

Part 2: Evidence Evaluation and Management of Conflicts of Interest

2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Key Words: [cardiac arrest](#) [cardiopulmonary resuscitation](#) [emergency](#) [resuscitation](#)

1 Introduction

This Part describes the process of creating the *2015 American Heart Association (AHA) Guidelines Update for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC)*, informed by the [2015 International Consensus on CPR and ECC Science With Treatment Recommendations \(CoSTR\)](#) publication.¹ The process for the 2015 International Liaison Committee on Resuscitation (ILCOR) systematic review is quite different when compared with the process used in 2010.² For the 2015 systematic review process, ILCOR used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (www.gradeworkinggroup.org) approach to systematic reviews and guideline development. For the development of this 2015 Guidelines Update, the AHA used the ILCOR reviews as well as the AHA definition of Classes of Recommendation (COR) and Levels of Evidence (LOE) (Table 1). This Part summarizes the application of the ILCOR GRADE process to inform the creation of 2015 Guidelines Update, and the process of assigning the AHA COR and LOE.

Table 1: 2015 - Applying Class of Recommendations and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care*

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Applying Class of Recommendations and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care*

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) Benefit >>> Risk

Suggested phrases for writing recommendations:

- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
 - Treatment/strategy A is recommended/indicated in preference to treatment B
 - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) Benefit >> Risk

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
 - Treatment/strategy A is probably recommended/indicated in preference to treatment B
 - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) Benefit ? Risk

Suggested phrases for writing recommendations:

- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) Benefit = Risk (Generally, LOE A or B use only)

Suggested phrases for writing recommendations:

- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) Risk > Benefit

Suggested phrases for writing recommendations:

- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

Level A

- High-quality evidence‡ from more than 1 RCTs
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

Level B-R (Randomized)

- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

Level B-NR (Nonrandomized)

- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

Level C-LD (Limited Data)

- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

Level C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE). A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective. * The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information). † For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated. ‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee. COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

2 Development of the 2015 Consensus on Science with Treatment Recommendations

2.1 Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

The 2015 CoSTR summarizes the published scientific evidence that was identified to answer specific resuscitation questions. ILCOR uses the GRADE system to summarize evidence and determine confidence in estimates of effect as well as to formulate treatment recommendations. GRADE is a consensus-crafted tool in wide use by many professional societies and reference organizations, including the American College of Physicians, the American Thoracic Society, and the Cochrane Collaboration, as well as the Centers for Disease Control and the World Health Organization. The choice of the GRADE approach was based on its increasingly ubiquitous use, practicality, and unique features. To our knowledge, the ILCOR evidence review process represents the largest application of the GRADE system in a healthcare-related review.

GRADE is a system to review evidence to determine the confidence in the estimate of effect of an intervention or the performance of a diagnostic test and to categorize the strength of a recommendation. GRADE requires explicit documentation of the evaluation of the evidence base specific to each outcome that was chosen and ranked as critical and important before the evidence review. The evidence is assessed by multiple criteria. Questions addressed in GRADE typically follow a PICO (population, intervention, comparator, outcome) structure for ease of mapping to available evidence (Figure 1).

Figure 1: Structure of questions for evidence evaluation

Confidence in the estimates of effect, synonymous with and reported more succinctly as quality, is reported by a synthesis of evidence informed by 1 or more studies as opposed to studies themselves. Quality is adjudicated by a 4-part ranking of our confidence in the estimate of effect (high, moderate, low, very low) informed by study methodology and the risk of bias. Studies start but do not necessarily end at high confidence for randomized controlled trials (RCTs), and they start but do not necessarily end at low confidence for observational studies. Studies may be downgraded for inconsistency, imprecision, indirectness, and publication bias and nonrandomized observational studies may be upgraded as the result of effect size, dose-response gradient, and plausible negative confounding; in other words, an underestimation of the association. The direction and strength of recommendations are driven by certainty of evidence effect estimates, values and preferences of patients, and, to some degree, clinicians' balance of positive and negative effects, costs and resources, equity, acceptability, and feasibility (Table 2).

Table 2: 2015 - From GRADE Evidence to Decision Factors for Making Strong Versus Weak Recommendations

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From GRADE Evidence to Decision Factors for Making Strong Versus Weak Recommendations

Factor	Relevant Question	Notes
Priority of problem	Is the problem addressed by the question important enough to make a recommendation?	Many problems may not be identified a priori as high enough importance to justify strong recommendations when weighed against other problems.
Balance of benefits and harms	Across outcomes, are the overall effects and confidence in those effects a net gain?	Most interventions, prognostications, and diagnostic tests have positive and negative consequences. Confidence in these estimates must be viewed in aggregate—do positive effects outweigh negative ones? Consideration must weigh outcomes by importance.
Certainty in the evidence	What is the overall certainty that these estimates will support a recommendation?	More certainty supports stronger recommendations, and vice versa.
Values and preferences	To what extent do the values and preferences of patients regarding outcomes or interventions vary?	Minimal variation and a strong endorsement of the outcomes or the interventions based on patients' values and preferences supports stronger recommendations. The lack of consistency in patients' values and preferences or a weak endorsement of the outcomes or the interventions supports weaker recommendations.
Costs and resources	Are these net results proportionate to the expenditures and demands of the recommended measure?	Factors such as manpower, time, distraction from other tasks, and monetary investment are viewed through local values. Lower costs of an intervention and greater cost-effectiveness support strong recommendations, and vice versa. Analysis should account for uncertainty in the calculated costs.
Equity	Are the net positive effects of the measure distributed justly?	Measures that improve disparities or benefit fairly may drive a stronger recommendation, and vice versa.
Acceptability	Across stakeholders, is the measure tractable?	To be strong, a recommendation ideally appeals to most.
Feasibility	Can the recommendation be implemented from a practical standpoint?	Something that is practical to achieve may support a strong recommendation, and vice versa.
Summary: To what extent do positive and negative consequences balance in the settings in question?		

Factor	Relevant Question	Notes
	outweighs positive <i>clearly</i> Negative outweighs positive <i>probably</i> Negative Negative and positive consequences balanced outweighs negative <i>probably</i> Positive outweighs negative <i>clearly</i> Positive	
	Strong recommendation against Weak recommendation against Weak recommendation for Strong recommendation for	
Considerations: Are there important subgroups that might be treated differently? Are there important concerns for implementation?		

2.2 The GRADE Development Tool

The GRADE Guideline Development Tool (www.guidelinedevelopment.org) provides a uniform interface in the form of standardized evidence profiles and sets forth a framework that enables the reviewer to synthesize the evidence and make a treatment recommendation.³

GRADE uniquely unlocks the often rigid linkage between one's confidence in the estimate of effect from the strength of a recommendation. Although the two are related, different factors (eg, costs, values, preferences) influence the strength of the recommendation independent of one's confidence in the estimate of effect. GRADE mandates explicit reasons for judgments in a transparent structure. The GRADE Guideline Development Tool³ requires consideration of all of these factors and documentation for each decision. To qualify recommendations, an evidence-to-recommendation framework is used to document all factors that shape the recommendation. Finally, with the GRADE Guideline Development Tool, summary of evidence and evidence profile tables are created. The tables summarize effect size, confidence in the estimates of effect (quality), and the judgments made to evaluate evidence at the level of outcomes. Quality is specified across each of multiple outcomes for the same population, intervention, and comparison, with judgments documented in explanatory notes.

