

## Scientific Knowledge Gaps and Clinical Research Priorities for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Identified During the 2005 International Consensus Conference on ECC and CPR Science With Treatment Recommendations

**A Consensus Statement From the International Liaison Committee on Resuscitation (American Heart Association, Australian Resuscitation Council, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, and the New Zealand Resuscitation Council); the American Heart Association Emergency Cardiovascular Care Committee; the Stroke Council; and the Cardiovascular Nursing Council**

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New guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) were published in November 2005.<sup>1,2</sup> Publication followed a systematic evaluation of scientific evidence that culminated in the 2005 International Consensus Conference on ECC and CPR Science With Treatment Recommendations hosted by the American Heart Association (AHA) in January 2005.<sup>3,4</sup> The new treatment recommendations from this meeting incorporated scientific advances made after publication of the 2000 guidelines and were published with the expectation that their worldwide implementation would help improve rates of survival from cardiac arrest and other life-threatening cardiopulmonary emergencies.

A new cycle of evidence evaluation has begun and is expected to be completed in 2010 with the publication of new and revised treatment recommendations. These recommendations will once again reflect the scientific knowledge gained during the intervening period. As the cycle begins, a unique opportunity exists to identify areas in greatest need of clinical research, with the expectation that key questions asked today may be answered in time for the 2010 guidelines. To this end, valuable information was obtained during the evidence evaluation process that led to the 2005 guidelines. Experts appointed to review specific resuscitation topics were asked not only to summarize the existing science but also to identify knowledge gaps. As a result, experts identified knowledge gaps in 276 preassigned topics. We have compiled and organized these knowledge gaps and, through a process of consultation and consensus, identified areas of priority for clinical research.

## Methods

Member organizations of the International Liaison Committee on Resuscitation (ILCOR), which includes the AHA, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, the Resuscitation Council of Southern Africa, the Australia and New Zealand Committee on Resuscitation, and the InterAmerican Heart Foundation, planned the process of evidence evaluation for the January 2005 evidence-based consensus conference on CPR and ECC.<sup>3</sup> ILCOR representatives established task forces on basic life support, advanced life support, neonatal resuscitation, pediatric resuscitation, interdisciplinary topics, and acute coronary syndromes. The AHA established 2 additional task forces on stroke and first aid. Each task force identified topics that required evidence evaluation and appointed international experts to review these topics with strict attention to conflicts of interest and transparency of process.<sup>5,6</sup> Each topic was assigned to a minimum of 2 reviewers who represented 2 different ILCOR member organizations, and most assigned reviews were completed. The result was that a total of 281 experts prepared 403 worksheets on 276 topics. Each reviewer was instructed to search a minimum of 5 databases (Medline, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, EMBASE, and AHA/EndNote [a library of references compiled by the AHA using EndNote that includes all citations used in previous resuscitation publications]) and to use a standardized evaluation form to rate the level and quality of evidence.<sup>7</sup> The original

worksheets are available on the Internet at <http://www.c2005.org> under "View the Evidence Evaluation Worksheet Data Supplement." Reviewers were also instructed to identify knowledge gaps within their assigned topics, which resulted in 1 or more gaps being identified in 199 of the 276 topics. These knowledge gaps were used to develop the present consensus statement.

The knowledge gaps were collated to minimize duplication, classified by specific task force topics, and submitted to the corresponding task force chairs for further review, editing, and identification of the 10 to 15 most important research priorities within each topic. The comprehensive lists of knowledge gaps with their corresponding research priorities have been posted in the online-only Data Supplement at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.186228/DC1> in the form of Appendixes 1 through 8. These research priorities were then organized into 4 categories: (1) resuscitation, (2) acute coronary syndromes, (3) stroke, and (4) first aid. Additional input was sought from resuscitation experts, and the revised lists were returned to the task force chairs for final update, revision, and approval.

## Results

### Research Priorities in Resuscitation of Adults, Children, and Neonates

The research priorities for adults, children, and neonates (Table 1) were combined because of substantial overlap among these age groups. The overlap was most evident in topics related to adult and pediatric resuscitation. Age-related differences and unique research priorities in the neonatal group were noted under each research priority. The original lists of knowledge gaps and priorities for each age group—as indicated in Methods—can be found in the online-only Data Supplement. The research priorities were grouped into broad categories, which, wherever possible, paralleled the sequence of interventions during a resuscitation episode. The categories included "medical emergency teams"; "recognition of cardiac arrest and its causes"; "body position"; "electrical defibrillation"; "blood flow generation"; "airway management"; "ventilation"; "oxygenation"; "pharmacological interventions"; "metabolic, temperature, and postresuscitation management"; "physiological monitoring and feedback"; "ethical issues"; "education and training"; and "outcomes."

