Published in final edited form as:
Acad Emerg Med. 2014 December ; 21(12): 1343–1349. doi:10.1111/acem.12541.

Sex- and Gender-specific Research Priorities in Cardiovascular Resuscitation: Proceedings from the 2014 *Academic Emergency Medicine* Consensus Conference Cardiovascular Resuscitation Research Workgroup

Jane G. Wigginton, MD,
Department of Surgery, Division of Emergency Medicine, University of Texas Southwestern Medical Center, Dallas, TX

Sarah M. Perman, MD, MSCE,
Department of Emergency Medicine, University of Colorado School of Medicine, Denver, CO

Gavin C. Barr, MD,
University of South Florida, Lehigh Valley Health Network, Allentown, PA

Alyson J. McGregor, MD, MA,
Department of Emergency Medicine at Warren Alpert Medical School of Brown University, Providence, RI

Andrew C. Miller, DO,
University of South Florida, Lehigh Valley Health Network, Allentown, PA

Anthony F. Napoli, MD,
Department of Emergency Medicine at Warren Alpert Medical School of Brown University, Providence, RI

Basmah Safdar, MD,
Department of Emergency Medicine, Yale University (BS), New Haven, CT

Kevin R. Weaver,
University of South Florida, Lehigh Valley Health Network, Allentown, PA

Steven Deutsch,
Irving Fire Department, Irving, TX

Tami Kayea, and
Dallas Fire-Rescue Department, Dallas, TX

Lance Becker, MD
Department of Emergency Medicine, University of Pennsylvania, Philadelphia, PA

Abstract

Address for correspondence and reprints: Jane G. Wigginton MD; jane.wigginton@utsouthwestern.edu.
The authors have no relevant financial information or potential conflicts to disclose.

Author Manuscript
Author Manuscript
Author Manuscript

Significant sex and gender differences in both physiology and psychology are readily acknowledged between men and women; however, data are lacking regarding differences in their responses to injury and treatment and in their ultimate recovery and survival. These variations remain particularly poorly defined within the field of cardiovascular resuscitation. A better understanding of the interaction between these important factors may soon allow us to dramatically improve outcomes in disease processes that currently carry a dismal prognosis, such as sudden cardiac arrest. As part of the 2014 *Academic Emergency Medicine* consensus conference "Gender-Specific Research in Emergency Medicine: Investigate, Understand, and Translate How Gender Affects Patient Outcomes," our group sought to identify key research questions and knowledge gaps pertaining to both sex and gender in cardiac resuscitation that could be answered in the near future to inform our understanding of these important issues. We combined a monthly teleconference meeting of interdisciplinary stakeholders from largely academic institutions with a focused interest in cardiovascular outcomes research, an extensive review of the existing literature, and an open breakout session discussion on the recommendations at the consensus conference to establish a prioritization of the knowledge gaps and relevant research questions in this area. We identified six priority research areas: 1) out-of-hospital cardiac arrest epidemiology and outcome, 2) customized resuscitation drugs, 3) treatment role for sex steroids, 4) targeted temperature management and hypothermia, 5) withdrawal of care after cardiac arrest, and 6) cardiopulmonary resuscitation training and implementation. We believe that exploring these key topics and identifying relevant questions may directly lead to improved understanding of sex- and gender-specific issues seen in cardiac resuscitation and ultimately improved patient outcomes.

The physiologic and psychological differences between men and women are well described, yet how these differences affect patients' responses to injury and resuscitation, and even their ultimate survival and neurologic status, remains poorly understood. While the effect of these important variations is currently elusive, significant observations are beginning to emerge in the field of resuscitation that may well help to harness these differences to optimize the way we treat patients in the very near future.

Sex-related differences between men and women may be thought of as differences driven by psychological or cultural factors and include the physiologic and biological differences between the sexes. Both are known to have significant influence on response to injury and therapy. By the culmination of the 2014 *Academic Emergency Medicine* consensus conference, we identified six key research areas in psychology and sociology of resuscitation, as well as sex-related differences in injury, response to therapy, and outcomes. These areas represent major gaps in our knowledge and are provocative and clinically important and deserve high priority with regard to gender- and sex-related differences in resuscitation.

METHODS

Consensus was reached on the priority questions using an iterative process through the four-part nominal group technique as described in the executive summary.[1] An iterative process was followed using monthly phone call discussions, preconference surveys, and open-ended feedback from the *Academic Emergency Medicine* peer reviewers. The details of the process followed by the cardiovascular work group have been described.[2] On May 13, 2014, a multidisciplinary group of participants and experts (emergency medicine, cardiology, nursing, research, federal and private funding agencies, patients, and prehospital providers) convened and voted on the final iteration of themes and questions in the area of cardiac resuscitation using Poll Everywhere. Descriptive statistics were calculated to tabulate the final list of questions presented below. Feedback from this session was incorporated into this final article.