2.3 Scientific Evidence and Evaluation Review System

In preparation for the 2015 systematic review process, ILCOR members, the AHA ECC staff, and compensated consultants collaborated to develop an online systematic review website. The Systematic Evidence Evaluation and Review System (SEERS) website was designed to support the management of workflow steps required to complete the ILCOR systematic reviews (in 2010, these were called worksheets) and capture the evidence extraction and evaluation data in reusable formats (Figure 2). The SEERS website facilitated the structured and consistent evidence review process, which enabled the task force members to finalize the CoSTR for each PICO question. Successful completion of the systematic review process ensured consistency in elements of the reviews from many different international reviewers.

Figure 2: ILCOR 2015 Consensus on Science work flow for all systematic reviews

2.4 Steps in the ILCOR 2015 Systematic Review Process

ILCOR created a comprehensive overview of the structured process that was used to support systematic reviews. The process was divided into 5 major categories, as outlined in Figure 2:

1. Question development: systematic review question development, using the PICO format (Figure 1)
2. Search strategy development
3. Evidence reviewer article selection
4. GRADE evidence review
5. Development of CoSTR.

2.4.1 ILCOR PICO Question Development

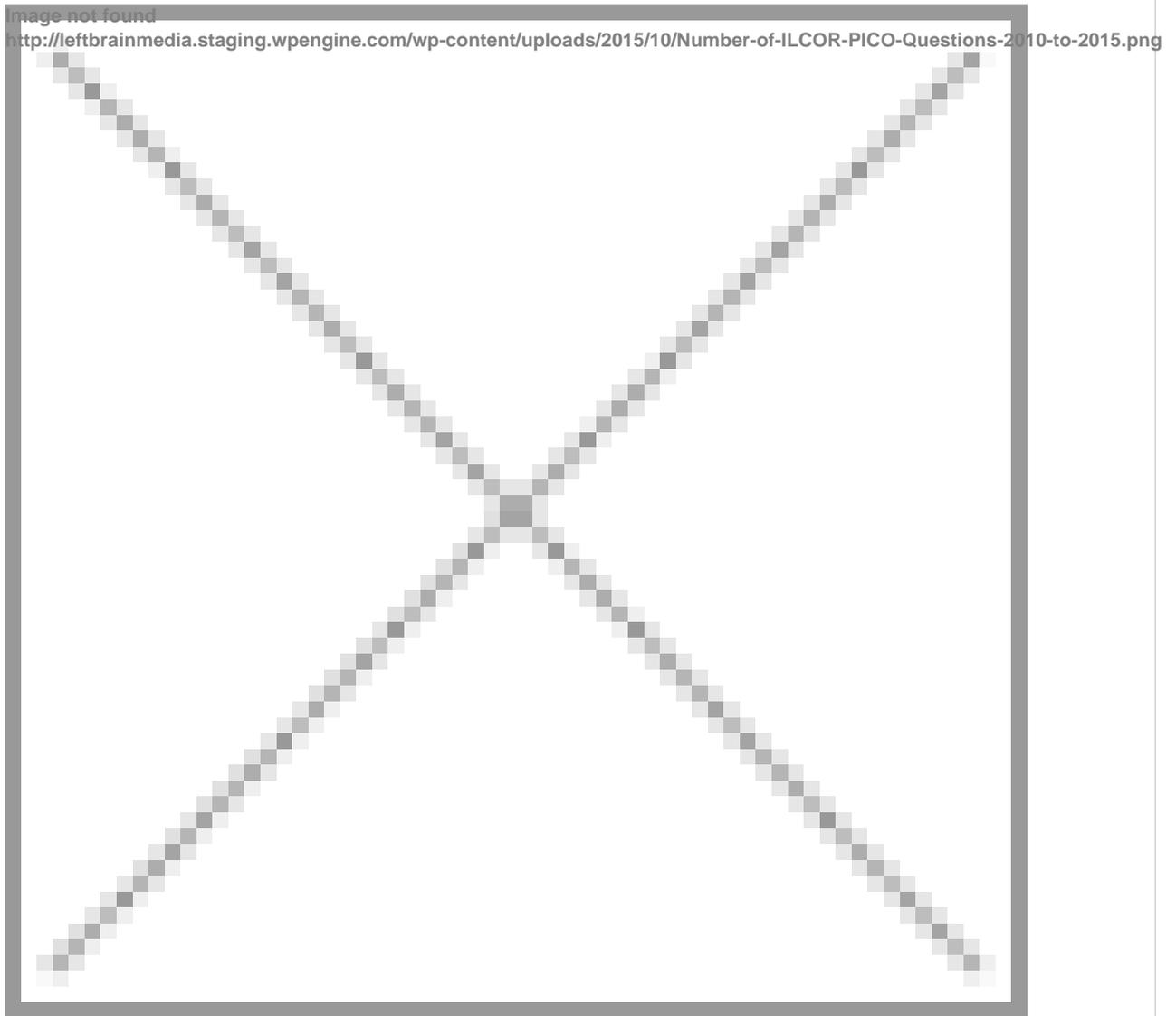
Shortly after the *2010 International Consensus on CPR and ECC Science With Treatment Recommendations* and the *2010 AHA Guidelines for CPR and ECC* were published, the 2015 ILCOR task forces reviewed the 274 PICO questions that were addressed in 2010 and generated a comprehensive list of 336 questions for potential systematic reviews in 2015. In addition, the new ILCOR task force, First Aid, developed 55 PICO questions that were initially prioritized for review. Questions were prioritized based on clinical controversy, emerging literature, and previously identified knowledge gaps. ILCOR task forces debated and eventually voted to select a focused group of questions. Of the 391 potential PICO questions generated by the task forces, a total of 165 (42%)

systematic reviews were completed for 2015 (Figure 3 and Figure 4). The number of PICO questions addressed by systematic reviews varied across task forces (Figure 4).

Consistent with adopting the GRADE guideline writing process, clinical outcomes for each PICO were selected and ranked on a 9-point scale as critical and important for decision making by each task force. The GRADE evidence tables were reported by outcome, based on the priority of the clinical outcome. After task force selection of PICO questions for review in 2015, individuals without any conflicts of interest (COIs) or relevant commercial relationships were identified and selected from task force members to serve as task force question owners. Task force question owners provided the oversight control to ensure progress and completion of each systematic review.

Figure 3: ILCOR process for prioritizing PICO questions for systematic reviews



Figure 4: Comparison of the number of systematic review questions (PICO questions)

2.4.2 ILCOR Search Strategy Development

Task force question owners worked in an iterative process with information specialists from St. Michael's Hospital Health Science Library in Toronto on contract as compensated consultants to the AHA. These information specialists created comprehensive literature search strategies. The information specialists collaborated with the task force question owners to create reproducible search strings that were customized for ease of use within the Cochrane Library (The Cochrane Collaboration, Oxford, England), PubMed (National Library of Medicine, Washington, DC), and Embase (Elsevier B.V., Amsterdam, Netherlands). Each search string was crafted with precision to meet the inclusion and exclusion criteria that were defined to balance the importance of sensitivity and specificity for a comprehensive literature search.