"Medical Emergency Teams" acknowledged the need to assess the potential impact of these teams on in-hospital cardiac arrest through early recognition of physiological deterioration and timely intervention. "Recognition of Cardiac Arrest and Its Causes" highlighted the need to develop better methods to recognize cardiac arrest and establish its origin and mechanism in order to tailor resuscitation efforts. "Body Position" focused on the relationship between positioning and airway management (especially in victims with a suspected cervical spine injury) and on development of alternative positions for performance of CPR.

"Electrical Defibrillation" identified the need to establish the optimal energy and sequence of electrical shocks, duration of chest compressions before and between electrical shocks, impact of real-time ventricular fibrillation waveform

**Table 1. Research Priorities in Resuscitation of Adults, Children, and Neonates**

## Medical Emergency Teams

- **Do medical emergency teams (also known as rapid response teams in the United States) reduce the incidence of in-hospital adult and pediatric cardiac arrest and improve outcomes?** Evaluate optimal personnel composition and proper triggers for team activation/consultation (eg, early warning scoring systems). For pediatric resuscitation, compare informal versus formal medical emergency teams and determine the effectiveness of scoring systems for proper team response.

## Recognition of Cardiac Arrest and Its Causes

- **Do techniques for establishing the presence, cause, and mechanisms of arrest (eg, cardiac versus asphyxial arrest) help tailor the resuscitation effort and improve outcome?** Determine reliable methods of establishing the presence of cardiac arrest and the need for resuscitation (eg, failure to respond to rescuers, presence/absence of signs of breathing). Consider methods to differentiate gasping (agonal breathing) from normal breathing and methods or devices to detect the presence (or absence) of cardiac activity. Identify effects of position (eg, face down) and presence of neck injury.

## Body Position

- **What are optimal body positions during and after resuscitation?** Investigate methods to secure airway patency and avoid spinal cord injury. Define alternative positions for resuscitation on the basis of the victim's age, rescuer's skills, cause of arrest (eg, trauma, drowning, intoxication, arrhythmia, or asphyxia), and recovery.

## Electrical Defibrillation

- **Do specific strategies for delivery of electrical shocks influence outcome?** Determine optimal energy level of initial shock (eg, 120, 150, 200, or 360 J) and of subsequent shocks (eg, fixed versus escalating). Determine optimal duration of CPR between defibrillation attempts. Determine optimal electrode position.
- **Does a period of chest compression before delivery of electrical shocks improve outcome?** Evaluate effects of duration of untreated cardiac arrest, witness status, bystander CPR, duration and quality of CPR, whether arrest occurs in the hospital or out of the hospital, and use of manual or automated defibrillation on patient outcome. Determine whether real-time VF waveform analysis may help identify optimal timing for delivery of electrical shocks.
- **What are the effects of electrical shocks on short- and long-term myocardial function?** Are electrical shocks detrimental to the ischemic heart? Assess these effects, particularly in the pediatric population.
- **What are the safety and efficacy of home defibrillation, public access defibrillation, and defibrillation by first responders?** Determine optimal AED algorithm (eg, single versus stacked shocks) and energy level of initial and subsequent shocks. Assess impact of added AED capability for monitoring and guiding the resuscitation effort.

## Blood Flow Generation

- **What are the safety and efficacy of compression-only CPR?** Identify settings that may benefit from compression-only CPR; consider the cause of cardiac arrest, airway patency, gas exchange coincident with chest compression, and presence of agonal breathing. Define duration for safe suspension of ventilation.
- **What are optimal compression depth, compression rate, duty cycle, and hand position during manual CPR?** Determine optimal compression timing, compression depth, compression rate, and duty cycle in relationship to hand position by measuring blood flow generation and outcomes after manual CPR. Consider factors such as age, gender, and body type of victims and rescuers, as well as ability to teach, learn, and retain skills.
- **What are the safety and efficacy of alternative closed-chest manual CPR techniques?** Investigate whether techniques such as high-frequency CPR, active compression-decompression CPR, phased thoracic-abdominal compression-decompression CPR, and interposed abdominal compression CPR improve resuscitation outcomes compared with standard manual CPR. Identify optimal compression rate, depth, duty cycle, time interval between components, and influence of mechanism of arrest (eg, cardiac versus asphyxial arrest).
- **What are the safety and efficacy of automated mechanical CPR techniques?** Consider compression techniques based on piston devices and load-distributing bands. Define optimal compression rate, depth, duty cycle, and influence of mechanism of arrest (eg, cardiac versus asphyxial arrest).
- **Do airway impedance threshold devices improve outcome from cardiac arrest and other low-flow states?** Consider safety and efficacy in relation to various resuscitation techniques.
- **Do interruptions in chest compression prompted by other CPR interventions compromise outcome?** Determine strategies to successfully incorporate the various ACLS tasks, such as airway management, vascular access, drug administration, rhythm analysis, and defibrillation, into resuscitation while minimizing hands-off time during chest compressions.

