/
4. Kim SH, et al. Association of blood glucose at admission with outcomes in patients treated with therapeutic hypothermia after cardiac arrest. Am J Emerg Med. 2014;32:900-4. doi: 10.1016/j.ajem.2014.05.004. PMID: 24928411. https://pubmed.ncbi.nlm.nih.gov/24928411/
5. Ettleson MD, et al. Hyperglycemia and insulin resistance in cardiac arrest patients treated with moderate hypothermia. J Clin Endocrinol Metab. 2014;99:E2010-4. doi: 10.1210/jc.2014-1449. PMID: 25033067. https://pubmed.ncbi.nlm.nih.gov/25033067/
6. Wang CH, et al. Associations between blood glucose level and outcomes of adult in-hospital cardiac arrest: a retrospective cohort study. Cardiovasc Diabetol. 2016;15:118. doi: 10.1186/s12933-016-0445-y. PMID: 27557653. https://pubmed.ncbi.nlm.nih.gov/27557653/
7. Minha S, et al. Routine Laboratory Indices as Predictor of Neurological Recovery in Post-Resuscitation Syndrome Patients Treated with Therapeutic Hypothermia. Isr Med Assoc J. 2017;19:296-299. PMID: 28513117. https://pubmed.ncbi.nlm.nih.gov/28513117/
8. Russo JJ, et al. Hyperglycaemia in comatose survivors of out-of-hospital cardiac arrest. Eur Heart J Acute Cardiovasc Care. 2018;7:442-449. doi: 10.1177/2048872616684685. PMID: 28045336. https://pubmed.ncbi.nlm.nih.gov/28045336/
9. Wang CH, et al. The association between long-term glycaemic control, glycaemic gap and neurological outcome of in-hospital cardiac arrest in diabetics: A retrospective cohort study. Resuscitation. 2018;133:18-24. doi: 10.1016/j.resuscitation.2018.09.017. PMID: 30261218. https://pubmed.ncbi.nlm.nih.gov/30261218/
10. Jung YH, et al. Association between Achievement of Estimated Average Glucose Level and 6-Month Neurologic Outcome in Comatose Cardiac Arrest Survivors: A Propensity Score- Matched Analysis. J Clin Med. 2019;8:1480. doi: 10.3390/jcm8091480. PMID: 31540352. https://pubmed.ncbi.nlm.nih.gov/31540352/
11. Wang CH, et al. Associations between intra-arrest blood glucose level and outcomes of adult in-hospital cardiac arrest: A 10-year retrospective cohort study. Resuscitation. 2020;146:103-110. doi: 10.1016/j.resuscitation.2019.11.012. PMID: 31786236. https://pubmed.ncbi.nlm.nih.gov/31786236/
12. Lee BK, et al. Glycated Hemoglobin is Associated with Glycemic Control and 6-Month Neurologic Outcome in Cardiac Arrest Survivors Undergoing Therapeutic Hypothermia. Neurocrit Care. 2020;32:448-458. doi: 10.1007/s12028-019-00758-9. PMID: 31187435. https://pubmed.ncbi.nlm.nih.gov/31187435/
13. Zhou D, et al. Proportion of time spent in blood glucose range 70 to 140 mg/dL is associated with increased survival in patients admitted to ICU after cardiac arrest: A multicenter observational study. Medicine (Baltimore). 2020;99:e21728. doi: 10.1097/MD.0000000000021728. PMID: 32872055. https://pubmed.ncbi.nlm.nih.gov/32872055/
14. Bang HJ, et al. Glucose control and outcomes in diabetic and nondiabetic patients treated with targeted temperature management after cardiac arrest. PLoS One. 2024;19:e0298632. doi: 10.1371/journal.pone.0298632. PMID: 38330019. https://pubmed.ncbi.nlm.nih.gov/38330019/
15. Oksanen T, et al. Strict versus moderate glucose control after resuscitation from ventricular fibrillation. Intensive Care Med. 2007 ;33:2093-100. doi: 10.1007/s00134-007-0876-8. PMID: 17928994. https://pubmed.ncbi.nlm.nih.gov/17928994/
16. Sunde K, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation. 2007;73:29-39. doi: 10.1016/j.resuscitation.2006.08.016. PMID: 17258378. https://pubmed.ncbi.nlm.nih.gov/17258378/