With commitment to a transparent systematic review process for 2015, ILCOR provided an opportunity for public comment on proposed literature search strategies. Members of the public were able to review search strategies and use the search strings to view the literature that would be captured. ILCOR received 18 public comments and suggestions based on the proposed search strategies and forwarded them to the task force chairs and task force question owners for consideration. This iterative process ensured that specific articles were captured during the evaluation process that may not have been initially retrieved by the search strategy.

2.4.3 ILCOR Evidence Reviewers' Article Selection

Upon completion of the public comment process, ILCOR invited topic experts from around the world to serve as evidence reviewers. Specialty organizations were also solicited to suggest potential evidence reviewers. The qualifications of each reviewer were assessed by the task force, and potential COIs were disclosed and

evaluated by the task force co-chairs and COI co-chairs. Evidence reviewers could not have any significant COI issues pertaining to their assigned topics. If a COI was identified, the topic was assigned to a different reviewer who was free from conflict.

Two evidence reviewers were invited to complete independent reviews of the literature for each PICO question. A total of 250 evidence reviewers from 39 countries completed 165 systematic reviews. The results of the search strategies were provided to the evidence reviewers. Each reviewer selected articles for inclusion, and the 2 reviewers came to agreement on articles to include before proceeding to the next step in the review process. If disagreement occurred in the selection process, the task force question owner served as a moderator to facilitate agreement between the reviewers. If necessary, the search strategy was modified and repeated based on feedback from the evidence reviewers. When final agreement was reached between the evidence reviewers on included studies, the systematic review process started.

2.4.4 ILCOR GRADE Evidence Review

The bias assessment process capitalized on existing frameworks for defining the risk of systematic error in research reporting through 3 distinct approaches. The Cochrane tool was used to evaluate risk of bias in randomized trials,^{4,5} whereas the QUADAS-2 instrument⁶ was used for included studies that supported diagnostic PICO questions. For non-RCTs that drew inferences on questions of therapy or prognosis, the GRADE working group risk-of-bias criteria⁷ were used as a series of 4 questions that emphasized sampling bias, the integrity of predictor and outcome measurements, loss to follow-up, and adjusting for confounding influences.^{7,8} Occasionally an existing systematic review would be uncovered that could formally address risk of bias as it pertained to a specific outcome. However, in most instances, the task forces used an empiric approach based on an amalgamation of risk from individual studies addressing a specific outcome. The 2 (or more) reviewers were encouraged to consolidate their judgments, with adjudication from the task force if needed. Agreed bias assessments were entered into a GRADE evidence profile table.

The GRADE Guideline Development Tool is a freely available online resource that includes the GRADE evidence profile table.⁹ GRADE Guideline Development Tool served as an invaluable aid to summarize important features, strengths, and limitations of the selected studies. To complete each cell of the evidence profile table, reviewers needed to apply judgments on the 5 dimensions of quality, including risk of bias, inconsistency, indirectness, imprecision, and other considerations (including publication bias). Quantitative data that described effect sizes and confidence intervals were also entered into the evidence profiles, although a more descriptive approach was used when pooling was deemed inappropriate. The GRADE Guideline Development Tool software calculated the quality of evidence for critical and important outcomes by row and, when therapy questions (the most common type) were addressed, generated impact estimates for groups at high, moderate, or low baseline risk as a function of the relative risk.

2.4.5 2015 ILCOR Development of Draft Consensus on Science With Treatment Recommendations

ILCOR developed a standardized template for drafting the consensus on science to capture a narrative of the evidence profile and reflect the outcome-centric approach emphasized by GRADE. The consensus on science reported (1) the importance of each outcome, (2) the quality of the evidence and (3) the confidence in estimate of effect of the treatment (or diagnostic accuracy) on each outcome, (4) the GRADE reasons for downgrading or upgrading the quality rating of the study, and (5) the effect size with confidence intervals or a description of effects when pooling was not done.

The ILCOR task forces created treatment recommendations when consensus could be reached. Within the GRADE format, 4 recommendations are possible: (1) strong recommendation in favor of a treatment or diagnostic test, (2) strong recommendation against a treatment or diagnostic test, (3) weak recommendation in favor of a treatment or diagnostic test, or (4) weak recommendation against a treatment or diagnostic test. A strong recommendation is indicated by the words “we recommend” and a weak recommendation is indicated by the words “we suggest.”

Within the GRADE Guideline Development Tool, an evidence-to-recommendation framework assisted reviewers in making explicit the values and preferences that drove their recommendations, especially when evidence was either uncertain or was a weaker determinant of the optimal course of action. In doing so, resource considerations were invoked rarely when an economic analysis was identified and reviewed as germane or when the balance of risks and harms were considered by the task force to be weighed clearly against potential benefits. When there was inadequate or conflicting evidence, the task force would indicate this insufficient

evidence with language such as, “The confidence in effect estimates is so low that the panel feels a recommendation to change current practice is too speculative.” If economic analyses were not available, or if the task forces thought that the appropriate recommendations could differ among the resuscitation councils based on training implications or structure or resources of out-of-hospital or in-hospital resuscitation systems, then the task forces occasionally made no recommendations, leaving that to the council guidelines.

The task force members reviewed, discussed and debated the evidence and developed wording on the summary consensus on science statements and on the treatment recommendations during in-person meetings and after the 2015 ILCOR International Consensus on CPR and ECC Science With Treatment Recommendations Conference, held in Dallas, Texas, in February 2015. In addition, the task forces met frequently by webinar to develop the draft documents that were submitted for peer review on June 1, 2015. As in 2005 and 2010, strict COI monitoring and management continued throughout the process of developing the consensus on science statements and the treatment recommendations, as described in [“Part 2: Evidence Evaluation and Management of Conflicts of Interest”](#) in the 2015 CoSTR.^{10,11}

2.5 Public Comment on the ILCOR Draft Consensus on Science With Treatment Recommendations

All draft recommendations were posted to allow approximately 6 weeks of public comment, including COI disclosure from those commenting. In addition, the ILCOR draft consensus on science statements and treatment recommendations developed during the January 2015 conference were posted the week after the conference, and 492 public comments were received through February 28, 2015, when the comment period closed. The CoSTR drafts were reposted to remain available through April 2015 to allow optimal stakeholder engagement and familiarity with the proposed recommendations.

3 Development of the 2015 Guidelines Update

The 2015 Guidelines Update serves as an update to the 2010 Guidelines. The 2015 Guidelines Update addresses the new recommendations that arose from the 2015 ILCOR evidence reviews of the treatment of cardiac arrest and advanced life support for newborns, infants, children, and adults.

3.1 Formation of the AHA Guidelines Writing Groups

The AHA exclusively sponsors the 2015 Guidelines Update and does not accept commercial support for the development or publication. The AHA ECC Committee proposed 14 Parts of the Guidelines, which differ slightly from the 2010 Parts (Table 3).

