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ILCOR SUMMARY STATEMENT

2018 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations Summary

ABSTRACT: The International Liaison Committee on Resuscitation has initiated a continuous review of new, peer-reviewed, published cardiopulmonary resuscitation science. This is the second annual summary of International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations that includes the most recent cardiopulmonary resuscitation science reviewed by the International Liaison Committee on Resuscitation. This summary addresses the role of antiarrhythmic drugs in adults and children and includes the Advanced Life Support Task Force and Pediatric Task Force consensus statements, which summarize the most recent published evidence and an assessment of the quality of the evidence based on Grading of Recommendations, Assessment, Development, and Evaluation criteria. The statements include consensus treatment recommendations approved by members of the relevant task forces. Insights into the deliberations of each task force are provided in the Values and Preferences and Task Force Insights sections. Finally, the task force members have listed the top knowledge gaps for further research.

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This is the second in a series of annual International Liaison Committee on Resuscitation (ILCOR) International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations (CoSTR) summary publications that summarize the ILCOR task force analyses of published resuscitation evidence. The review this year addresses the use of antiarrhythmic drugs for the management of adult and pediatric cardiac arrest and the period immediately after return of spontaneous circulation (ROSC). Draft CoSTRs were posted online on April 19, 2018,[1] and included the data reviewed and draft treatment recommendations with comments accepted through May 15, 2018. The draft Advanced Life Support (ALS) CoSTR was viewed by ≈4459 visitors (5 comments), and the Pediatric CoSTR was viewed by ≈1183 visitors (2 comments). A total of 8 CoSTRs are now available online, and they have been viewed by ≈11 000 visitors.

This summary statement contains the final wording of the CoSTR as approved by the task forces and by the ILCOR member councils. This statement differs in several respects from the website draft CoSTRs: The language used to describe the evidence is not restricted to standard Grading of Recommendations, Assessment, Development, and Evaluation terminology, making it more transparent to a wider audience; the Values and Preferences and Task Force Insights sections have been

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Table 1. GRADE Terminology for Strength of Recommendation and Criteria for Evidence Quality Assessment

Strength of Recommendation			
Strong Recommendation = We Recommend		Weak Recommendation = We Suggest	
Evidence Quality Assessment Criteria			
Study Design	Quality of Evidence	Lower If	Higher If
Randomized trial	High Moderate	Risk of bias Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding would reduce demonstrated effect or would suggest a spurious effect when results show no effect
Observational study	Low Very low		

GRADE indicates Grading of Recommendations, Assessment, Development, and Evaluation.

Table 2. GRADE Terminology

Risk of bias	Study limitations in randomized trials include lack of allocation concealment, lack of blinding, incomplete accounting of patients and outcome events, selective outcome reporting bias, and stopping early for benefit. Study limitations in observational studies include failure to apply appropriate eligibility criteria, flawed measurement of exposure and outcome, failure to adequately control confounding, and incomplete follow-up.
Inconsistency	Criteria for inconsistency in results include the following: Point estimates vary widely across studies; CIs show minimal or no overlap; statistical test for heterogeneity shows a low *P* value; and the I^2 is large (a measure of variation in point estimates resulting from among-study differences).
Indirectness	Sources of indirectness include data from studies with differences in population (eg, OHCA instead of IHCA, adults instead of children), differences in the intervention (eg, different CV ratios), differences in outcome, and indirect comparisons.
Imprecision	Low event rates or small sample sizes will generally result in wide CIs and therefore imprecision.
Publication bias	Several sources of publication bias include tendency not to publish negative studies and the influence of industry-sponsored studies. An asymmetrical funnel plot increases suspicion of publication bias.
Good practice statements	Guideline panels often consider it necessary to issue guidance on specific topics that do not lend themselves to a formal review of research evidence. The reason might be that research into the topic is unlikely to be located or would be considered unethical or infeasible. Criteria for issuing a nongraded good practice statement include the following: There is overwhelming certainty that the benefits of the recommended guidance will outweigh harms, and a specific rationale is provided; the statements should be clear and actionable to a specific target population; the guidance is deemed necessary and might be overlooked by some providers if not specifically communicated; and the recommendations should be readily implementable by the specific target audience to which the guidance is directed.

CV indicates compression-ventilation; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IHCA, in-hospital cardiac arrest; and OHCA, out-of-hospital cardiac arrest.

expanded to provide more transparency about the rationale for treatment recommendations; and finally, the task forces have prioritized knowledge gaps requiring future research studies.

The CoSTRs are based on task force analysis of the data and use the Grading of Recommendations, Assessment, Development, and Evaluation approach. This analysis is detailed in a systematic review published by the Knowledge Synthesis Unit[2] and the ILCOR topic experts. This Grading of Recommendations, Assessment, Development, and Evaluation approach rates the quality of evidence that supports the intervention effects (predefined by the PICO [population, intervention, comparator, outcome] question) as high, moderate, low, or very low. Randomized controlled trials (RCTs) begin the analysis as high-quality evidence, and observational studies begin the analysis as low-quality evidence. Five factors may lead to a downgrade of the quality of evidence, and 3 factors may enable an upgrade of the quality of the evidence (Tables 1 and 2). Each statement includes the pertinent outcome data listing both relative risk with 95% CI and risk difference (RD) with 95% CI. The RD is the absolute difference between the risks and is calculated by subtracting the risk in the control group from the risk in the intervention group. This absolute effect enables a more clinically useful assessment of the magnitude of the effect of an intervention and enables calculation of the number needed to treat (number needed to treat=1/RD).

Outcome measures were ranked by the task forces by using an approach that is being applied consistently for all ILCOR PICO questions. Longer-term, patient-centered outcomes are considered more important than process variables and shorter-term outcomes.[3,4] In making these rankings, the task forces considered that shorter-term outcomes (eg, termination of ventricular fibrillation, ROSC, survival to hospital admission) are a useful measure of antiarrhythmic drug efficacy.