## Airway Management

- **Do specific methods and adjuncts foster superior airway patency and ventilation?** Determine the effectiveness of methods for opening the airway, removing foreign bodies (eg, chest compression, finger sweep, abdominal thrust, chest thrust, and backslaps), and securing airway patency. Compare supraglottic airway devices with bag-mask devices or endotracheal intubation. For neonatal resuscitation, consider whether chest compression may interfere with effective ventilation, whether emergency medications and surfactant can be delivered and meconium suctioned, and whether placement of an LMA can be taught (eg, are airway management skills retained longer than endotracheal intubation skills?).
- **Can CO<sub>2</sub> detectors or other devices reliably confirm correct placement of endotracheal tubes and monitor stability during transport?** Consider various CO<sub>2</sub> analyzers and esophageal detection devices.

## Ventilation

- **What is the optimal compression-to-ventilation ratio during CPR?** Consider mechanisms of arrest (eg, cardiac versus asphyxial arrest) and age of the victim (eg, 30:2, 15:2, or 5:1 ratio for pediatric resuscitation). Determine indications for interrupting ventilation during CPR and duration of such interruptions.
- **What are the optimal tidal volumes and respiratory frequency?** Determine hemodynamic effects of changes in intrathoracic pressure in relation to tidal volume, frequency, and duration of each breath. Consider the effects of cardiac arrest origin (eg, cardiac versus asphyxial arrest), presence of airway disease (eg, asthma or emphysema), and age of the victim.
- **What is the optimal ventilatory strategy for neonatal resuscitation in the delivery room?** Consider airway pressures, inspiratory times, devices, timing, volumes in relation to gestational age (eg, term versus preterm neonates), mechanical versus manual, PEEP, and CPAP (eg, mask, nasal mask, nasal prongs, nasopharyngeal tube, or endotracheal tube).
- **Are there options for providing feedback to rescuers to ensure correct ventilation rates and tidal volumes?** Determine whether hyperventilation can be prevented during resuscitation.

**Table 1. Continued**

## Oxygenation

- **What are the safety and efficacy of supplementary oxygen provided during BLS?** For neonatal resuscitation, define optimal oxygen concentration during delivery room resuscitation (eg, room air versus oxygen-enriched air).

## Pharmacological Interventions

- **Are vasopressin, epinephrine, or a combination of the 2 safe and effective for shock-resistant VF, pulseless VT, pulseless electrical activity, or asystole?** Identify optimal doses and timing of drug delivery and effects on postresuscitation organ function (if vasopressors are indeed effective). Consider novel and more selective vasopressors (eg,  $\alpha$ -methylnorepinephrine) and pharmacological “cocktails” (eg, epinephrine and a  $\beta$ -adrenergic blocker).
- **Are antiarrhythmic drugs safe and effective for VF or pulseless VT?** Consider the effects of antiarrhythmic drugs on survival, including the safety and efficacy of the aqueous formulation of amiodarone.
- **Do  $\beta$ -adrenergic blocking agents improve survival from cardiac arrest?** Consider the effects of selectivity and duration of action.
- **Does administration of atropine during cardiac resuscitation improve outcome?** Consider dose-response effects on pulseless electrical activity and asystole.
- **Does administration of fibrinolytic agents and other agents that interfere with coagulation and blood clot formation during cardiac resuscitation improve outcome?** Consider origin of cardiac arrest (eg, pulmonary embolism, acute coronary syndrome).
- **Do agents that target pathways of ischemia and reperfusion injury improve survival from cardiac arrest?** Consider novel agents with preclinical supportive evidence, such as mitochondrial ATP-sensitive K<sup>+</sup> channel openers, opioid receptor agonists, Na<sup>+</sup>-H<sup>+</sup> exchanger inhibitors, and growth factors such as erythropoietin and others.
- **What are the safety and efficacy of alternative routes of drug delivery (eg, endotracheal, intraosseous) during cardiac resuscitation?** Consider agents, dosing, overall effects on resuscitation interventions (eg, delayed intravenous drug delivery), and potential adverse pulmonary and hemodynamic effects in relation to underlying lung disease and age.
- **Does timing of drug delivery influence outcome?** Determine whether early drug administration (ie, before a defibrillation attempt) improves outcomes compared with current strategy (ie, after failure of initial resuscitation attempts).