2025 Evidence Update
ALS 3522 – Prophylactic Antibiotics Post-ROSC

Worksheet Author(s): Shannon Fernando, Ian Drennan, Markus Skrifvars; externally reviewed Michael Klompas,
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / Research Question:
Population: Adult patients following return of spontaneous circulation from cardiac arrest in any setting (in-hospital and out-of-hospital)
Intervention: Early/prophylactic antibiotics
Comparators: Delayed/clinically-driven administration
Outcomes: Any clinical outcomes

Year of last full review: 2019: Couper *et al*., *Resuscitation*, 2019: https://pubmed.ncbi.nlm.nih.gov/31085216/
Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST: We suggest against the use of prophylactic antibiotics in patients following return of spontaneous circulation. (weak recommendation, low certainty of evidence). (2020 CoSTR)

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
Developed search strategy
1. exp Heart Arrest/
2. exp Cardiopulmonary Resuscitation/
3. exp Out-of-Hospital Cardiac Arrest/
4. exp Heart Massage/
5. (cardiac adj arrest).mp.
6. (cardiopulmonary adj resuscitation).mp.
7. (chest adj compression*).mp.
8. (cardiac adj compression*).mp.
9. exp Anti-Bacterial Agents/
10. exp Antibiotic Prophylaxis/
11. exp Anti-Infective Agents/
12. exp ANTIMICROBIAL STEWARDSHIP/
13. antibiotic*.mp.
14. anti-biotic*.mp.
15. antimicrobial*.mp.
16. anti-microbial*.mp.
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
18. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
19. 17 and 18

New Search strategy: (for a new PICOST should be outlined here as per Evidence Update Process): Same as above
Database searched: Medline, Embase
Time Frame: (existing PICOST) – updated from end of last search (please specify): June 1, 2016-January 27th, 2024
Time Frame: (new PICOST) – at the discretion of the Task Force (please specify)
Date Search Completed: January 27th, 2024
Search Results (Number of articles identified and number identified as relevant): 1741, 7 eligible studies: 2 RCTs and 5 observational studies. 2 new studies: 1 RCT (Francois *et al*., *NEJM*, 2019); 1 observation (Harmon *et al*., *Resuscitation*, 2020)

Summary of Evidence Update:

Relevant Guidelines or Systematic Reviews

Organization (if relevant); Author; Year Published	Guideline or systematic review	Topic addressed or PICO(S)T	Number of articles identified	Key findings	Treatment recommendations
Couper et al., 2019	Systematic Review	Efficacy of antibiotic prophylaxis in adult patients following out-of-hospital or in-hospital cardiac arrest.	11 (included abstracts)	Antibiotic prophylaxis was not associated with increased survival, increased survival with good neurological outcome, ICU length of stay, or incidence of pneumonia (including VAP)	

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
ANTHARTIC: Francois *et al*., *N Engl J Med*, 2019	**Study Aim:** Evaluate the efficacy and safety of preventative, short-term antibiotics in patients with out-of-hospital cardiac arrest **Study Size:** 194	**Inclusion Criteria:** Adult patients (³ 18 years of age) hospitalized in the ICU after an out-of-hospital cardiac arrest, with shockable rhythm, and treated with 32-34 degrees targeted temperature management	**Intervention:** 2-day antibiotic therapy (amoxicillin-clavulanate at a dose of 1g and 200mg IV respectively, three times per day for 2 days **Comparison:** Saline in the same frequency	**1° endpoint:** Early ventilator-associated pneumonia. **Results:** Incidence of early VAP was lower with antibiotic prophylaxis than with placebo (19 patients [19%] vs. 32 [34%]; HR 0.53; 95% CI: 0.31-0.92). No difference in secondary endpoints, including mortality or duration of mechanical ventilation.	**Study Limitations:** Focused only on out-of-hospital cardiac arrest, and only on patients receiving TTM. Patients with overt aspiration were not included.