BACKGROUND

Antiarrhythmic drugs have a potential role in the treatment of cardiac arrest with ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT) that is refractory to electric defibrillation attempts.[5,6] This update on the role of antiarrhythmic drugs was prioritized by the ALS Task Force after publication of an RCT comparing amiodarone, lidocaine, and placebo[7] following the 2015 ALS CoSTR.[5,6] The Pediatric Task Force took the opportunity to rereview the most recent pediatric published evidence.

The reported incidence of adult VF/pVT cardiac arrest varies according to the precise definitions used and the population studied. For treated adult out-of-hospital cardiac arrest (OHCA), an initial arrest rhythm of VF/pVT was documented in 4.1% to 19.8% of arrests in a series from 7 Asian countries,[8] 27.9% in a series from Australia and New Zealand,[9] an average of 22.2% (range, 4.4%–50%) in a series from 27 European countries,[10] and 21.3% in a report from the United States.[11] There are far fewer international data for adult in-hospital cardiac arrest (IHCA), and the reported incidence of initial VF/pVT is 18.9% in Italy,[12] 16.9% in the United Kingdom,[13] and 19.5% in the United States.[14]

An initial cardiac arrest rhythm of VF/pVT is less common in children than in adults, although the frequency varies greatly by age. In OHCA, an initial documented rhythm of VF/pVT has been reported in 3% to 14% of pediatric arrests in the All-Japan Utstein Registry,[15–19] in 7% of pediatric arrests in Australia,[20] in 4% to 12% of pediatric arrests in Sweden,[21] and in 6% to 7.8% of pediatric arrests in the United States.[22–26] The frequency of VF/pVT as an initial arrest rhythm is typically lowest in children <5 years of age, averaging 1% to 6%,[15,18,19,21] and higher in adolescents, averaging 18% to 20% in Japan,[15,18] 17% in Sweden,[21] and 15% to 19.4% in the United States.[22,23] Fewer data are available on the frequency of VF/pVT as the first reported arrest rhythm in pediatric IHCA. An initial rhythm of VF/pVT has been reported in 9% of pediatric IHCA cases in Australia.[27] In the American Heart Association's Get With The Guidelines–Resuscitation registry of IHCA events in 3 pediatric cohorts with enrollment in overlapping years, 10% to 14% demonstrated an initial rhythm of VF/pVT.[28–30] In a small multicenter/multicountry series of 40 IHCA events in 37 children who had a high incidence (56.8%) of cardiac disease and of previous cardiac arrests (24.3%), VF/pVT was the first assessed rhythm in 42.5% of events.[31]

Antiarrhythmic drugs are used to treat VF/pVT only if this rhythm persists after attempted defibrillation (ie, shock delivery). In a large RCT (n=23 711) of continuous or interrupted chest compressions during adult cardiopulmonary resuscitation (CPR) for OHCA,[32] 22.5% of patients had an initial rhythm of VF/pVT, and ≈6.7% of all patients received an antiarrhythmic drug (amiodarone, 4.7%; lidocaine, 2%). In a large observational study (n=108 079) of airway management using data from the Get With The Guidelines–Resuscitation registry of IHCA events, ≈18% of all patients had an initial rhythm of VF/pVT, and 25% of all patients received an antiarrhythmic drug (amiodarone, 17%; lidocaine, 8%) during attempted resuscitation.[33]

Reports of antiarrhythmic drug use during treatment of pediatric cardiac arrest are extremely limited. Two cohort series published from the Get With The Guidelines–Resuscitation registry of IHCA events enrolled patients in overlapping years. In the first study of 1005 consecutive pediatric patients enrolled from 2000 to 2004, 10% had initial VF/pVT and 27% had VF/pVT at some time during the arrest. A total of 24% of all patients received an antiarrhythmic drug. Amiodarone was administered to 23% and lidocaine to 47% of those patients with VF/pVT.[29] Another larger series from the same registry enrolled 553 children with VF/pVT from 2000 to 2005. Nearly half (49%) of those who had VF/pVT were treated with an antiarrhythmic drug; 19.5% of those with VF/pVT received amiodarone. Approximately two-thirds of the children who received amiodarone also received lidocaine.[34]

In the following sections, we include the predefined PICO question addressed by the systematic review; the summary CoSTR; the values, preferences, and insights of the task force during the consensus process; and the priority knowledge gaps. The summary CoSTR for adults is described first, followed by that for children and infants.

THE POPULATION, INTERVENTION, COMPARATOR, OUTCOME, STUDY DESIGNS, AND TIME FRAME

Population

Adults and children in any setting (in hospital or out of hospital) with cardiac arrest and a shockable rhythm (VF/pVT) at any time during CPR or immediately after ROSC were included.

Intervention

Intervention included administration (intravenous or intraosseous) of an antiarrhythmic drug during CPR or immediately (within 1 hour) after ROSC.

Comparators

Comparators included another antiarrhythmic drug or placebo or no drug during CPR or immediately (within 1 hour) after ROSC.

Outcomes

Survival to hospital discharge with good neurological outcome and survival to hospital discharge were ranked as critical outcomes. ROSC was ranked as an important outcome. For an antiarrhythmic drug given within 1 hour of ROSC, rearrest was included as an important outcome.

Study Designs

RCTs and nonrandomized studies (non-RCTs, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion.

Time Frame

All years and all languages were included as long as there was an English abstract; unpublished studies (eg, conference abstracts, trial protocols) were excluded.

The literature search was updated to August 15, 2017. A search of the MEDLINE, Embase, and Cochrane Library identified 9371 records after removal of duplicates. After the records were screened, 409 full-text articles were assessed for eligibility. Fourteen adult RCTs (16 articles) and 19 non-RCTS (18 adult studies, 1 pediatric study, 22 articles) were considered by the task forces to develop the CoSTR.