## Metabolic, Temperature, and Postresuscitation Management

- **What are the safety and efficacy of resuscitative and postresuscitative hypothermia?** Determine the influence of age (eg, neonate, child, and adult); optimal timing for initiation, duration, and discontinuation of hypothermia; and optimal target temperature. Consider mechanism of arrest (eg, cardiac versus asphyxial arrest).
- **What is the optimal blood glucose concentration during and after resuscitation?** Determine whether tight glucose control improves outcome. Determine the optimal range of blood glucose concentration, methods of insulin administration, doses, indications, and end points. In neonates, assess the impact of early diagnosis of hypoglycemia and define blood glucose concentrations that may increase risk of brain injury after resuscitation.
- **Do vasoactive and inotropic agents given during the postresuscitation phase for myocardial dysfunction and hemodynamic instability improve outcome?** Determine agents, doses, indications, and end points.
- **What is the optimal temperature management for neonatal resuscitation in the delivery room (especially for preterm infants)?** Consider the effects of barriers to reduce heat loss from the head. Assess the effects of transparent membranes on heat exchange (eg, characterize evaporative, radiant, convective, and conductive heat gain and loss) and immature skin. Investigate the effects of hypothermia on long-term outcome in infants with encephalopathy. Determine the optimal depth and duration of hypothermia and the most effective method for initiating, maintaining, and discontinuing hypothermia.

## Physiological Monitoring and Feedback

- **Do strategies for real-time physiological monitoring during CPR and the postresuscitation phase enable feedback for directive and/or corrective action, resulting in improved outcome?** Investigate the effect of continuous analysis of VF waveform, expired CO<sub>2</sub>, depth and rate of compression, ventilation rate, and other measurements during CPR. Identify specific phases of cardiac resuscitation (eg, electrical, hemodynamic, and metabolic) to target priority interventions. Consider the effects of real-time feedback for directive and/or corrective action to optimize postresuscitation heart and brain function.
- **What is the impact of new technology developed to detect and quantify shock states?**

## Ethical Issues

- **What are the effects of family member presence during cardiac resuscitation?** Consider parents and children in particular.
- **What is the optimal approach for delivery room ethics when addressing initiation and discontinuation of resuscitation?**
- **What is the impact of advance directives on resuscitation efforts?** Consider “ideal” forms and dissemination of information.

## Education and Training

- **What are the safety and efficacy of methods for self-instruction in CPR in the community?**
- **Does the training status of lay responders influence willingness to perform CPR?** Consider the effects of training content (eg, chest compression only versus chest compression and ventilation). Assess cost-effectiveness and impact on resuscitation outcomes.
- **What are the optimal methods for training in AED use?** Determine the minimum training required (if training is necessary) and investigate factors that impact skills retention.
- **What are the optimal methods for acquisition and retention of BLS/ACLS skills?** Assess the impact of traditional lectures/practice sessions, computer programs, self-instruction videos, audiovisual aids, etc. Consider the impact of student type (eg, layperson versus healthcare provider), retraining intervals, work-related refresher courses, ability of written test scores to reflect competency, and impact of training on resuscitation outcomes. Determine the influence of the instructor’s training and experience.
- **What are the risks of infection (or other adverse events) during CPR training?**

## Outcomes

- **What is the quality of life of cardiac arrest survivors?**
- **What are valid surrogate outcomes for survival and functional recovery that can be used in cardiac arrest studies to facilitate patient enrollment and follow-up?**
- **Which outcomes are appropriate for evaluation of specific interventions (eg, termination of VF for an antiarrhythmic or electrical therapy versus return of spontaneous circulation or neurologically intact survival)?**
- **What are therapeutic end points for shock resuscitation in children?**

VF indicates ventricular fibrillation; AED, automated external defibrillator; ACLS, advanced cardiovascular life support; LMA, laryngeal mask airway; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure; BLS, basic life support; and VT, ventricular tachycardia.



analysis, short- and long-term effects of electrical shocks on the myocardium (especially in children), and issues related to home and public-access defibrillation, as well as defibrillation by first responders. “Blood Flow Generation” highlighted the need to define settings in which compression-only CPR is more effective, to understand and optimize the various determinants of blood flow during manual and mechanical chest compression, to assess the impact of airway impedance threshold devices, and to develop strategies for minimizing interruptions during chest compressions while effectively integrating the various resuscitation interventions.

“Airway Management” focused on techniques to secure upper-airway patency, methods to provide ventilation (comparing bag-mask ventilation with ventilation through an advanced airway), techniques to confirm and monitor advanced airway placement, and issues of training in airway management. In the neonatal area, research priorities focused on assessing the effectiveness of various upper-airway interventions and ventilation, including techniques on meconium suctioning, administration of surfactant, and administration of drugs. “Ventilation” emphasized the need to define age-related compression-to-ventilation ratios and tidal volumes and to develop methods for providing real-time feedback that minimize adverse effects of ventilation on venous return. “Oxygenation” focused on defining oxygen needs during basic life support and delivery room resuscitation in neonates.