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)
Harmon *et al*., *Resuscitation*, 2020	Study Type: Observational study; post-hoc analysis of patients enrolled in the TTM trial (Nielsen *et al*., *N Engl J Med*, 2013). Study Size: 696	Inclusion Criteria: Adult (³ 18 years of age), unconscious (GCS < 8) patients, resuscitated from cardiac arrest of a presumed cardiac cause, with return of spontaneous circulation of at least 20 minutes	1° endpoint: Infection (composite outcome including pneumonia or bacteremia). Results: In the initial logistic regression model, prophylactic antibiotics (of any kind) was associated with a lower risk of pneumonia (adjusted OR 0.64 [95% CI: 0.46-0.90]).	Observational study evaluating association. Does not specify antibiotics used. Does not adjust for important confounders using appropriate methods for causal inference (e.g., stepwise selection of candidate variables for model inclusion).

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
Overall, there was reduction of early VAP (on day 1-7 after admission) with prophylactic antibiotics seen in the ANTHARTIC trial,[1] which was of high quality. However, this trial did not find that there were any differences in any patient-important outcomes, such as short-term mortality, duration of mechanical ventilation, and ICU length of stay. In addition, evidence from a new observational study also demonstrated the prophylactic antibiotics reduced incidence of pneumonia (did not differentiate between HAP, VAP, aspiration, etc.),[2] but similarly did not show differences in patient-important outcomes.

Given the above, there is insufficient evidence to warrant a full systematic review for this question.

Reference list:

1. François B, Cariou A, Clere-Jehl R, et al. Prevention of Early Ventilator-Associated Pneumonia after Cardiac Arrest. N Engl J Med 2019;381(19):1831-1842. (In eng). DOI: 10.1056/NEJMoa1812379.
2. Harmon MBA, Hodiamont CJ, Dankiewicz J, et al. Microbiological profile of nosocomial infections following cardiac arrest: Insights from the targeted temperature management (TTM) trial. Resuscitation 2020;148:227-233. (In eng). DOI: 10.1016/j.resuscitation.2019.11.033.

2025 Evidence Update
ALS 3607 – Point of Care Ultrasound for CA – Etiology

Worksheet Author(s): Zelop, CM, Welsford M, Drennan,I
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / Research Question:
Population: Adults in any setting (in-hospital [IHCA] or out-of-hospital [OHCA]) with cardiac arrest.
Intervention: A particular finding on point-of-care ultrasound during CPR
Comparators: A external confirmatory test or process including some component other than point-of-care ultrasound
Outcomes: A specific etiology or pathophysiologic state that led to cardiac arrest
Study Designs: Randomized and non-randomized cohort studies (prospective and retrospective) and case-control studies with data on both point of care ultrasound findings and an external reference standard to contribute to a contingency table (i.e. true positive, false positive, false negative, true negative). Animal studies, ecological studies, case series, case reports, narrative reviews, abstracts, editorials, comments, letters to the editor, or unpublished studies will not be included.
Timeframe: All years and all languages were included as long as there is an English abstract. Literature search updated through October 6, 2021.

Year of last full review: 2021

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

We suggest against using point-of-care ultrasound to exclude myocardial infarction, cardiac tamponade, and pulmonary embolism as the cause of cardiac arrest (weak recommendation, very low certainty evidence). Some point-of-care ultrasound findings may increase the likelihood of these causes, but should be interpreted with extreme caution and in the specific clinical context (weak recommendation, very low certainty evidence).

Current Search Strategy
Pubmed
1 "cardiac arrest" OR "heart arrest" OR "myocardial contraction" OR "cardiopulmonary arrest" OR "Heart Arrest"[Mesh] OR "heart attack" OR "myocardial infarction" OR "Myocardial Infarction"[Mesh]
2 CPR OR "cardiopulmonary resuscitation" OR "Cardiopulmonary Resuscitation"[Mesh] OR "advanced cardiac life support" OR ACLS OR "Advanced Cardiac Life Support"[Mesh] OR "basic life support" OR resuscitation OR "Resuscitation"[Mesh]
3 "cardiac massage" OR "heart massage" OR "Heart Massage"[Mesh] OR "chest compression" OR "chest compressions" OR compression*
4 "artificial respiration" OR “mechanical ventilation” OR “artificial ventilation” OR "Respiration, Artificial"[Mesh]
5 Defibrillat* OR "Electric Countershock"[Mesh]
6 2 OR 3 OR 4 OR 5
7 Ultrasonograph* OR ultrasound* OR "ultra sound" OR ultrasonic* OR sonograph* OR sonogram* OR "Ultrasonography"[Mesh] OR Echocardiogra* OR "Echocardiography"[Mesh]
8 1 AND 6 AND 7