USE OF ANTIARRHYTHMIC DRUGS DURING RESUSCITATION OF ADULTS WITH VF/pVT CARDIAC ARREST OR IMMEDIATELY AFTER ROSC

Consensus on Science

The systematic review included searches to identify comparative data on the use of antiarrhythmic drugs, including amiodarone versus placebo, lidocaine versus placebo, amiodarone versus lidocaine, magnesium versus placebo, bretylium versus placebo, lidocaine versus bretylium, amiodarone versus nifekalant, lidocaine versus nifekalant, and lidocaine versus sotalol. Given the availability of comparative data from RCTs, the ALS Task Force did not focus on the data from non-RCTs when evaluating the estimated effect size of these drugs and included only data from the RCTs in the meta-analyses in this document. The reason is that the 18 adult observational studies identified had substantial heterogeneity and unmeasured confounders, including "resuscitation time bias."[35]

The amiodarone versus placebo comparison is based on 2 RCTs: the ARREST trial (Amiodarone in the Out-of-Hospital Resuscitation of Refractory Sustained Ventricular Tachyarrhythmias)[36] and the ROC-ALPS trial (Resuscitation Outcomes Consortium Amiodarone, Lidocaine, or Placebo Study).[7] The amiodarone versus lidocaine comparison is based on 2 RCTs: the ALIVE trial (Amiodarone Versus Lidocaine in Prehospital Ventricular Fibrillation Evaluation)[37] and the ROC-ALPS trial.[7] For results of these trials, we have provided pooled estimates and individual study estimates (the reasons are described later in the Values and Preferences and ALS Task Force Insights section). No RCTs were identified that addressed the use of antiarrhythmic drugs immediately after ROSC (defined as within 1 hour after ROSC). The summary of findings and point estimates are shown in Table 3.

Table 3. Summary of Findings: Antiarrhythmic Drugs for Adult Cardiac Arrest With Refractory VF/pVT

Outcomes (Importance)	Participants (Studies), n	Certainty of the Evidence (GRADE)	RR (95% CI)	Anticipated Absolute Effects, n	
				Risk With Standard Care	RD With Intervention+ Standard Care
Amiodarone vs placebo					
Survival to hospital discharge with good neurological outcome (combined) (Critical)	2526 (2 RCTs)[7,36]	Very low	1.13 (0.95–1.36)	146 per 1000	19 more per 1000 (from 7 fewer to 53 more)
Survival to hospital discharge with good neurological outcome (Cordarone) (Critical)	504 (1 RCT)[36]	Very low	1.11 (0.59–2.10)	66 per 1000	7 more per 1000 (from 27 fewer to 72 more)
Survival to hospital discharge with good neurological outcome (Nexterone) (Critical)	2022 (1 RCT)[7]	Moderate	1.13 (0.94–1.37)	166 per 1000	22 more per 1000 (from 10 fewer to 61 more)
Survival to hospital discharge (combined) (Critical)	2530 (2 RCTs)[7,36]	Very low	1.14 (0.98–1.33)	195 per 1000	27 more per 1000 (from 4 fewer to 64 more)
Survival to hospital discharge (Cordarone) (Critical)	504 (1 RCT)[36]	Very low	1.02 (0.65–1.59)	132 per 1000	3 more per 1000 (46 fewer to 78 more)
Survival to hospital discharge (Nexterone) (Critical)	2026 (1 RCT)[7]	Moderate	1.16 (0.99–1.37)	210 per 1000	34 more per 1000 (2 fewer to 78 more)
ROSC (combined) (Important)	2537 (2 RCTs)[7,36]	Very low	1.13 (0.93–1.37)	345 per 1000	45 more per 1000 (from 24 fewer to 128 more)
ROSC (Cordarone) (Important)	504 (1 RCT)[36]	Very low	1.27 (1.02–1.59)	345 per 1000	93 more per 1000 (from 7 more to 204 more)
ROSC (Nexterone) (Important)	2033 (1 RCT)[7]	Moderate	1.04 (0.92–1.17)	346 per 1000	14 more per 1000 (from 28 fewer to 59 more)

(*Continued*)