“Pharmacological Interventions” highlighted the need to assess the outcome effects of drugs for which proof of ultimate survival benefit is lacking, such as vasopressor agents, antiarrhythmic drugs, and atropine. Additional research priorities included assessment of  $\beta$ -adrenergic blockers, with consideration of selectivity and duration of action, fibrinolytic drugs and other agents that interfere with coagu-

lation and blood clot formation, novel vasopressor agents, and novel compounds targeting reperfusion injury, such as mitochondrial ATP-sensitive  $K^+$  channel openers, opioid receptor agonists,  $Na^+-H^+$  exchanger inhibitors, and erythropoietin. Research priorities were also identified in routes and timing of drug delivery. “Metabolic, Temperature, and Postresuscitation Management” acknowledged the need to evaluate the effectiveness and management of hypothermia during and after resuscitation. Other research priorities included blood glucose management and use of vasoactive and inotropic drugs during the postresuscitation phase. For neonatal resuscitation, research priorities also included the effects of barriers on heat exchange. “Physiological Monitoring and Feedback” focused on critical needs for real-time monitoring of physiological variables during and after cardiac resuscitation for directive and corrective action.

“Ethical Issues” included evaluating the effects of the presence of family members during a resuscitation attempt, initiation and discontinuation of life support, and the impact of advance directives. “Education and Training” identified the need to assess the impact of methods for CPR self-instruction, training status of lay responders, methods to promote acquisition and retention of resuscitation skills, and risks associated with training. Finally, “Outcomes” emphasized the need to develop methods to assess quality of life in survivors of cardiac arrest and to identify valid surrogate measurements of ultimate outcome. For children, identification of therapeutic end points for shock resuscitation was deemed a priority.

### Research Priorities in Acute Coronary Syndromes

Categories of research priorities in acute coronary syndromes (Table 2) included “Prehospital and Emergency Department

**Table 2. Research Priorities in Acute Coronary Syndromes**

#### Prehospital and Emergency Department Assessment

- **What are the safety and efficacy of 12-lead ECG acquisition and computerized interpretation used by BLS providers to identify patients with STEMI?**

#### Antiplatelet Agents

- **Does a higher loading dose of clopidogrel offer additional benefit?** Consider doses of 600 and 900 mg.
- **What is the time-dependent efficacy of glycoprotein IIb/IIIa receptor inhibitors administered in the prehospital setting?** Investigate safety of prehospital administration.

#### Heparin

- **What are the safety and efficacy of prehospital and emergency department administration of unfractionated or low-dose low-molecular-weight heparin in unstable angina and NSTEMI?**
- **What is the optimal dose of low-molecular-weight heparin for prehospital and in-hospital care of patients with STEMI, balancing safety and efficacy in all age groups?**

#### $\beta$ -Adrenergic Blockers

- **What are the safety and efficacy of prehospital and emergency department administration of  $\beta$ -blockers?**

#### Reperfusion Strategies

- **What are the safety and efficacy of PCI compared with fibrinolytic agents for patients with STEMI?** Consider early presenters (ie, within 3 hours from onset of symptoms) and cost-effectiveness.
- **What are the safety and efficacy of prehospital bypass to a facility with PCI capability?**
- **What are the safety and efficacy of community hospital fibrinolysis and transfer for PCI?**
- **What are the safety and efficacy of prehospital interventions (ie, 12-lead ECG and advance emergency department notification, fibrinolysis, or bypass to PCI site) on STEMI in rural and urban settings?** Consider cost-effectiveness.

BLS indicates basic life support; STEMI, ST-segment–elevation myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; and PCI, percutaneous coronary intervention.

**Table 3. Research Priorities in Stroke**

## Stroke Centers

- **What are the safety and efficacy of stroke centers?**
- **What are optimal criteria for transfer of hospitalized patients to a stroke center?** Consider timing of transfer.

## Pharmacological Interventions

- **What are the safety and efficacy of blood pressure management in ischemic stroke?**
- **What are the criteria for risk stratification of patients considered for intravenous r-tPA?** Assess age, timing, and blood pressure.
- **Are there options for extending the 3-hour window for intravenous r-tPA?** Consider novel methods for patient selection.
- **What are the safety and efficacy of intra-arterial fibrinolysis and mechanical clot extraction in acute ischemic stroke?**

## Metabolic Management

- **What are the safety and efficacy of blood glucose control?** Consider timing, trigger level for implementing glucose control, target level, and duration.
- **What are the safety and efficacy of supplementary oxygen provided in acute stroke?** Consider normobaric and hyperbaric oxygen therapy.