Cochrane
EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 20, 2024>
EBM Reviews - ACP Journal Club <1991 to February 2024>
EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>

EBM Reviews - Cochrane Clinical Answers <February 2024>
EBM Reviews - Cochrane Central Register of Controlled Trials <February 2024>
EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>
EBM Reviews - Health Technology Assessment <4th Quarter 2016>
EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>

1 ("cardiac arrest" or "heart arrest" or "myocardial contraction" or "cardiopulmonary arrest").mp. or Heart Arrest/ or "heart attack".mp. or "myocardial infarction".mp. or Myocardial Infarction/ [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw] 44328
2 (CPR or "cardiopulmonary resuscitation").mp. or Cardiopulmonary Resuscitation/ or "advanced cardiac life support".mp. or ACLS.mp. or Advanced Cardiac Life Support/ or "basic life support".mp. or resuscitation.mp. or Resuscitation/ [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw] 10740
3 ("cardiac massage" or "heart massage").mp. or Heart Massage/ or "chest compression".mp. or "chest compressions".mp. or compression*.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw] 12566
4 ("artificial respiration" or "mechanical ventilation" or "artificial ventilation").mp. or Respiration, Artificial/ [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw] 19566
5 Defibrillat*.mp. or Electric Countershock/ [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw] 5533
6 2 or 3 or 4 or 5 44728
7 (Ultrasonograph* or ultrasound* or "ultra sound" or ultrasonic* or sonograph* or sonogram*).mp. or Ultrasonography/ or Echocardiogra*.mp. or Echocardiography/ [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw] 78168
8 1 and 6 and 7 254
9 limit 8 to yr="2019 -Current" 104

Embase <1974 to 2024 March 29>

1 ("cardiac arrest" or "heart arrest" or "myocardial contraction" or "cardiopulmonary arrest").tw. or heart arrest/ or "heart attack".tw. or "myocardial infarction".tw. or heart infarction/ 561256
2 ("cardiopulmonary resuscitation" or "advanced cardiac life support" or ACLS).tw. or advanced cardiac life support/ or "basic life support".tw. or resuscitation.tw. or resuscitation/ 166770
3 ("cardiac massage" or "heart massage").tw. or heart massage/ or "chest compression".tw. or "chest compressions".tw. 10545
4 ("artificial respiration" or "mechanical ventilation" or "artificial ventilation").tw. or artificial ventilation/ 211139
5 Defibrillation.mp. or exp defibrillation/ or exp cardioversion/ 43227
6 2 or 3 or 4 or 5 398753
7 (Ultrasonography or ultrasound or "ultra sound" or ultrasonic or sonograph or sonogram).tw. or echography/ or Echocardiography.tw. or echocardiography/ 1202936
8 1 and 6 62674
9 7 and 8 6257
10 limit 9 to yr="2019 -Current" 2792
11 limit 10 to (english language and "remove preprint records") 2768
12 limit 11 to article 1637
13 limit 12 to human 1543
14 limit 13 to "remove medline records" 696

Database searched: Pubmed, Embase and Cochrane
Time Frame: (existing PICOST) – 2021-2024

Date Search Completed: April 2024
Search Results The search revealed 1642 references with 110 duplicates removed leaving 1542 references.

Reference review of title and abstract revealed 33 manuscripts for full text evaluation yielding 0 studies for full text abstraction.

Summary of Evidence Update:

Reviewer Comments:

Given no new studies to evaluate, an updated scoping or systematic review is not indicated

Reference list:

Reynolds JC, Nicholson TC, O'Neil BJ, Drennan I, Issa M, Welsford M, Andersen LW, Ber K, Böttiger BW, Couper K, Deakin CD, Granfeldt A, Holmberg MJ, Hsu CH, Lavonas EJ, Morley PT, Morrison LJ, Nolan JP, Parr MJ, Sandroni C, Skrifvars M, Soar J. Diagnostic Test Accuracy with Point-of-Care Ultrasound During Cardiopulmonary Resuscitation to Indicate the Etiology of Cardiac Arrest: Consensus on Science with Treatment Recommendations [Internet]. Brussels, Belgium: International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support Task Force, 2022