Table 3. Continued

Outcomes (Importance)	Participants (Studies), n	Certainty of the Evidence (GRADE)	RR (95% CI)	Anticipated Absolute Effects, n	
				Risk With Standard Care	RD With Intervention+ Standard Care
Lidocaine vs placebo					
Survival to hospital discharge with good neurological outcome (Critical)	2039 (1 RCT)[7]	Moderate	1.05 (0.87–1.28)	166 per 1000	8 more per 1000 (from 22 fewer to 46 more)
Survival to hospital discharge (Critical)	2041 (1 RCT)[7]	Moderate	1.13 (0.96–1.32)	210 per 1000	27 more per 1000 (from 8 fewer to 67 more)
ROSC (Important)	2051 (1 RCT)[7]	High	1.16 (1.03–1.29)	346 per 1000	55 more per 1000 (from 10 more to 100 more)
Amiodarone vs lidocaine					
Survival to hospital discharge with good neurological outcome (Critical)	1951 (1 RCT)[7]	Moderate	1.08 (0.89–1.30)	175 per 1000	14 more per 1000 (from 19 fewer to 52 more
Survival to hospital discharge (combined) (Critical)	2302 (2 RCTs)[7,37]	Very low	1.04 (0.89–1.22)	207 per 1000	8 more per 1000 (from 23 fewer to 45 more)
Survival to hospital discharge (lidocaine with polysorbate 80) (Critical)	347 (1 RCT)[37]	Very low	1.67 (0.57–4.88)	30 per 1000	20 more per 1000 (from 13 fewer to 116 more)
Survival to hospital discharge (Critical)	1955 (1 RCT)[7]	Moderate	1.03 (0.88–1.21)	237 per 1000	7 more per 1000 (from 28 fewer to 50 more)
ROSC (Important)	1966 (1 RCT)[7]	Moderate	0.90 (0.80–1.01)	399 per 1000	40 fewer per 1000 (from 80 fewer to 4 more)
Magnesium vs placebo					
Survival to hospital discharge with good neurological outcome (Critical)	332 (3 RCTs)[38–40]	Very low	2.08 (0.87–4.97)	35 per 1000	38 more per 1000 (from 5 fewer to 140 more)
Survival to hospital discharge (Critical)	437 (4 RCTs)[38–41]	Very low	1.07 (0.62–1.86)	90 per 1000	6 more per 1000 (from 34 fewer to 77 more)
ROSC (Important)	437 (4 RCTs)[38–41]	Very low	0.97 (0.77–1.24)	327 per 1000	4 more per 1000 (from 83 less to 92 more)
Bretylium vs placebo					
Survival to hospital discharge (Critical)	29 (1 RCT)[42]	Very low	4.28 (0.60–30.26)	91 per 1000	298 more per 1000 (from 43 fewer to 535 more)
Lidocaine vs bretylium					
Survival to hospital discharge (Critical)	237 (2 RCTs)[43,44]	Very low	0.84 (0.51–1.36)	235 per 1000	38 fewer per 1000 (from 143 fewer to 66 more)
ROSC (Important)	237 (2 RCTs)[43,44]	Very low	1.23 (0.78–1.92)	496 per 1000	114 more per 1000 (from 109 fewer to 456 more)
Amiodarone vs nifekalant					
Survival to hospital discharge with good neurological outcome (Critical)	30 (1 RCT)[45]	Very low	1.00 (0.31–3.28)	267 per 1000	0 more per 1000 (from 184 fewer to 608 more)
Survival to hospital discharge (Critical)	30 (1 RCT)[45]	Very low	2.00 (0.76–5.24)	267 per 1000	267 more per 1000 (from 77 fewer to 536 more)
ROSC (Important)	30 (1 RCT)[45]	Very low	1.43 (0.75–2.73)	467 per 1000	201 more per 1000 (from 117 fewer to 807 more)
Lidocaine vs nifekalant					
Survival to hospital discharge (Critical)	28 (1 RCT)[46]	Very low	…	0 per 1000	0 more per 1000
ROSC (Important)	22 (1 RCT)[46]	Very low	0.23 (0.06–0.92)	625 per 1000	481 fewer per 1000 (from 587 fewer to 50 fewer)
Lidocaine vs sotalol					
Survival to hospital discharge with good neurological outcome (Critical)	129 (1 RCT)[47]	Low	6.10 (0.32–115.76)	0 per 1000	43 more per 1000 (from 23 fewer to 120 more)
Survival to hospital discharge (Critical)	129 (1 RCT)[47]	Low	2.17 (0.44–10.80)	33 per 1000	39 more per 1000 (from 19 fewer to 327 more)
ROSC (Important)	129 (1 RCT)[47]	Low	1.41 (0.84–2.37)	267 per 1000	109 more per 1000 (from 43 fewer to 365 more)

GRADE indicates Grading of Recommendations, Assessment, Development, and Evaluation; RCT, randomized controlled trial; RD, risk difference; ROSC, return of spontaneous circulation; RR, relative risk; and VF/pVT, ventricular fibrillation/pulseless ventricular tachycardia.

Amiodarone Versus Placebo

The combined evidence from 2 RCTs (the ARREST and ROC-ALPS trials) comparing amiodarone with placebo for OHCA showed, with very low certainty, no statistically significant difference in survival to hospital discharge with good neurological outcome (n=2526), survival to hospital discharge (n=2530), or ROSC (n=2537).[7,36] The quality of this combined evidence was downgraded because of concerns about risk of bias, indirectness, and imprecision. The ARREST trial[36] risk of bias was noted because investigators did not report intention-to-treat data. Although the ROC-ALPS trial enrolled patients from 2013 to 2015, the risk of indirectness was noted because resuscitation practice at the time of the patient enrollment for the ARREST trial (1994–1997) differed substantially from current practice. An additional risk of indirectness resulted from the fact that the placebo groups in both trials received polysorbate 80. Concerns about differences in resuscitation practice at the time of patient enrollment and about the use of the polysorbate 80 placebo are discussed further in the Values and Preferences and ALS Task Force Insights section of this article. The wide CIs around the point estimates, the number of events, and a sample size that did not meet the optimal information size criteria resulted in a downgrade for imprecision; this raises concerns that both studies may have been underpowered to detect a clinically meaningful treatment effect.[48]

One RCT, the ARREST trial, involved 504 patients and compared the Cordarone (amiodarone in polysorbate 80) preparation of amiodarone with an active polysorbate 80 placebo.[36] This study showed, with very low certainty, no statistically significant difference in survival to hospital discharge with good neurological outcome or survival to hospital discharge. However, it did show a statistically significant increase in ROSC. For the same reasons given for the combined data stated earlier, the quality of this evidence was downgraded because of concerns about risk of bias, indirectness, and imprecision.

One RCT, the ROC-ALPS trial, compared the Nexterone preparation of amiodarone with saline placebo. This trial showed, with moderate certainty, no statistically significant difference in survival to hospital discharge with good neurological outcome (n=2022), survival to hospital discharge (n=2026), or ROSC (n=2033).[7] The quality of the evidence was downgraded because of concerns about imprecision that related to wide CIs around the point estimates, the number of events, and a sample size that did not meet the optimal information size criteria.

Lidocaine Versus Placebo

One RCT, the ROC-ALPS trial, compared lidocaine with placebo.[7] This study showed, with moderate certainty, no statistically significant difference in survival to hospital discharge with good neurological outcome (n=2039) or survival to hospital discharge (n=2041). The quality of the evidence was downgraded because of concerns about imprecision related to wide CIs around the point estimates, the number of events, and a sample size that did not meet the optimal information size criteria.

The same RCT (ROC-ALPS) compared lidocaine with placebo and involved 2051 patients. This trial showed, with high certainty, a statistically significant increase in ROSC favoring lidocaine.[7]

Amiodarone Versus Lidocaine

One RCT (ROC-ALPS) compared amiodarone with lidocaine and showed, with moderate certainty, no statistically significant difference in survival to hospital discharge with good neurological outcome (n=1951), survival to hospital discharge (n=1955), or ROSC (n=1966).[7] The quality of the evidence was downgraded because of concerns about imprecision that related to wide CIs around the point estimates, the number of events, and a sample size that did not meet the optimal information size criteria.