Table 3: 2015 - Contents of 2010 Guidelines Compared With 2015 Guidelines Update

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Contents of 2010 Guidelines Compared With 2015 Guidelines Update	
2010 Guidelines	2015 Guidelines Update
Executive Summary	Executive Summary
Evidence Evaluation and Management of Potential or Perceived Conflicts of Interest	Evidence Evaluation and Conflict of Interest
Ethics	Ethical Issues
CPR Overview	Systems of Care and Continuous Quality Improvement*†
Adult Basic Life Support	Adult Basic Life Support and Cardiopulmonary Resuscitation Quality*†

2010 Guidelines	2015 Guidelines Update
Electrical Therapies: Automated External Defibrillators, Defibrillation, Cardioversion and Pacing	Defibrillation content embedded in other Parts
CPR Techniques and Devices	Alternative Techniques and Ancillary Devices for Cardiopulmonary Resuscitation
Adult Advanced Cardiovascular Life Support	Adult Advanced Cardiovascular Life Support††
Post-Cardiac Arrest Care	Post-Cardiac Arrest Care
Acute Coronary Syndromes	Acute Coronary Syndromes
Adult Stroke	Relevant Stroke content embedded in other Parts
Cardiac Arrest in Special Situations	Special Circumstances of Resuscitation
Pediatric Basic Life Support	Pediatric Basic Life Support and Cardiopulmonary Resuscitation Quality†
Pediatric Advance Life Support	Pediatric Advanced Life Support††
Neonatal Resuscitation	Neonatal Resuscitation
Education, Implementation, and Teams	Education
First Aid	First Aid
Legend: CPR- Cardiopulmonary Resuscitation; AED - automated external defibrillator,*Includes prehospital stroke †Includes AED defibrillation ††Includes manual defibrillation	

In particular, content from 2010 Parts (electrical therapies, adult stroke) have been incorporated into other Parts, and a new Part that addresses systems of care and continuous quality improvement has been added. The committee nominated a slate of writing group chairs and writing group members for each Part. Writing group chairs were chosen based on their knowledge, expertise, and previous experience with the Guidelines development process. Writing group members were chosen for their knowledge and expertise relevant to their Part of the Guidelines. In addition, each writing group included at least 1 young investigator. The ECC Committee approved the composition of all writing groups before submitting them to the AHA Officers and Manuscript Oversight Committee for approval.

Part 15 of the Guidelines Update, "[First Aid](#)," is jointly sponsored by the AHA and the American Red Cross. The writing group chair was selected by the AHA and the American Red Cross, and writing group members were nominated by both the AHA and the American Red Cross and approved by the ECC Committee. The evidence review for this Part was conducted through the ILCOR GRADE evidence review process.

Before confirmation, all Guidelines writing group chairs and members were required to complete an AHA COI disclosure of all current healthcare-related relationships. The declarations were reviewed by AHA staff and the AHA officers. All writing group chairs and a minimum of 50% of the writing group members were required to be free of relevant COIs and relationships with industry. During the 2015 Guidelines development process, writing group members were requested to update their disclosure statements every 3 months.

3.2 Classification of AHA Guidelines Recommendations

In developing the 2015 Guidelines Update, the writing groups used the latest version of the AHA format for COR and LOE (Table 1). The COR indicates the strength that the writing group assigns the recommendation, based on the anticipated magnitude and certainty of benefit relative to risk. The LOE is assigned based on the type, quality, quantity, and consistency of scientific evidence supporting the effect of the intervention.

3.2.1 2015 AHA Classes of Recommendation

Both the 2010 Guidelines and the 2015 Guidelines Update used the AHA Classification system that includes 3 main classes of positive recommendations: Class I, Class IIa, and Class IIb (Figure 5).

Figure 5: Class of Recommendation comparison between 2010 Guidelines and 2015 Guidelines Update

A Class I recommendation is the strongest recommendation, indicating the writing group's judgment that the benefit of an intervention greatly outweighs its risk. Such recommendations are considered appropriate for the vast majority of clinicians to follow for the vast majority of patients, with infrequent exceptions based upon the judgment of practitioners in the context of the circumstances of individual cases; there is greater expectation of adherence to a Class I recommendation.

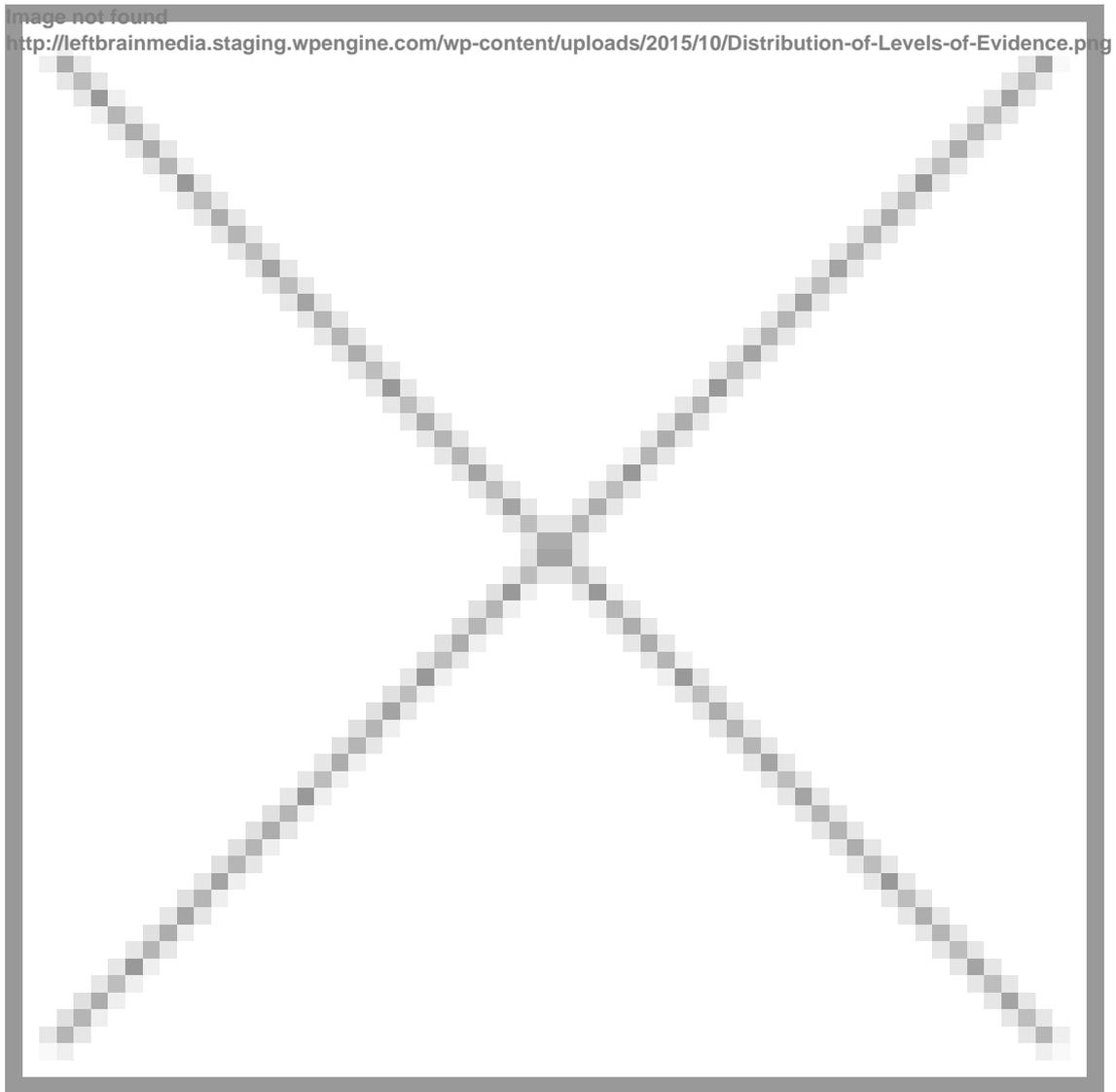
Class IIa recommendations are considered moderate in strength, indicating that an intervention is reasonable and generally useful. Most clinicians will follow these recommendations most of the time, although some notable exceptions exist. Class IIb recommendations are the weakest of the positive recommendations for interventions or diagnostic studies. Class IIb recommendations are identified by language (eg, "may/might be reasonable or may/might be considered") that indicates the intervention or diagnostic study is optional because its effect is unknown or unclear. Although the clinician may consider the treatment or diagnostic study with a Class IIb recommendation, it is also reasonable to consider other approaches.