## Neuroprotective Therapies

- **What is the role of therapeutic hypothermia in acute stroke?** Consider timing, duration, degree, cooling method (eg, surface, endovascular, localized, or systemic), rate of rewarming, patient selection, and concomitant interventions (eg, recanalization, antiplatelet agents).
- **Can neuroprotective agents improve clinical outcome with and without concomitant recanalization strategies?** Consider novel agents with preclinical supportive evidence.

## Transient Ischemic Attack

- **What are the criteria for risk stratification and admission and discharge decisions?**

## Intracerebral Hemorrhage

- **What is the optimal method for managing intracerebral hemorrhage that occurs spontaneously or is associated with oral anticoagulation?** Consider optimal blood pressure management, metabolic management, and direct therapies for limiting hematoma and edema expansion.

r-tPA indicates recombinant tissue plasminogen activator.

Assessment,” “Antiplatelet Drugs,” “Heparin,” “ $\beta$ -Adrenergic Blockers,” and “Reperfusion Strategies.” “Pre-hospital and Emergency Department Assessment” focused on the use of the 12-lead ECG in patients with ST-segment-elevation myocardial infarction. “Antiplatelet Drugs” emphasized the need to determine the optimal dose of clopidogrel and the time dependency of prehospital administration of glycoprotein IIb/IIIa receptor inhibitors. “Heparin” focused on prehospital and emergency department formulation of the drug and dosing for ST-segment-elevation and non-ST-segment-elevation myocardial infarction. “ $\beta$ -Adrenergic Blockers” focused on prehospital use. “Reperfusion Strategies” included prehospital administration of fibrinolytic drugs and various strategies for triage of patients for percutaneous coronary intervention.

**Research Priorities in Stroke**

Categories of research priorities in stroke (Table 3) included “Stroke Centers,” “Pharmacological Interventions,” “Metabolic Management,” “Neuroprotective Therapies,” “Transient Ischemic Attack,” and “Intracerebral Hemorrhage.” “Stroke Centers” identified the need to assess the safety and efficacy of stroke centers and to determine appropriate triage protocols. “Pharmacological Interventions” highlighted blood pressure management, use of intravenous recombinant tissue plasminogen activator, and local procedures for clot extraction. “Metabolic Management” included the need to define optimal strategies for control of blood glucose and oxygen supplementation. “Neuroprotective Therapies” focused on hypothermia and pharmacological agents and their interaction with concomitant interventions. “Transient Ischemic Attack” identified the need for risk stratification and triage. “Intracerebral Hemorrhage” focused on

the management of spontaneous bleeding and bleeding associated with oral anticoagulation.

**Research Priorities in First Aid**

Categories of research priorities in first aid (Table 4) included “Bleeding,” “Joint Injury,” “Skin Burns,” “Bone Fracture,” “Spinal Injury,” “Local Cold Injury,” “Snake Bite,” “Oral Poisoning,” “Allergic Reaction,” and “Oxygenation.” “Bleeding” highlighted the need to evaluate the safety and efficacy of tourniquets and of novel technologies for control of bleeding. “Joint Injury” and “Skin Burns” highlighted various issues related to cold therapy. “Bone Fracture” identified the need to assess the impact of straightening fractures and stabilization of injured extremities. “Spinal Injury” identified issues related to recognition of spinal injury by first aid responders and immobilization techniques. “Local Cold Injury” focused on identifying optimal methods to rewarm body parts. “Snake Bite” emphasized the need for data regarding the safety and efficacy of compressive wrapping for elapid and nonelapid snake bites. “Oral Poisoning” focused on charcoal administration and its use by the public. “Allergic Reaction” identified issues of recognition and assisting victims with self-administration of epinephrine. “Oxygenation” related to the safety and efficacy of administration of oxygen to dyspneic victims.

**Discussion**

The clinical research priorities identified in the present statement are the result of a process of consensus and consultation among experts and reflect unresolved clinical problems related to resuscitation and emergency management of acute coronary syndromes, stroke, and first aid. New

**Table 4. Research Priorities in First Aid**

## Bleeding

- **What are the safety and efficacy of tourniquet use?** Assess lives saved versus limbs lost or left with ischemic contractures. Investigate optimal duration of tourniquet use, considering damage to underlying tissue. Develop criteria for safe release. Consider the type of tourniquet. Determine the urgency or inevitability of amputation after a tourniquet has been left in place for >6 hours. Consider special circumstances such as combat casualties.
- **What are the safety and efficacy of emerging technologies for control of bleeding?**

## Joint Injury

- **What are the safety and efficacy of cooling an injured joint in an extremity?** Consider mode, duration, and frequency of cold therapy. Assess the effects of subcutaneous fat on the efficacy of cold treatment and additive effects of a compression wrap with cold therapy.

## Skin Burns

- **What are the safety and efficacy of cooling thermal cutaneous burns?** Consider temperature (eg, room temperature versus cold water), risk of hypothermia, means (eg, gels versus water), and treatment after cooling (eg, dry versus wet dressings).