Two RCTs, the ALIVE trial[37] and the ROC-ALPS trial,[7] compared amiodarone with lidocaine and involved 2302 patients. These trials showed, with very low certainty, no statistically significant difference in survival to hospital discharge.[7,37] The quality of this combined evidence was downgraded because of concerns about risk of indirectness and imprecision. The ALIVE trial[37] was at risk of indirectness because resuscitation practice at the time of patient enrollment (1995–2001) differed substantially from current practice. In addition, lidocaine was mixed with polysorbate 80, a preparation that is not used commercially; the effects of adding polysorbate 80 to the lidocaine are uncertain. The wide CIs around the point estimates, the number of events, and a sample size that did not meet the optimal information size criteria resulted in a downgrade for imprecision.

One RCT (the ALIVE trial) compared amiodarone with lidocaine mixed with polysorbate 80 and involved 347 patients. This trial showed, with very low certainty, no statistically significant difference in survival to hospital discharge.[37] The quality of this evidence was downgraded because of concerns about indirectness and imprecision for the reasons given previously.

Magnesium Versus Placebo

Three RCTs comparing magnesium with placebo and involving 332 patients showed, with very low certainty, no statistically significant difference in survival to hospital discharge with good neurological outcome.[38–40] The quality of this evidence was downgraded because of risk of bias, imprecision, and indirectness. The risk of bias resulted from uncertainties about allocation concealment and blinding of clinicians and outcome assessors.

The wide CIs around the point estimates, the number of events, and a sample size that did not meet the optimal information size criteria resulted in the downgrade for imprecision. The risk of indirectness was noted because resuscitation practice at the times of patient enrollment (all 3 studies completed enrollment before the publication of the 2000 International Consensus recommendations and 2000 council guidelines) differed substantially from current practice, and 2 of these studies[39,40] included patients who had arrest rhythms other than VF/pVT.

Four RCTs (the 3 studies cited in the previous paragraph[38–40] plus an additional study[41]) compared magnesium with placebo and involved 437 patients. These studies showed, with very low certainty, no statistically significant difference in survival to hospital discharge or ROSC.[38–41] The quality of this evidence was downgraded because of concerns about risk of bias and imprecision for reasons given previously. In all 4 studies, patients were treated according to pre-2000 resuscitation guidelines, which differ considerably from current practice. As a result, all 4 studies were downgraded for indirectness.

Bretylium Versus Placebo

One RCT comparing bretylium with placebo in 29 patients showed, with very low certainty, no statistically significant difference in survival to hospital discharge.[42] The quality of this evidence was downgraded because of concerns about risk of bias, indirectness, and imprecision. The risk of bias resulted from uncertainties about sequence generation, allocation concealment, and blinding of participants. The risk of indirectness was noted because resuscitation practice at the time of patient enrollment (well before 2000) differed substantially from current practice. The wide CIs around the point estimates, the number of events, and a sample size that did not meet the optimal information size criteria resulted in the downgrade for imprecision.

Lidocaine Versus Bretylium

Two RCTs comparing lidocaine with bretylium in 237 patients showed, with very low certainty, no statistically significant difference in survival to hospital discharge or ROSC.[43,44] The quality of this evidence was downgraded because of concerns about risk of bias, indirectness, and imprecision. The risk of bias resulted from uncertainties about sequence generation, allocation concealment, and blinding of participants. The risk of indirectness was present because resuscitation practice at the time of patient enrollment for both studies (well before 2000) differed substantially from current practice. The wide CIs around the point estimates, the number of events, and a sample size that did not meet the optimal information size criteria resulted in the downgrade for imprecision.

Amiodarone Versus Nifekalant

One controlled trial comparing amiodarone with nifekalant in 30 patients (enrolled 2007–2009) showed, with very low certainty, no statistically significant difference in survival to hospital discharge with good neurological outcome, survival to hospital discharge, or ROSC.[45] The quality of this evidence was downgraded because of concerns about risk of bias and imprecision. The risk of bias resulted from concerns about sequence generation and allocation concealment and uncertainties about blinding of participants and outcome assessors. The wide CIs around the point estimates, the number of events, and a sample size that did not meet the optimal information size criteria resulted in the downgrade for imprecision.

Lidocaine Versus Nifekalant

One controlled trial comparing lidocaine with nifekalant showed, with very low certainty, no statistically significant difference in survival to hospital discharge (n=28) or ROSC (n=22).[46] The quality of this evidence was downgraded because of concerns about risk of bias, imprecision, and indirectness. The risk of bias resulted from concerns about sequence generation and allocation concealment, uncertainties about blinding of participants and outcome assessors, and incomplete reporting of outcomes. The imprecision resulted from the fact that the sample size for survival to hospital discharge did not meet the optimal information size criteria, and the effect estimate could not be determined because there were no survivors in either arm. For the outcome of ROSC, the CIs around the point estimates were wide, and the sample size was too small. The study was downgraded for indirectness because at the time of study enrollment (2001–2004), resuscitation practice differed substantially from current practice.

Lidocaine Versus Sotalol

One controlled trial comparing lidocaine with sotalol showed, with low certainty, no statistically significant difference in survival to hospital discharge with good neurological outcome (n=129), survival to hospital discharge (n=129), or ROSC (n=129).[47] The quality of this evidence was downgraded as a result of concerns about imprecision because the CIs around the point estimates were wide, because of the number of events, and because the sample size did not meet the optimal information size criteria. The study was downgraded for indirectness because the study enrolled patients before publication of the 2005 ILCOR CoSTR and council guidelines recommendations that resulted in substantial alterations in resuscitation practice.

Treatment Recommendations

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

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

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

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

Values and Preferences and ALS Task Force Insights

In making these recommendations, the ALS Task Force considered the following.

Amiodarone or Lidocaine

We considered the predefined and reported bystander-witnessed arrest subgroup (n=1934) analysis of the ROC-ALPS study[7] that showed a significant improvement with an antiarrhythmic drug for the critical outcome of survival to hospital discharge. Specifically, survival was higher with amiodarone (27.7%) or lidocaine (27.8%) than with placebo (22.7%). This absolute RD was significant for amiodarone (5.0%; 95% CI, 0.3–9.7; *P*=0.04) or lidocaine (RD, 5.2%; 95% CI, 0.5–9.9; *P*=0.03) compared with placebo but not for amiodarone compared with lidocaine (RD, −0.1%; 95% CI, −5.1 to 4.9; *P*=0.97).