The past AHA format for COR contained only 1 negative classification, a Class III recommendation. This classification indicated that the therapy or diagnostic test was not helpful, could be harmful, and should not be used. In the 2015 Guidelines Update, there are 2 types of Class III recommendations, to clearly distinguish treatments or tests that may cause harm from those that have been disproven. A Class III: Harm recommendation is a strong one, signifying that the risk of the intervention (potential harm) outweighs the benefit, and the intervention or test should not be used. The second type of Class III recommendation, the Class III: No Benefit, is a moderate recommendation, generally reserved for therapies or tests that have been shown in high-level studies (generally LOE A or B) to provide no benefit when tested against a placebo or control. This

recommendation signifies that there is equal likelihood of benefit and risk, and experts agree that the intervention or test should not be used.

3.2.2 2015 AHA Levels of Evidence

In the 2010 Guidelines, only 3 LOEs were used to indicate the quality of the data: LOEs A, B, and C. LOE A indicated evidence from multiple populations, specifically from multiple randomized clinical trials or meta-analyses. LOE B indicated that limited populations were evaluated, and evidence was derived from a single randomized trial or nonrandomized studies. LOE C indicated that either limited populations were studied or the evidence consisted of case series or expert consensus. In this 2015 Guidelines Update, there are now 2 types of LOE B evidence, LOE B-R and LOE B-NR: LOE B-R (randomized) indicates moderate-quality evidence from 1 or more RCTs or meta-analyses of moderate-quality RCTs; LOE B-NR (nonrandomized) indicates moderate-quality evidence from 1 or more well-designed and executed nonrandomized studies, or observational or registry studies, or meta-analyses of such studies. LOE C-LD (limited data) now is used to indicate randomized or nonrandomized observational or registry studies with limitations of design or execution or meta-analyses of such studies, or physiologic or mechanistic studies in humans. LOE C-EO (expert opinion), indicates that evidence is based on consensus of expert opinion when evidence is insufficient, vague, or conflicting. Animal studies are also listed as LOE C-EO (Figure 6).

Figure 6: Level of Evidence comparison between 2010 and 2015 AHA Guidelines Update

3.3 Development of AHA Classes of Recommendation and Levels of Evidence Informed by the 2015 ILCOR Evidence Review Using GRADE

The AHA COR and LOE framework (Table 1) differs from the framework used by GRADE. As a result, the leadership of the ECC Committee identified a group of experts in methodology to create tools for the 2015 Guidelines Update writing groups to use in developing recommendations informed by the ILCOR GRADE evidence review. Members of this writing group met by conference call weekly from October 27, 2014, to January 12, 2015, to validate the tools and ensure consistency in application. Frameworks for conversion were debated, settled by consensus, and then validated by applying them to specific ILCOR evidence reviews, again using a consensus process. Table 4 and Figure 7, Figure 8, and Figure 9 demonstrate the final tools that were used to guide the various guideline writing groups.

3.3.1 Identification of 2015 Guidelines Update Levels of Evidence, Informed by ILCOR Consensus on Science and GRADE Systematic Review

As the first step in the development of a guidelines recommendation, the writing group reviewed the studies cited in the GRADE evidence profile (Table 4) and assigned a Level of Evidence by using the AHA definitions for Levels of Evidence (Table 1). Evidence characterized as “high” by the GRADE process generally is consistent with an AHA LOE A. Evidence characterized as moderate in the GRADE process generally corresponds to an AHA LOE B-R for randomized or LOE B-NR for non-randomized, and evidence characterized by the GRADE process as low or very low generally meets the definitions of AHA LOE C-LD or LOE C-EO. Non-recommendations are not listed as a Level of Evidence. If the guidelines writing group determined that there was insufficient evidence, the writing group could make a recommendation noting that it was based on expert opinion

(LOE C-EO) or could make no recommendation at all. It is important to note that this framework is not absolute; the writing group's judgment may determine that the Level of Evidence is higher or lower than the ILCOR characterization of the evidence when a treatment or diagnostic test is applied to the population or under the conditions for which a Guidelines recommendation is made. In this circumstance, the writing group will explain the discrepancy between the GRADE analysis of evidence and the AHA LOE. This will help maintain transparency and make the process reproducible in the future (see Table 4).

Table 4: 2015 - Converting the GRADE Level of Evidence to the AHA ECC Level of Evidence

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Converting the GRADE Level of Evidence to the AHA ECC Level of Evidence	
GRADE Level of Evidence*	Starting Point for AHA ECC Level of Evidence (to be adjusted as determined by the Writing Group)
High GRADE LOE/confidence in the estimates of effect	Convert to AHA ECC LOE A for: High-quality evidence exists (well-designed, well- executed studies, each directly answers question, uses adequate randomization, blinding, allocation concealment, and is adequately powered, uses ITT analysis, with high follow-up rates). Evidence from >1 RCT, meta-analysis of high-quality RCTs, RCTs corroborated by high-quality registry studies.
Moderate GRADE LOE/confidence in the estimates of effect	Convert to AHA ECC LOE B-R for: Moderate-quality evidence from RCTs or meta- analysis of moderate quality RCTs.
Low GRADE LOE/confidence in the estimates of effect (low or very low confidence is caused by limitations in risk of bias for included studies, inconsistency, imprecision, indirectness, and publication bias)	Convert to AHA ECC LOE B-NR for: Moderate-quality evidence from well-designed and well-executed nonrandomized, observational, or registry studies or meta-analysis of same.
Very low GRADE LOE/confidence in the estimate of effect (low or very low confidence is caused by limitations in risk of bias for included studies, inconsistency, imprecision, indirectness, and publication bias)	Convert to AHA ECC LOE C-LD for: Randomized or nonrandomized observational or registry studies with limitations of design or execution (including but not limited to inadequate randomization, lack of blinding, inadequate power, outcomes of interest are not pre-specified, inadequate follow-up, or based on subgroup analysis) or meta-analyses with such limitations; or if physiologic or mechanistic studies in human subjects.
GRADE non-recommendation	Convert to AHA ECC LOE C- EO for: Consensus of expert opinion based on clinical experience.

Clarification: The American Heart Association (AHA) classification is applied to the body of evidence supporting an individual recommendation, based largely on design and quality of studies addressing the clinical question (see above). Although the International Liaison Committee on Resuscitation (ILCOR) Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendation attempts to consider factors such as resource allocation, the individual councils (eg, the AHA) are best able to identify the patients or subsets of patients, outcomes, and conditions that are most important to consider in the translation of science to guidelines. **Disclaimer:** The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed. **Legend:** * The GRADE process labels a body of evidence across outcomes based on the lowest Level of Evidence (LOE) for the most critical outcome. ECC indicates Emergency Cardiovascular Care; ITT, intention-to-treat; and RCT, randomized controlled trial.