2025 Evidence Update
ALS 3608 – Point of Care Ultrasound for CA – Prognostication

Worksheet Author(s): Zelop, CM, Welsford M, Drennan,I
Task Force: Advanced Life Support
Conflicts of Interest: none

PICOST / Research Question: ***(Attach SAC representative approved completed PICOST template)***
Population: Adults in any setting (in-hospital [IHCA] or out-of-hospital [OHCA]) with non-traumatic cardiac arrest.
Intervention: A particular finding on point-of-care echocardiography during CPR
Comparators: The absence of that finding or a different finding on point-of-care echocardiography during CPR
Outcomes: Clinical outcomes, including, but not necessarily limited to, return of spontaneous circulation, survival to hospital admission, survival/survival with a favorable neurological outcome at hospital discharge, and survival/survival with a favorable neurological outcome beyond hospital discharge. The final included outcomes will depend on the available data and subsequent outcome prioritization by the ILCOR task forces.

Study Designs:
Randomized and non-randomized cohort studies (prospective and retrospective) and case-control studies with data on both point of care ultrasound findings and an external reference standard to contribute to a contingency table (i.e. true positive, false positive, false negative, true negative).
Animal studies, ecological studies, case series, case reports, narrative reviews, abstracts, editorials, comments, letters to the editor, or unpublished studies will not be included.
Year of last full review: (*insert year where this PICOST was most recently reviewed):* 2019

Current ILCOR Consensus on Science and Treatment Recommendation for this PICOST:
Treatment Recommendations:
We suggest against using point-of-care echocardiography for prognostication during cardiopulmonary resuscitation (weak recommendation, very low certainty of evidence).

Current Search Strategy (for an existing PICOST) included in the attached approved PICOST
Pubmed
1 "cardiac arrest" OR "heart arrest" OR "myocardial contraction" OR "cardiopulmonary arrest" OR "Heart Arrest"[Mesh] OR "heart attack" OR "myocardial infarction" OR "Myocardial Infarction"[Mesh]
2 CPR OR "cardiopulmonary resuscitation" OR "Cardiopulmonary Resuscitation"[Mesh] OR "advanced cardiac life support" OR ACLS OR "Advanced Cardiac Life Support"[Mesh] OR "basic life support" OR resuscitation OR "Resuscitation"[Mesh]
3 "cardiac massage" OR "heart massage" OR "Heart Massage"[Mesh] OR "chest compression" OR "chest compressions" OR compression*
4 "artificial respiration" OR “mechanical ventilation” OR “artificial ventilation” OR "Respiration, Artificial"[Mesh]
5 Defibrillat* OR "Electric Countershock"[Mesh]
6 2 OR 3 OR 4 OR 5
7 Ultrasonograph* OR ultrasound* OR "ultra sound" OR ultrasonic* OR sonograph* OR sonogram* OR "Ultrasonography"[Mesh] OR Echocardiogra* OR "Echocardiography"[Mesh]
8 1 AND 6 AND 7

Cochrane
EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 20, 2024>
EBM Reviews - ACP Journal Club <1991 to February 2024>
EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>
EBM Reviews - Cochrane Clinical Answers <February 2024>

EBM Reviews - Cochrane Central Register of Controlled Trials <February 2024>
EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>
EBM Reviews - Health Technology Assessment <4th Quarter 2016>
EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>

1 ("cardiac arrest" or "heart arrest" or "myocardial contraction" or "cardiopulmonary arrest").mp. or Heart Arrest/ or "heart attack".mp. or "myocardial infarction".mp. or Myocardial Infarction/ [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw] 44328
2 (CPR or "cardiopulmonary resuscitation").mp. or Cardiopulmonary Resuscitation/ or "advanced cardiac life support".mp. or ACLS.mp. or Advanced Cardiac Life Support/ or "basic life support".mp. or resuscitation.mp. or Resuscitation/ [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw] 10740
3 ("cardiac massage" or "heart massage").mp. or Heart Massage/ or "chest compression".mp. or "chest compressions".mp. or compression*.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw] 12566
4 ("artificial respiration" or "mechanical ventilation" or "artificial ventilation").mp. or Respiration, Artificial/ [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw] 19566
5 Defibrillat*.mp. or Electric Countershock/ [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw] 5533
6 2 or 3 or 4 or 5 44728
7 (Ultrasonograph* or ultrasound* or "ultra sound" or ultrasonic* or sonograph* or sonogram*).mp. or Ultrasonography/ or Echocardiogra*.mp. or Echocardiography/ [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw] 78168
8 1 and 6 and 7 254
9 limit 8 to yr="2019 -Current" 104