The survival to hospital discharge in the ROC-ALPS trial was also higher among amiodarone recipients than placebo recipients in the emergency medical services–witnessed arrest subgroup (n=154).[7] Survival was higher with amiodarone (38.6%) than with placebo (16.7%). This was associated with earlier drug use: The time from cardiac arrest to the first dose of trial drug was 11.7±5.8 minutes for those with emergency medical services–witnessed arrest versus a time from 9-1-1 call to the first study drug of 19.3±7.1 minutes for those with non–emergency medical services–witnessed cardiac arrest.

We did not identify any RCTs comparing outcomes of amiodarone or lidocaine for IHCA. We acknowledge that drug delivery during resuscitation is typically much earlier in the inpatient setting,[49,50] raising the possibility that these drugs may be beneficial for the IHCA population. However, we also acknowledge that there is a lack of RCT data for IHCA.

In making a weak recommendation, we considered the reported small increase in the short-term outcome of ROSC in those treated with amiodarone in the 1999 ARREST study[36] and in those treated with lidocaine in the 2016 ROC-ALPS study.[7] Neither drug was associated with a difference in the longer-term outcomes that were ranked as critical: survival or good neurological survival to hospital discharge. The systematic review identified no data on the outcomes of health-related quality of life or burdens and costs of treatment.

The ALS Task Force recognizes that the selected values for outcomes (we ranked ROSC as an important outcome) may not be the same as those that patients and families would choose. It is possible that patients who will not survive to hospital discharge and their families may value patient ROSC because it may provide family members with some preparation time before a final declaration of death. This is a knowledge gap. Patients, families, and society may also place a value on ROSC that is based on the possibility of organ donation and the continued support needed to enable organ donation. The task force also recognizes that ROSC may lead to an increased burden on healthcare systems if patients do not survive to hospital discharge.

In ROC-ALPS,[7] there was no difference between amiodarone and lidocaine in survival or good neurological outcome at hospital discharge, and the task force made the same weak recommendation for both amiodarone and lidocaine. In the 2015 CoSTR,[5,6] the quality of the evidence favoring amiodarone was rated as moderate, whereas the quality of the evidence for lidocaine was rated as very low.

Given the high-quality evidence for improved ROSC with lidocaine from the ROC-ALPS,[7] the task force considered giving a stronger recommendation for lidocaine than amiodarone. However, the lack of difference for critical outcomes (survival and survival with favorable neurological outcome on hospital discharge) between the drugs led the task force to assign the same level of recommendation and quality of evidence for both drugs.

We considered the differences between the 2 RCTs with amiodarone versus placebo (ie, the ARREST trial[36] and the ROC-ALPS trial[7]) and the 2 RCTs with amiodarone versus lidocaine (ie, the ALIVE trial[37] and the ROC-ALPS trial[7]). We discussed the benefits of pooling data versus keeping the studies separate in the systematic review and meta-analyses. The benefits of increasing precision of an estimate of effect were weighed against the detrimental effects of combining distinctly different studies. We have provided pooled estimates based on combining studies and analyzed those from the individual studies. The following issues with the ARREST study[36] and ROC-ALPS[7] trial were considered for the amiodarone versus placebo comparison:

1. The ARREST study included patients with VF/pVT at any stage in the resuscitation attempt who had received 3 shocks. In comparison, the ROC-ALPS study included only those with an initial arrest rhythm of VF/pVT who had received at least 1 shock. The actual number of shocks given before the trial drug in the ARREST study was a mean of 5 (SD, ±2; median, 4) and in the ROC-ALPS study was a median of 3 (interquartile range, 2–4).

2. The ARREST study used an amiodarone in polysorbate 80 preparation and compared it with a polysorbate 80 placebo. The potential effects of polysorbate 80 are debated: It may have hemodynamic effects (possible transient hypotension), so there is a possibility that the control was harmed by an active placebo. The task force did not identify any human or animal studies comparing the effects of polysorbate 80 with 0.9% sodium chloride during CPR for shock-refractory VF/pVT. The effect of polysorbate 80 on the outcomes of the ARREST study is therefore unknown.
3. The ROC-ALPS trial used the Nexterone formulation of amiodarone and an inactive placebo (0.9% sodium chloride). Nexterone is a newer formulation of amiodarone that uses the diluent Captisol (a sulfobutyl ether β-cyclodextrin) instead of polysorbate 80.
4. There were considerable changes in the management of refractory VF/pVT between the time of patient enrollment in the ARREST trial (1994–1997) and the time of patient enrollment in the ROC-ALPS trial (2013–2015). Many of the practices used in the ARREST study (published in 1999 with patients enrolled 1994–1997) were consistent with recommendations in the 1992 American Heart Association "Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiac Care,"[51] including initial delivery of 2 slow rescue breaths and a pause for pulse check before initiation of chest compressions, recommended compression depth of 1.5 to 2 in (4–5 cm) at rate of 80 to 100 per minute, use of a compression-ventilation ratio of 15:2, use of monophasic defibrillators to deliver up to 3 stacked shocks without intervening compressions, use of escalating energy levels, and pauses in compressions during charging before shock delivery. By the time patients were enrolled in the ROC-ALPS trial, ILCOR recommendations and council guidelines had been revised in 2005 and again in 2010, replacing the 1992 recommendations with new approaches such as delivery of 1 shock followed by immediate CPR, compression rate of at least 100 per minute, and other approaches designed to minimize interruptions in chest compressions as part of the delivery of high-quality CPR.
5. We are unable to ascertain the intention-to-treat population for the ARREST study and thus can compare only the per-protocol analysis.