3.3.2 Identification of 2015 Guidelines Class of Recommendation, Informed by ILCOR Consensus

Treatment Recommendation Based on GRADE

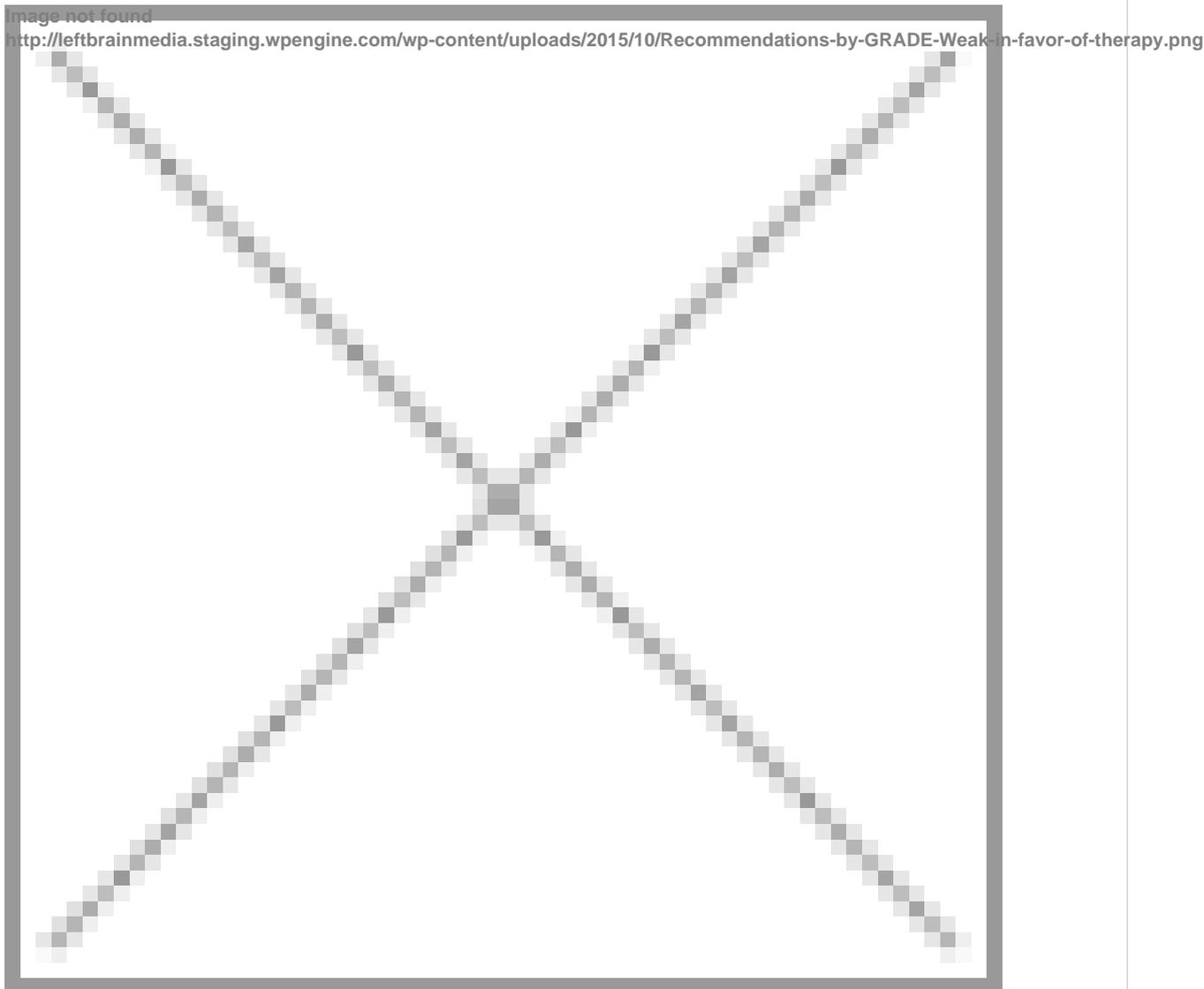
The second step in making a 2015 Guidelines Update recommendation is to determine the strength of the recommendation. In many cases, after an extensive evidence review such as that completed by ILCOR, the strength and direction of the ILCOR treatment recommendation will be similar to the strength and direction of the recommendation in the 2015 Guidelines Update. However, in its Clinical Practice Guidelines Methodology Summit Report, the AHA task force on practice guidelines¹² notes that the strength of recommendation and strength of evidence are each hierarchical but separate. The classification table itself notes “COR and LOE are determined independently, ie, any Class of Recommendation may be paired with any Level of Evidence” (Table 1).

The writing groups for the 2015 Guidelines Update were charged to carefully consider the 2015 ILCOR evidence review and the ILCOR consensus treatment recommendations in light of local training systems and the structure and resources of out-of-hospital and in-hospital resuscitation systems. In addition, the writing groups weighed the balance between benefits and risks and the quality of studies providing the evidence. The writing group considered the precision, qualifications, conditions, setting, outcomes, and limitations of the evidence reviewed when making a final assessment. Generally, when strong ILCOR recommendations were in favor of a treatment or diagnostic test, the AHA Guidelines writing groups also provided Class I or IIa recommendations (Figure 7). When weak ILCOR recommendations were in favor of a treatment or diagnostic test, the AHA Guidelines writing groups typically provided a Class IIa, IIb, or a Class III: No Benefit recommendation (Figure 8). If the AHA Guidelines writing group reached a decision that significantly differed in either strength (eg, a strong GRADE recommendation conversion to an AHA Class IIb recommendation) or direction of a recommendation, from that reported by the ILCOR evidence review, the writing group typically included a brief explanation of the rationale for the difference.

Figure 7: Developing AHA ECC recommendation informed by GRADE strong recommendation in favor of therapy or diagnostic or prognostic test



Figure 8: Developing AHA ECC recommendation informed by GRADE weak recommendation in favor of therapy or diagnostic or prognostic test