Embase <1974 to 2024 March 29>

1 ("cardiac arrest" or "heart arrest" or "myocardial contraction" or "cardiopulmonary arrest").tw. or heart arrest/ or "heart attack".tw. or "myocardial infarction".tw. or heart infarction/ 561256
2 ("cardiopulmonary resuscitation" or "advanced cardiac life support" or ACLS).tw. or advanced cardiac life support/ or "basic life support".tw. or resuscitation.tw. or resuscitation/ 166770
3 ("cardiac massage" or "heart massage").tw. or heart massage/ or "chest compression".tw. or "chest compressions".tw. 10545
4 ("artificial respiration" or "mechanical ventilation" or "artificial ventilation").tw. or artificial ventilation/ 211139
5 Defibrillation.mp. or exp defibrillation/ or exp cardioversion/ 43227
6 2 or 3 or 4 or 5 398753
7 (Ultrasonography or ultrasound or "ultra sound" or ultrasonic or sonograph or sonogram).tw. or echography/ or Echocardiography.tw. or echocardiography/ 1202936
8 1 and 6 62674
9 7 and 8 6257
10 limit 9 to yr="2019 -Current" 2792
11 limit 10 to (english language and "remove preprint records") 2768
12 limit 11 to article 1637
13 limit 12 to human 1543
14 limit 13 to "remove medline records" 696

Database searched: Pubmed Embase Cochrane
Time Frame: 2019-2024
Date Search Completed: April 2024
Search Results (Number of articles identified and number identified as relevant):

Summary of Evidence Update:

The search revealed 1642 references with 110 duplicates removed leaving 1542 references.
Reference review of title and abstract revealed 33 manuscripts for full text evaluation yielding 5 studies for full text abstraction.

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)**
SHoC-ED2 study Beckett, N et al. 2019	**Study Type:** Retrospective Health Records review on emergency department (ED) patients Study Size (180 patients)	**Inclusion Criteria:** Adult patients selected for transport to ED without prior advanced cardiac life support with non-traumatic cardiac arrest from 2010-2014 underwent point of care ultrasound (POCUS) during resuscitation Those with shockable rhythms and no POCUS performed were excluded	**1° endpoint:** **Aim:** To assess whether combining POCUS and EKG rhythm findings better predicts outcomes during CPR in the emergency department (ED) Primary outcomes measure included performance of diagnostic tests (initial EKG alone, initial POCUS (cardiac activity) alone or combined EKG and POCUS) to predict failure to achieve return of spontaneous circulation (ROSC), and secondary outcomes of failure to survive to hospital admission and failure to survive to hospital discharge. (sensitivity = ability to predict death) Of 264 cases, 84 were excluded and 180 cases were available for analysis 45 (25%) had cardiac activity on EKG and 21 (11.1%) had cardiac activity on initial POCUS exam 15 (8.3%) had activity on both 129 (71.1) had no activity on either test	For adult patients arriving to ED with non-shockable cardiac arrest, the use of POCUS independently or in combination with EKG rhythm more accurately predicted death than EKG alone. No combination reliably predicted survival Variable delays until performance of POCUS may explain inconsistencies of documentation of results EKG and POCUS findings are probably not independent variables. The absence of cardiac activity on POCUS or on both EKG and POCUS together better predicts negative outcomes in cardiac arrest than EKG alone. No test reliably predicts survivability