The following issues with the ALIVE study[37] were considered for the amiodarone versus lidocaine comparison:

1. Many of the practices used to manage patients in the ALIVE study (study published in 2002, patients enrolled 1995–2001) have been superseded, as noted previously.
2. The ALIVE study included patients with initial VF/pVT who received 3 shocks, adrenaline, and a fourth shock, whereas the ROC-ALPS trial included those with an initial arrest rhythm of VF/pVT who received at least 1 shock. The actual number of shocks given before the trial drug in the ALIVE study was a mean of 5 (SD, ±2; median, 4) and in the ROC-ALPS trial was a median of 3 (interquartile range, 2–4).
3. In the ALIVE study, lidocaine was mixed with polysorbate 80 (the diluent for amiodarone) to improve blinding because polysorbate 80 is viscous. It is unknown whether the addition of polysorbate 80 (with potential hemodynamic effects) to lidocaine adversely affected outcomes in the lidocaine group.

We note that the reported risk of harm associated with amiodarone or lidocaine use during cardiac arrest was small. Specifically, the ROC-ALPS trial[7] reported a small increase in the need for temporary pacing in the first 24 hours after ROSC in the amiodarone group compared with the lidocaine and placebo groups (4.9% versus 3.2% versus 2.7%) in the per-protocol population (P=0.02). There was, however, no difference among patients who received amiodarone, lidocaine, or placebo in the percent of patients with a poor neurological outcome (modified Rankin Scale score 4 or 5) at hospital discharge (5.4% for amiodarone versus 6.1% for lidocaine versus 4.3% for placebo) in the per-protocol population.

Magnesium

We did not identify any RCTs published since the 2015 CoSTR[5,6] that evaluated the role of magnesium in the treatment of VF/pVT. The 4 RCTs evaluated in the 2015 CoSTR reported the outcomes of a total of 437 patients,[38–41] with the most recent study published in 2002, which noted that the enrolled patients were treated in a manner consistent with the 1992 European resuscitation guidelines.[52] Two of these studies included patients who had arrest rhythms other than VF/pVT.[39,40] In making a suggestion against the routine use of magnesium for refractory VF/pVT cardiac arrest, we recognize that there are specific circumstances in which magnesium could be considered during refractory VF/pVT (eg, hypomagnesemia, torsades de pointes).

Bretylium, Nifekalant, and Sotalol

In making no recommendation about the use of bretylium, nifekalant, or sotalol, we considered guidance from the Grading of Recommendations, Assessment, Development, and Evaluation handbook.[53] We recognize that bretylium is not available in most settings for clinical use and is not part of current council guidelines internationally. We did not identify any RCTs that compared nifekalant with a placebo. We identified only the single very small RCT with 30 patients that compared amiodarone with nifekalant[45] and another very small RCT with 28 patients that compared lidocaine with nifekalant.[46] Sotalol is not part of current council guidelines internationally.

The role of β-blocker drugs during and after cardiac arrest remains a knowledge gap. The ILCOR member resuscitation councils can best determine whether to recommend any change in current practice concerning these drugs.

Prophylactic Use of Antiarrhythmic Drugs Immediately After ROSC

We did not identify any RCTs for the prophylactic use of antiarrhythmic drugs in patients during the first hour after ROSC following a VF/pVT cardiac arrest, and we have identified this as a knowledge gap. No recommendation was made for or against prophylactic antiarrhythmic drugs after ROSC in the 2015 CoSTR,[5,6] after analysis of 2 observational studies,[54,55] and we have not identified any additional evidence to support a recommendation.

Additional Peer-Reviewed Evidence and Additional ALS Task Force Insights

We identified 1 additional RCT that met our inclusion criteria.[56] This RCT of subjects experiencing OHCA compared amiodarone, lidocaine, and saline placebo for patients with an initial nonshockable rhythm that later transitioned to a shockable rhythm. This study was underpowered for the primary end point of survival to hospital discharge.

Finally, the ALS Task Force recognizes that all the currently available RCTs are underpowered to detect any small effect sizes of antiarrhythmic drugs that could lead to many more survivors. For example, a 1% absolute increase in survival from OHCA with an antiarrhythmic drug could lead to ≈600 additional survivors in North America each year.[7] To detect these small differences for critical outcomes (survival to discharge and good neurological survival) requires very large RCTs (tens of thousands of patients), and these may not be feasible. In the absence of large RCTs, combining data by using approaches such as network meta-analyses and sensitivity analyses of the meta-analyses and by using data from large observational studies or large registries in addition to RCTs could potentially overcome the shortcomings (inadequately powered RCTs, study quality, changes in resuscitation technique over time) in the evidence reviewed for this CoSTR.

ALS Task Force Knowledge Gaps

Current knowledge gaps for the use of antiarrhythmic drugs in adult refractory VF/pVT include but are not limited to the following:

- For VF/pVT cardiac arrest, do antiarrhythmic drugs improve patient-centered outcomes (survival with good neurological outcome, health-related quality of life), and do the outcomes differ within or across specific populations (OHCA or IHCA) or conditions (eg, witnessed arrest, monitored arrest, bystander CPR, number of shocks, CPR quality)?
- Does the use of epinephrine (adrenaline) affect the effectiveness of antiarrhythmic drugs during CPR for VF/pVT cardiac arrest and, if so, how?
- Is the use of multiple antiarrhythmic drugs (eg, amiodarone followed by lidocaine) more effective than the use of a single drug during CPR for VF/pVT cardiac arrest?
- Is there a difference in effectiveness between intravenous and intraosseous antiarrhythmic drug administration during CPR for VF/pVT cardiac arrest, and does the intraosseous site (humeral, tibial, other) make a difference?
- Does nifekalant improve critical outcomes compared with placebo or alternative antiarrhythmic drugs during CPR for VF/pVT cardiac arrest?
- Does treatment with prophylactic antiarrhythmic drugs (including β-blockers) given immediately after ROSC improve outcome following VF/pVT cardiac arrest?