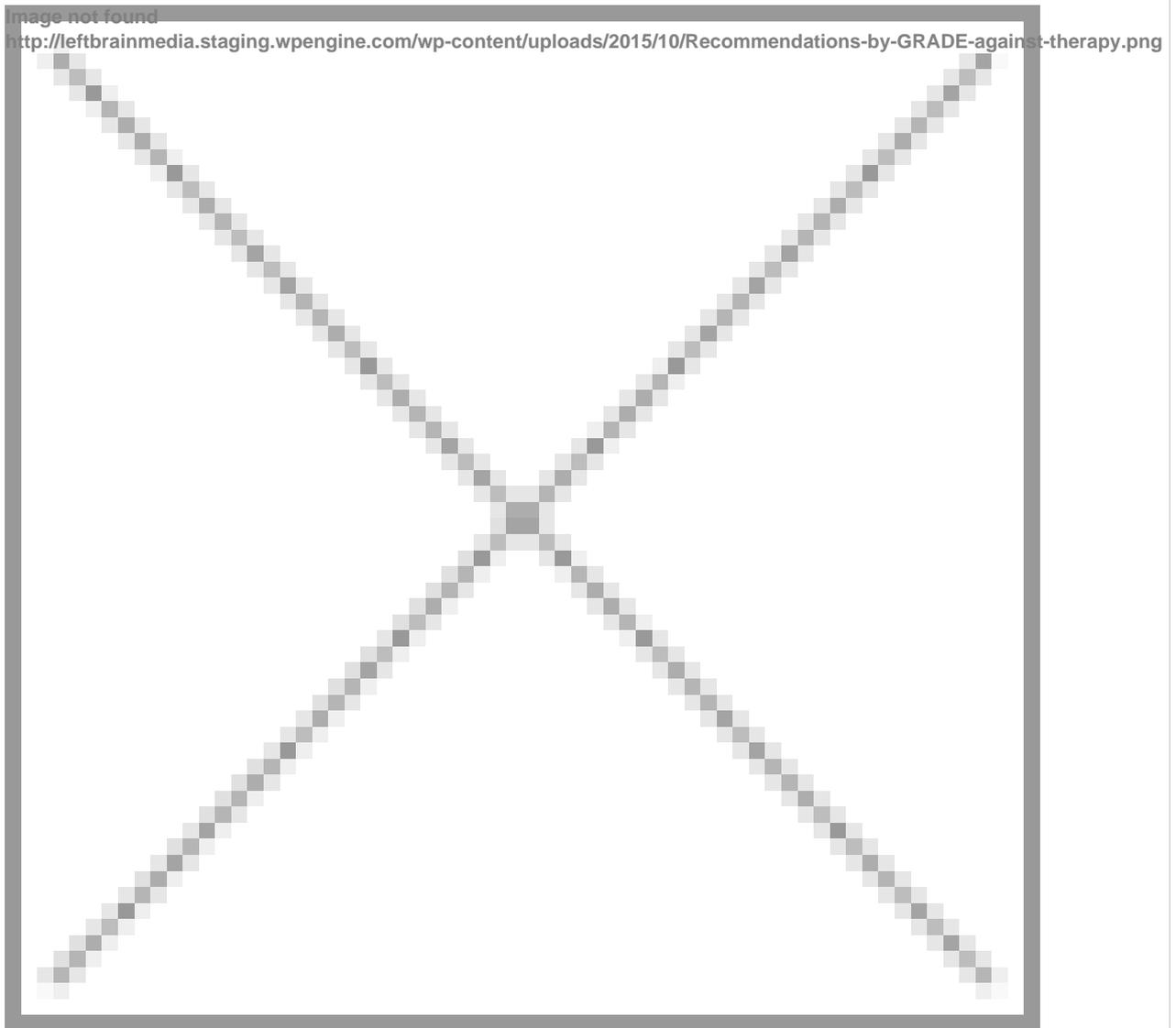


Ideally, strong recommendations from a scientific organization are supported by a high LOE. However, there are few prospective RCTs and blinded clinical trials conducted in resuscitation. As a result, it may be necessary for authors of this 2015 Guidelines Update to make recommendations to improve survival, even in the absence of such high-quality evidence. Such was the case in 2005, when the AHA and many other resuscitation councils changed the treatment of pulseless arrest associated with a shockable rhythm (ie, ventricular fibrillation [VF] or pulseless ventricular tachycardia [pVT]) from a recommendation of 3 stacked shocks to recommending delivery of single shocks followed by immediate CPR. Although there were no studies documenting improved survival from VF/pVT cardiac arrest with this approach, single shocks delivered by biphasic defibrillators had a much higher first-shock success than monophasic defibrillators, and experts felt strongly that reducing interruptions in compressions would improve survival. This change in 2005, coupled with emphasis to minimize interruptions in chest compressions, was associated with significant increases in survival from prehospital cardiac arrest associated with VF or pVT.^{13,14}

It is important to note that the AHA CORs are generally positive, whereas the ILCOR recommendations based on the GRADE process may recommend for or against an intervention or diagnostic study. This will inevitably create some inconsistency between ILCOR recommendations and AHA Guidelines recommendations. For treatments and diagnostic tests that ILCOR provided a weak recommendation against, the AHA Guidelines writing groups might reach a decision to recommend for or against a therapy with a Class IIb (weak, permissive) recommendation for the therapy under particular circumstances or a Class III: No Benefit or Class III: Harm recommendation. When ILCOR provided no recommendation, the AHA Guidelines writing group often reached a decision to provide a Class IIb or a Class III: No Benefit recommendation (Figure 9). As noted previously, if the

AHA Guidelines writing group reached a decision that significantly differed in either strength (eg, a weak GRADE recommendation but a strong AHA COR) or direction of a recommendation from that reported by the ILCOR evidence review, the writing group typically included a brief explanation of the rationale for the difference. The writing group chair of any of the AHA Guidelines was free to direct questions to the ILCOR task force writing group co-chairs to clarify the evidence or even to suggest wording or qualification of a recommendation.

Figure 9: Developing AHA ECC recommendation informed by GRADE strong or weak recommendation against therapy or diagnostic or prognostic test



3.4 Writing Group Voting Procedures

During the writing of the 2015 Guidelines Update, writing group members were asked to express support for or disagreement with the wording of the recommendations, and the recommendations were reworded until consensus was reached. During every discussion, writing group members disclosed any COIs before they spoke on a topic. Writing group chairs were aware of the conflicts reported by the writing group members, and the chairs were charged with ensuring that such disclosure occurred consistently. The writing group also formally voted on every recommendation contained in the 2015 Guidelines Update, after review by the AHA Science Advisory Coordinating Committee. Writing group members recused themselves from voting on any recommendations that involve relevant relationships with industry or any other COI. A tracking sheet was developed and ballots maintained as part of the permanent files of the 2015 Guidelines Update.

4 Integrating Science Into Practice Guidelines

Implementation or knowledge translation is both a continuum and an iterative process, and it is integral to improving survival¹⁵ (Figure 10).

Figure 10: The Utstein Formula of Survival, emphasizing the 3 components essential to improve survival

In the first instance, systematic review and synthesis are required to define the current state of knowledge. Results must then be conveyed in a manner that is appropriate and understandable to knowledge users, such as the 2015 Guidelines Update. Despite various societies investing heavily in evidence synthesis and guideline renewal, downstream translation of evidence into practice is frequently deficient and/or delayed.^{16,17} The developing field of implementation science is the study of interventions aimed at addressing deficiencies in knowledge translation. The National Institutes of Health defines implementation science as “the study of methods to promote the integration of research findings and evidence into healthcare policy and practice. It seeks to understand the behavior of healthcare professionals and other stakeholders as a key variable in the sustainable uptake, adoption, and implementation of evidence-based interventions.”¹⁸ Both knowledge translation and implementation science are critical to continual quality improvement. It is not sufficient to define best practices; evaluation of implementation and adherence are needed (implementation science), and where gaps in evidence uptake exist, tools and strategies to remedy the situation are required (knowledge translation). Ultimately, an iterative plan-do-study-act process can help move policy and clinical care toward best practices over time.¹⁹ More on continuous quality improvement and viewing resuscitation as a system of care can be found in [“Part 4: Systems of Care.”](#)