			47 (26.1%) achieved ROSC 18(10%) survived to hospital admission 3 (1.7%) survived to hospital discharge Less than 1% of patients with asystole on EKG and absence of cardiac activity on POCUS survived to hospital discharge As predictors of failure to achieve ROSC, EKG had a sensitivity of 82.7% and a specificity of 54.6%, POCUS had a sensitivity of 98.2% and a specificity of 34% In patients with EKG asystole, POCUS had a sensitivity of 98.2% (93.6%-99.8%) and specificity of 16.0% (4.54%-36.08%)	
Quantitative Characterization of left ventricular function during pulseless electrical activity using echocardiography during out of hospital cardiac arrest (OHCA) from the Real-Time Evaluation and Assessment Sonography Outcomes Network (REASON) investigators Teran, F et al. 2021	Retrospective assessment (secondary analysis) of prospectively collected data (multi-site observational study) Study size (312 consecutive patients yielding only 84 in the final cohort meeting image quality requirements	Inclusion criteria: Subset of 796 OHCA from REASON cohort with pulseless electrical activity (PEA) as the initial rhythm during the initial echocardiography evaluation	Primary outcome: Association of Left ventricular shortening fraction (LFSF) and outcomes during cardiac arrest: return of spontaneous circulation (ROSC) Secondary outcome: Survival to hospital admission LFSF was calculated from clips using a post hoc M-mode image for calculation LFSF was analyzed both as a continuous	The use of echocardiography in this study potentially revealed the heterogeneity of cardiac function associated with PEA Limitations: Bias and misclassification are Potential confounders Protocol not standardized for time of echocardiographic assessment

	and ability to measure a valid LVSF)		variable and a categorical variable Effects of resuscitation time and LVFS were analyzed using a cox proportional hazards model to evaluate the hazard corresponding to length of resuscitation. Subjects who died defined as those who did not achieve ROSC were censored. Only 91 (29.2%) had images with enough quality to perform measurement of LVFS and 7 revealed abnormal segmental and septal motion abnormalities to preclude measurement of LFSF The mean value for LFSF who achieved ROSC was 21.04% (SD 19.21) versus 11.67% in those who did not achieve ROSC ($p< 0.05$) The mean value of LVSF in patients who survived to hospital admission from emergency department was 10.54% (SD 17.2) versus 14.73% (SD 16.62) ($p < 0.05$) Multivariate regression revealed an association with only the primary outcome of ROSC (OR 1.04, 95% CI 1.01-1.08) Predicted probability of ROSC was 75% for LVFS between 23.4%-96% (fourth quartile) compared to 47% for	

			LVFS 0-4.7% (first quartile)	
The Role of Cardiac Arrest Sonographic exam (CASE) in predicting the outcome of CPR; a cross- sectional study Masoumi, B et al. 2021	Prospective observational study Study size N= 151	Inclusion: Adult patients without trauma presenting to emergency department (ED) in cardiac arrest and non- shockable rhythm Subxiphoid view ultrasound (US) Was performed 10 sec rhythm check Exclusion: Failure to undergo US, short resuscitation less than 4 minutes, other reasons 175-24 = 151 patients	Association of US findings and patient outcomes were analyzed Additionally, etiology for cardiac arrest was assessed evaluating for causes during pulse checks 1) Presence of absence of cardiac activity 2) Presence of effusion 3) Presence of tamponade 4) Presence of potential pulmonary embolism 43/151 demonstrated cardiac activity on initial US Rate of asystole was 89/151 Return of spontaneous circulation (ROSC) was achieved in 36 (23.8%) 20 (13.2%) survived to hospital admission and 7(4.6%) survived to hospital discharge Cardiac activity on first scan was associated with ROSC OR: 6.9, $p < 0.001$, survival to hospital admission OR: 17.8; $p < 0.001$ and survival to hospital	US evals were prospective and available 24/7 depending upon experience level of the ED physician Treating physicians were not blinded to US findings Small sample size In non-traumatic cardiac arrest with non-shockable rhythm, the presence of pulseless electrical activity and cardiac activity on US are associated with ROSC and survival to hospital discharge

			discharge 17.4; p = 0.001 No patient survived when cardiac standstill duration increased to 6 minutes. Performance of screening ultrasound for ROSC: Accuracy = 79.5% (72.1-85.6) Sensitivity = 83.5% (75.4-89.8) Specificity = 66.7% (49-81.4) Hospital Discharge: Accuracy = 74.3% (67.1-81.5) Sensitivity = 74.3% (66.4-81.2) Specificity = 85.7% (42.1- 99.6 Potentially reversible causes of cardiac arrest were detected in 15 case and 4 of them survived to hospital discharge	
Comparison of outcomes between pulseless electrical activity (PEA) by electro-cardiography (EKG) and pulseless myocardial activity by echocardiography in out of hospital cardiac arrest (OHCA) secondary analysis from a	Secondary analysis of prospective multicenter observational study Study size = 793 With 1943 pauses in CPR	Inclusion: Atraumatic OHCA presenting in either asystole or PEA by EKG who had echocardiography performed during pauses in CPR	Primary outcome was divergence in electrical activity on EKG versus myocardial activity on echocardiography 28.6% of CPR pauses revealed differences between EKG and echocardiography The most common was preserved electrical but no myocardial activity.	Patients in CA demonstrate different electrical activity by EKG and mechanical activity via echocardiography Treating physicians were not blinded to results Adjudicating reviewer agreed with real time echo interpretations with a kappa = 0.63