USE OF ANTIARRHYTHMIC DRUGS IN INFANTS AND CHILDREN WITH VF/pVT CARDIAC ARREST

Consensus on Science

Previous CoSTR statements evaluating the use of antiarrhythmic drugs during pediatric VF/pVT cardiac arrest, including the 2015 ILCOR Pediatric CoSTR,[57,58] have included extrapolated evidence from adult OHCA studies and case series of children with life-threatening ventricular arrhythmias but not cardiac arrest. The ILCOR Pediatric Task Force concluded the 2015 review with a weak recommendation suggesting that amiodarone or lidocaine may be used for the treatment of pediatric shock-resistant VF/pVT (weak recommendation, very low-quality evidence).[57,58]

The Pediatric Task Force agreed that this 2018 ILCOR CoSTR would not review evidence extrapolated from studies of adult cardiac arrest. Any such extrapolation would result in very low-quality evidence as a consequence of indirectness because, regardless of location, the causes and presentation of children in cardiac arrest differ substantially from the causes and presentation of adults in cardiac arrest. When the initial pediatric cardiac arrest rhythm is VF/pVT, the infant or child often has congenital heart disease, inherited arrhythmia syndromes, commotio cordis, or cardiomyopathies that can influence presentation, treatment, and response to therapy. Subsequent VF/pVT can develop after pediatric resuscitation from an initial bradyasystolic arrest rhythm that is typically associated with hypoxic/asphyxial arrest in

children with preexisting shock or respiratory failure. In contrast, adult cardiac arrest with VF/pVT is often sudden, precipitated by acute coronary artery obstruction and myocardial ischemia.[59]

For this 2018 update, there were no additional pediatric studies beyond the single study that formed the basis of the 2015 CoSTR. This study consists of data from an observational cohort of infants and children with IHCA from the Get With The Guidelines–Resuscitation registry.[30] For this 2018 CoSTR, the Pediatric Task Force rereviewed this study by using the current ILCOR systematic review process and the 2018 PICO question to determine whether amiodarone or lidocaine, administered in any setting (OHCA or IHCA) at any time during resuscitation or within 1 hour after ROSC, was associated with improvement in the critical outcomes of survival to hospital discharge with good neurological outcome or survival to hospital discharge or the important outcome of ROSC or decreased rearrest after ROSC. The review identified no data on the use of antiarrhythmics to guide recommendations for pediatric OHCA.

For the critical outcome of survival to hospital discharge, the task force analyzed the single observational cohort study with 302 patients.[30] This cohort study was downgraded for lack of a control, indirectness (ie, patients were enrolled during an 8-year period of 2000–2008; in the years 2000–2005, international recommendations for CPR and pediatric ALS differed substantially from current practice), risk of bias (ie, from a voluntary registry), and imprecision (ie, timing of drug administration and adverse events were not reported). This study found no difference in effect for lidocaine compared with amiodarone (25% versus 17%; *P*=NS; relative risk, 1.50; 95% CI, 0.90–2.52); there were 84 survivors per 1000 patients treated (range, <17 to >256, no statistically significant effect).[30]

For the important outcome of ROSC, in the same in-hospital observational study with 302 patients (quality downgraded as noted previously), ROSC was associated with a higher percentage of the children who received lidocaine than those who received amiodarone (64% versus 44%; *P*=0.004; relative risk, 1.46; 95% CI, 1.13–1.88), 202 more per 1000 treated (range, 57–386; number needed to treat, 5; 95% CI, 3–18).[30]

Treatment Recommendations

We suggest that amiodarone or lidocaine be used in the treatment of pediatric shock-refractory VF/pVT (weak recommendation, very low-quality evidence).

Values and Preferences and Pediatric Task Force Insights

In making this recommendation, the task force considered the following.

We placed a higher value on the use of in-hospital pediatric registry data over extrapolation of data from studies of adult cardiac arrest. Although 3 adult RCTs compared lidocaine, amiodarone, and placebo, the populations studied are substantially different from both pediatric (prepubertal) and adolescent populations. The adult studies were heavily populated by subjects >50 years of age and specifically excluded patients <18 years of age. In addition, the pediatric and adult studies do not consistently distinguish between primary and subsequent VF and their outcomes on the basis of drug therapies. The distinction between initial and subsequent VF is an important one because pediatric survival from subsequent VF is much lower than the survival from initial VF/pVT.[28,30] Although the causes of IHCA and OHCA in children may differ, the task force feels that extrapolation of pediatric IHCA data to pediatric OHCA is reasonable.

The task force has low confidence in the quality of the data from the single study available for analysis.[30] This study included patients enrolled before the publication of the 2005 CoSTR and council guidelines. The 2005 guidelines differed considerably from previous recommendations, with new emphasis on minimizing interruptions in chest compressions as part of overall high CPR quality to improve resuscitation outcomes.

The task force chose the critical and important outcomes for this review on the basis of outcomes available in the literature and acceptable outcomes in the discipline. Longer-term outcomes, particularly functional outcomes, are more desirable but are not available at this time. Furthermore, patient-centric outcomes may differ from those of the task force. Patients and families may place a higher value on short-term ROSC to give family members time to prepare for the child's death or for organ donation. In addition, the patient and family may value survival, even with moderate neurological disability, over death.

Pediatric Task Force Knowledge Gaps

- Do antiarrhythmic drugs improve outcomes (including patient- and family-centered outcomes) from pediatric OHCA or IHCA with VF/pVT? Do these drugs improve survival in specific populations of infants and children or under specific conditions?
- Does the timing of antiarrhythmic drug administration with respect to defibrillation or epinephrine influence drug effectiveness?
- Is there a difference in antiarrhythmic effectiveness and adverse events based on the cause of the arrest (eg, channelopathy versus structural heart disease versus ischemia versus drug overdose) or for the treatment of initial versus subsequent VF/pVT?
- Does the use of antiarrhythmic drugs influence the cost-effectiveness, health equity, or resource requirements for infants and children who develop cardiac arrest with VF/pVT?

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Disclosures

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*Modest.

†Significant.

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Lorrel E. Brown	University of Louisville	Northwestern Cardiovascular Young Investigators' Forum Stamler Grant (This unrestricted grant of $10 000 was awarded for work on CPR in laws in high school. The funds are being used for research regarding best practices for CPR instruction for the lay public.)†	None	None	None	None	None	None
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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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