Performance metrics are a crucial component of the iterative implementation cycle. Many common assessments of healthcare professionals’ competence and performance have inherent strength and weaknesses.²⁰ Although challenging, the development and adoption of performance measures have been shown to improve processes of care linked to improvements in patient outcome.²¹ The value of standardized performance measures lies in the ability to reliably assess clinical care and identify gaps. Metrics allow for self-assessment, regional and national benchmarking, and evaluation of clinical interventions. The importance of standardized performance measures

has been recognized by The Joint Commission, Centers for Medicare and Medicaid Services, and the National Quality Forum,²² and the recently released Institute of Medicine Report on Cardiac Arrest.²³ The AHA Get With The Guidelines® initiative builds on this by providing additional financial, educational, and analytical resources to facilitate performance measure adoption, data collection, and assessments of quality.²¹ The AHA Get With The Guidelines program has led to improvements in the care of patients with cardiovascular disease that are significant and beyond what would typically be expected over time.²¹ Additionally, the Get With The Guidelines program has been integral in identifying and reducing or eliminating disparities in care based on race and sex.²¹ The success of in-hospital performance measures and the investment in prehospital clinical trials in cardiac arrest have led to the creation and adoption of national performance measures for care provided in the prehospital environment.²⁴ The Resuscitation Outcomes Consortium's focus on quality of CPR metrics as a requirement of the RCTs has led to a steady increase in survival across all participating sites.¹⁴

A variety of tools and strategies can be used to promote evidence uptake and guideline adherence. Protocol driven care bundles²⁵ and checklists²⁶ have been shown to reduce the incidence of serious complications^{25,26} and mortality.²⁶ Simple interventions, such as institutional-specific protocols and order sets, are effective at improving guideline compliance.²⁷ Smart technology, such as real-time CPR feedback devices, provides data on factors such as chest compression rate, depth, and fraction, prompting provider self-correction and improved performance²⁸ and improved survival.²⁹ Selection of knowledge translation tools and strategies for a given situation or setting should be informed by the best available evidence.

5 The Future of ECC Guidelines

In previous cycles, we conducted comprehensive literature reviews and systematic reviews in a batch-and-queue manner to update consensus on science with treatment recommendations every 5 years. The new recommendations then informed revision of training materials every 5 years. This model may not be optimal for responding to emerging peer-reviewed data and might delay implementation of new or emerging research findings. This 2015 cycle marks the transition from batch-and-queue to a continuous evidence-review process. A critical feature of this continuous-review process will be the creation of a transparent and easily accessible, editable version of the most recent systematic reviews and treatment recommendations. This format of comprehensive systematic review with treatment recommendations will occur in an online, living website that will be updated as ILCOR completes evidence reviews.

At any time, the ILCOR task forces may identify clinical questions as high priority for review based on new clinical trials, perceived controversies in patient care, emerging differences in constituent council training materials or algorithms, new publications, Cochrane Reviews, or feedback from the public. On an ongoing basis, the task force will conduct systematic reviews and evidence evaluations for the questions designated as highest priority. Any change in treatment recommendations resulting from these reviews that is endorsed by the task force and the ILCOR Resuscitation Councils will be incorporated into existing resuscitation recommendations and posted to the ILCOR online comprehensive treatment recommendations (<http://www.ilcor.org/seers> to follow these developments). Any change in treatment recommendation may be immediately peer reviewed and published as an interim Scientific Statement in traditional journals if the task force thinks that enhanced dissemination is required. If the treatment recommendation is not changed or not of critical impact for immediate implementation for patient care, the new recommendation will be updated simply by indicating the date of the most recent systematic review posted to the website and periodically summarized on a routine basis.

The continuous review process should allow more rapid translation of prioritized new science to treatment recommendations and, ultimately, implementation. This process also should improve the workflow for the task forces by allowing concentrated effort on the highest-priority clinical questions rather than an every-5-year effort to review a large number of selected clinical questions.

6 Summary

The process used to generate the 2015 Guidelines Update has been remarkably different from prior releases of the Guidelines. The combination of (1) ILCOR process of selecting a reduced number of priority topics for review, (2) using the GRADE process of evaluation, and (3) merging the Grade recommendations with the current prescribed AHA classification system to assign LOE and COR is unique to the 2015 Guidelines Update. Thus, the 2015 Guidelines Update is leaner compared with the 2010 Guidelines publication because fewer topics were addressed by the 2015 ILCOR evidence review process than were reviewed in 2010. There were a total of 685 recommendations in the 2010 Guidelines, and there are a total of 315 recommendations in the 2015 Guidelines Update. The number of systematic reviews is lower in 2015; however, the quality of the reviews may

be higher and more consistent based on the involvement of information specialists, the rigorous oversight of the SEERS process, and the use of the GRADE process of review.

An examination of the data in Table 5 reveals a substantial gap in resuscitation science available to answer important resuscitation questions. Of all 315 recommendations made in the 2015 Guidelines Update, only 3 (1%) are based on Level A evidence, and only 78 (25%) are a Class I recommendation.

Table 5: Class of Recommendation and Levels of Evidence for the 2015 Guidelines Update: Demonstrating the Gap in Resuscitation Science

Open table in a [new window](#)

Class of Recommendation and Levels of Evidence for the 2015 Guidelines Update: Demonstrating the Gap in Resuscitation Science						
Class of Recommendation	LOE A	LOE B-R	LOE B-NR	LOE C-LD	LOE C-EO	Total
I	0	8	17	27	28	80
IIa	0	12	12	40	10	74
IIb	0	23	11	80	26	140
III: No Benefit	2	3	0	0	0	5
III: Harm	0	1	4	3	7	15
Total	2	47	44	150	71	314

Legend: LOE, Level of Evidence; NR, non-randomized; R, randomized;

Most of the guidelines are based on Level C evidence (218/315, 69%) or Class II recommendations (217/315, 69%) (Table 5). When comparing levels of recommendations, there is a modest increase from 23.6% of Class I recommendations in 2010 to 25% in 2015 without much change in Class II recommendations, at 67% in 2010 and 68% in 2015 (Figure 5). There was a decrease in recommendations classified as Level B evidence from 37% in 2010 to 30% (LOE B-R and LOE B-NR) in 2015 (Figure 6). However, in contrast, **there was an increase in recommendations based on Level C evidence from 54% in 2010 to 69% in 2015**. These observations must be tempered with the fact that the PICO questions were selected by the task force in 2015 based on their critical or controversial nature or new science and, as such, their inclusion reflects a selection bias in the sample, whereas PICO questions in 2010 represented the true scope of work as determined by the task force. Nonetheless, even without comparative statistics, these data suggest a persistent huge knowledge gap for resuscitation science that has not been sufficiently addressed in the past 5 years. This gap in resuscitation science needs to be addressed through targeted future research funding. It is anticipated that new science will quickly be translated into Guideline Updates as a result of the continuous review process ILCOR will employ.

7 Authorship and Disclosures

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Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honorary	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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13. Michael Shuster	Mineral Springs Hospital Emergency Medicine	None	None	None	None	None	AHA Paid Consultant †	AHA Consultant

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group 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.

7.2 Acknowledgements

The authors on this writing group wish to acknowledge the 313 evidence reviewers contributing to the 2010 Guidelines and the additional 250 evidence reviewers contributing to the 2015 Guidelines Update, through the completion of the systematic reviews. In addition, the quality of this work is a reflection of the oversight of the GRADE expert, Dr. Eddy Lang, and the Evidence Evaluation expert, Dr. Peter T. Morley, with advice from a representative subgroup of ILCOR (the Methods Committee, under the leadership of Professor Ian G. Jacobs) as well as the countless hours of mentorship and oversight provided by the task force chairs and task force members.

8 Footnotes

The American Heart Association requests that this document be cited as follows:

American Heart Association. Web-based Integrated Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care – [Part 2: Evidence Evaluation and Management of Conflicts of Interest](#). ECCguidelines.heart.org.

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