## Bone Fracture

- **What are the safety and efficacy of stabilizing an extremity with a suspected fracture?** Assess the effects of straightening angulated long bone fractures.

## Spinal Injury

- **What are the safety and efficacy of spinal stabilization of a victim with suspected spinal injury?** Consider the ability to assess risk of spinal injury and stabilize the victim with adjunct devices. Assess incidence.

## Local Cold Injury

- **What are the safety and efficacy of rewarming body parts for localized cold injury?** Consider methods for active rewarming.

## Snake Bite

- **What are the safety and efficacy of compressive wrapping for a bite by a coral snake (elapid)?** Consider applicability to nonelapid snake bites.

## Oral Poisoning

- **What are the safety and efficacy of charcoal administration?** Assess impact on clinical outcomes, considering subgroups at higher risk of harm. Assess use by the public.

## Allergic Reactions

- **What are the safety and efficacy of assisting victims with self-administration of epinephrine?** Consider the ability of lay rescuers to recognize severe allergic reactions.

## Oxygenation

- **What are the safety and efficacy of oxygen administration in a dyspneic patient?**

scientific information is needed regarding prevention, recognition, treatment, monitoring, outcomes evaluation, ethics, and education. These research priorities are being published to help guide decision making by scientists, researchers, institutional review boards, funding agencies, policymakers, and all those concerned with advancing resuscitation and emergency management of acute coronary syndromes, stroke, and first aid. New information arising from clinical research hopefully may lead to rapid improvement in clinical practice by incorporation of the new information into the 2010 evidence evaluation process, with subsequent formulation of treatment recommendations. These recommendations do not exclude the possibility that new areas of research may emerge in the interim and take priority over areas identified in the present document.

Studies that examine clinically important events with robust statistical methodology have the greatest potential to impact clinical practice. Hospital discharge with intact neurological function is considered the most meaningful clinical end point in relation to cardiac resuscitation. This end point may be strengthened by standardization of postresuscitation treatment and minimization of uncontrolled variables. If adequately powered and carefully executed, a study with this end point may provide a definitive answer to a specific

question and may therefore qualify for level 1 evidence in support of a Class I recommendation.<sup>7</sup> Although such studies are optimal, there are reasons beyond cost and feasibility for conducting smaller studies of alternative end points, such as return of spontaneous circulation and hospital admission rate. For example, new concepts may require initial testing in a small group of patients to address safety, refine protocols, and provide initial evidence of efficacy. Other studies may require focus on physiologically relevant measurements as proof of concept before controlled clinical trials can be conducted. Likewise, studies related to acute coronary syndromes, stroke, and first aid may have end points related to preservation of function and reduction of disability. Some of these research priorities will require initial laboratory/animal studies before clinical research is possible. Education studies are also critical for developing more effective methods of translating current and newly acquired knowledge into information that can be used by rescuers and the public.

The most useful clinical advances result from a continuous cycle of scientific discovery, acquisition of knowledge, translational research, and clinical trials followed by dissemination and implementation of new treatment recommendations. Funding is essential to advance this cycle. In the area of

resuscitation, past initiatives include the Post-Resuscitation and Initial Utility in Life Saving Efforts conference,<sup>8,9</sup> which was charged with developing strategies for future resuscitation research (<http://www.nhlbi.nih.gov/meetings/pulse/index.htm>). This initiative stimulated new grants for basic science research in resuscitation and for the development of new technology for monitoring and performing resuscitation. Another critical initiative was the establishment of the Resuscitation Outcomes Consortium, which currently encompasses 10 regional clinical centers (8 in the United States and 2 in Canada) and a data coordinating center that provides infrastructure for collaborative resuscitation trials (<https://roc.uwctc.org/tiki/tiki-index.php>). The AHA supports the National Registry of CardioPulmonary Resuscitation, which is a large, prospective cohort study of patients with in-hospital cardiac arrest (<http://www.nrcpr.org>). In the United Kingdom, the Resuscitation Council supports the National Audit of Pediatric Resuscitation, which is charged with collection of data on pediatric resuscitation from centers throughout the United Kingdom (<http://www.resus.org.uk/pages/naprupdt.htm>). Ongoing support as part of established extramural research programs originates from the National Heart, Lung, and Blood Institute and the AHA in the United States; the Institutes of Circulatory Respiratory Health of the Canadian Institutes of Health Research; the Heart and Stroke Foundation of Canada; the British Heart Foundation, the Resuscitation Council, and the Department of Health in the United Kingdom; the Deutsche Stiftung für Herzforschung in Germany; the National Heart Foundation of Australia; and the Laerdal Foundation in Norway.