large prospective study Gaspari et al. 2021			Return of spontaneous circulation was less likely in patients with PEA (39.9%) than with pulseless mechanical activity by echo (51.0) but there was no difference in survival to hospital discharge Survival to hospital discharge was 2.4% (95%CI 1.3-4.5) for patients with PEA versus 3.4% (95%CI 1.7-6.5)	
Prognosticating return of spontaneous circulation (ROSC) using ultrasonography in cardiac arrest (CA) patients undergoing cardiopulmonary resuscitation Ravinthiran P et al. 2023	Prospective study Study size = 52	Inclusion: Out of hospital and emergency department in hospital patients in CA who had point of care ultrasound early (first 10 seconds) during resuscitation (POCUS)	Primary outcome: patient outcomes based upon POCUS eval of cardiac activity. Among 52 patients in cardiac arrest, 11 had discernable cardiac activity and 41 did not. 6/11(55%) had ROSC Only 2/49 (5%) without cardiac activity had ROSC (p=0.0003)	Very small sample size 75% sensitivity, 88.6% specificity, 54.5% positive predictive value and 95.1% negative predictive value for the detection of cardiac activity on POCUS for the prediction of ROSC

Reviewer Comments: *(including whether this PICOST should have a systematic or scoping review*)
The value of point of care ultrasound (POCUS) to prognosticate outcomes for patients in cardiac arrest continues to be debated. Our updated search reveals a small number of studies plagued by low sample sizes with wide confidence limits and clinical heterogeneity of both POCUS parameter analyzed and clinical outcomes. Lack of the ability to blind the resuscitators to the POCUS parameter under study will potentially bias the outcome of any study. Lack of agreement in interpretation of acquired views prevalent in all studies underscores the inherent real time clinical challenges of image acquisition under time constraints and level of experience of the resuscitation operators.

Teran 2021, 233 utilizing the measurement of shortening fraction on patients in cardiac arrest with a non-shockable rhythm demonstrates the heterogeneity of ventricular function in those patients with pulseless electrical activity.

The results of this evidence update do not support a formal scoping or systematic review

Knowledge gaps point to the potential value of transesophageal echocardiography as the ultimate POCUS tool for detection of etiology and quantification of myocardial function which could better inform prognosis.

Reference list:

1) Beckett N, Atkinson P, Fraser J, et al. Do combined ultrasound and electrocardiogram-rhythm findings predict survival in emergency department cardiac arrest patients? The Second Sonography in Hypotension and Cardiac Arrest in the Emergency Department (SHoC-ED2) study. CJEM. 2019;21(6):739-743. doi:10.1017/cem.2019.397
2) Teran F, Paradis NA, Dean AJ, Delgado MK, Linn KA, Kramer JA, et al. Quantitative characterization of left ventricular function during pulseless electrical activity using echocardiography during out-of-hospital cardiac arrest. Resuscitation. 2021;167:233-41.
3) Masoumi B, Azizkhani R, Heydari F, Zamani M, Nasr Isfahani M. The Role of Cardiac Arrest Sonographic Exam (CASE) in Predicting the Outcome of Cardiopulmonary Resuscitation; a Cross-sectional Study. Arch Acad Emerg Med. 2021; 9(1): e48. https://doi.org/10.22037/aaem.v9i1.1272.
4) Gaspari R, Weekes A, Adhikari S, Noble VE, Nomura JT, Theodoro D, et al. Comparison of outcomes between pulseless electrical activity by electrocardiography and pulseless myocardial activity by echocardiography in out-of-hospital cardiac arrest; secondary analysis from a large, prospective study. Resuscitation. 2021;169:167-72.