Despite these important resuscitation-specific initiatives and ongoing nonspecific funding mechanisms, additional support is needed to reduce death due to sudden cardiac arrest. Ischemic heart disease is the leading cause of death in high-income as well as low- and middle-income countries,<sup>10</sup> and  $\approx 50\%$  of those deaths are attributed to sudden cardiac arrest.<sup>11</sup> It is estimated that every year,  $\approx 330\,000$  individuals in the United States<sup>12</sup> and 700 000 in Europe<sup>13</sup> have an episode of sudden cardiac arrest. Efforts to restore life require not only that cardiac activity be reestablished but that injury to vital organs be prevented, minimized, or reversed. Unfortunately, with current resuscitation methods, the rate of hospital discharge with capability for independent living is disappointingly low, ranging from  $<2\%$ <sup>14–17</sup> to between 2% and 10%<sup>18–20</sup> in many large urban areas, but rarely exceeding 15%.<sup>21,22</sup> Many conditions other than ischemic heart disease can precipitate cardiac arrest, including those related to respiratory conditions, especially in the pediatric population. Accordingly, there is an urgent need for a substantial increase

in research funding for resuscitation. Increased funding is also needed for research on the emergency management of acute coronary syndromes, stroke, and first aid.

In addition to funding limitations, research on resuscitation and other emergencies faces a critical challenge because it is usually impossible to obtain prospective consent before administration of an investigational intervention. In 1993, the US Food and Drug Administration (FDA) placed a moratorium on resuscitation research because of concern that existing regulations on informed consent were not being met,<sup>23</sup> bringing to a virtual halt all interventional resuscitation research in the United States. A series of subsequent initiatives involving discussions between the FDA and industry in 1993, a congressional hearing in May 1994, a coalition conference of academic, medical, and research organizations in October 1994, and an FDA-sponsored public forum in January 1995 concluded in October 1996 with the enactment of parallel regulations by the FDA and the US Department of Health and Human Services that provided an exception to the requirement for informed consent under certain emergency circumstances (21 CFR part 50.24).<sup>24,25</sup> These regulations provided a mechanism for conducting research on life-threatening conditions without prior consent through a process of community consultation and public notification (<http://www.fda.gov/oc/ohrt/irbs/except.html>). These regulations are still debated,<sup>26,27</sup> have not gained full acceptance in the community,<sup>28</sup> have imposed regulatory burdens for investigators and institutional review boards, and have limited the number of clinical trials on resuscitation.<sup>29,30</sup> In Europe, a directive known as the Clinical Trials Directive was introduced in April 2001 by the European Parliament and the Council of the European Union. This directive threatens to significantly restrict resuscitation research by requiring that informed consent be obtained before subjects can be recruited into clinical trials of medical products.<sup>31</sup> Investigators from several European countries are currently lobbying for amendments to the directive that could enable a waiver or deferral of consent so that unconscious patients can be enrolled in clinical trials without the delays inherent to obtaining consent.<sup>32</sup> However, important randomized studies have been completed recently under the guidance of these new regulations on both sides of the Atlantic.<sup>33–37</sup>

Initiatives and policies aimed at improving funding and developing regulations to enable research in resuscitation and other emergencies are predicted to have a major impact on developing more effective therapies, saving more lives, driving public health policies, and attracting new investigators to the field. We trust that the present international consensus statement will create incentive and facilitate efforts to expand research in resuscitation and other emergencies.



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## Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
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Ian Jacobs	University of Western Australia	None	None	None	None	None	None
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Graham Nichol	University of Washington	Coinvestigator, Resuscitation Outcomes Consortium Data Coordinating Center	Unrestricted grants from Cardiac Science; Medtronic ERS; Philips Heart; Zoll, Inc	Innercool, Inc; Radiant Medical, Inc	None	Northfield Laboratories, Inc	Medic One Foundation: member of board
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Arno Zaritsky	University of Florida College of Medicine	NIH R-21 grant on hypothermia in children, project completed	None	None	None	Vital Signs	None
David A. Zideman	Hammersmith Hospitals NHS Trust, London, UK	None	None	None	None	None	None

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VA indicates Veterans Administration; NHLBI, National Heart, Lung, and Blood Institute; BLS, basic life support; NIH, National Institutes of Health; UK, United Kingdom; and NHS, National Health Service (UK).

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**Scientific Knowledge Gaps and Clinical Research Priorities for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Identified During the 2005 International Consensus Conference on ECC and CPR Science With Treatment Recommendations: A Consensus Statement From the International Liaison Committee on Resuscitation (American Heart Association, Australian Resuscitation Council, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, and the New Zealand Resuscitation Council); the American Heart Association Emergency Cardiovascular Care Committee; the Stroke Council; and the Cardiovascular Nursing Council**

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