CONSENSUS RESULTS

Six major themes related to cardiovascular resuscitation that had high levels of agreed-upon importance are described in the following six sections. Additional questions of interest from the conference discussion are presented in Table 1.

Recommendation 1: Cardiac Arrest Epidemiology and Outcomes

Studies indicate that patients' sex plays a role in both the presentation and the survival following out-of-hospital cardiac arrest (OHCA). Studies consistently show that men have a threefold higher incidence of OHCA than women across all age groups, and women have worse prehospital factors (older age, fewer witnessed arrests, bystander cardiopulmonary resuscitation [CPR], or shockable rhythms).[3] Data are controversial regarding survival depending on how it is defined; after adjusting for prehospital factors, more women are resuscitated to hospital admission,[4,5] but fewer survive to discharge. Survival for women is better in nonventricular arrhythmias compared to ventricular arrhythmias. A few studies evaluating the interaction of sex and age noted a survival advantage in younger women (younger than 55 years) of presumed premenopausal age, implicating endogenous sex steroids as potentially protective.[6,7] A similar survival benefit has been seen in women following inpatient cardiac arrests.[8]

The sex-specific variation in survival may possibly be attributed to the protective role of estrogen as an antiapoptotic, anti-inflammatory, and mitochondria-stabilizing agent that is thought to "switch off" the death cascade. In addition, higher estrogen levels in premenopausal women potentially lower their coronary artery disease risk. Women also have increased chest wall compliance, which may lead to improved circulation during CPR, and differences in pharmacobiology may make it easier to resuscitate them. Airaksinen et al.[9] proposed that women are protected by a more intense vagal activation after sudden coronary occlusion compared to men, leading to a protective antiarrhythmic effect. Finally, improved survival in women could be due to a differential mechanism of acute coronary syndrome compared to men. Women are more likely to have structurally normal hearts when presenting with acute ischemia. There are higher proportions of microvessel disease, plaque rupture, vasospasm, and slow coronary flow causing acute infarction in women, while men most often experience an anatomical obstruction of the coronary arteries. It is possible that these lesions most often seen in females offer some degree of protection against the development of arrhythmias following acute coronary events. This could also potentially explain the lower frequency of rhythms amenable to defibrillation or cardioversion seen in women than men.

Priority Question

1. Can OHCA survival be improved by resuscitating men and women differently due to their physiologic differences in coronary artery disease?

Recommendation 2: Resuscitation Drugs

Pharmacogenomics is the field of analyzing how genetic makeup (including sex and race) affects an individual's response to medications. This area emphasizes the importance of reviewing and studying sex-based differences in drug efficacy and toxicity profiles. Four major factors seem to contribute to sex-based differences in responses to drugs, including bioavailability, distribution, metabolism, and elimination. These differences may be the result of fat content and other variations in body composition, gastric emptying time, cytochrome P450 activity, and numerous other factors. Importantly, it has been found that if a man and a woman receive the same amount per kilogram of the same drug, a significantly different effect may be achieved (as well as duration of effect). For example, healthy young females receiving a single bolus of 75 or 100 mg of intravenous lidocaine have a 62% larger volume of distribution and 50% longer elimination half-life than their male counterparts.[10] Additionally, the effect of the drug may be different based on the route of administration. Finally, data are lacking regarding the male versus female physiologic responses to cardiac drugs during the low-flow state typical of cardiac arrest, as well as the response to these drugs during reperfusion.

Priority Questions

1. Could sex-specific resuscitation drugs, in which drugs and drug combinations are optimized for each sex's unique makeup, improve resuscitation outcomes?
2. Could dosing requirements of resuscitation drugs differ between the sexes?

Recommendation 3: Sex Steroids as Acute Resuscitation Drugs

Several studies have noted that women of childbearing age have both improved survival to hospital discharge and ultimate better neurologic outcomes following cardiac arrest, compared with older female counterparts and men, implicating endogenous sex steroids as having an effect on our ability to successfully resuscitate patients following cardiac arrest.[7,8,11] Despite this interesting and potentially clinically significant observation, there are few bench studies and no identified clinical trials evaluating the use of sex steroids as acute resuscitation drugs in those experiencing cardiac arrest.

Of the three major sex steroids (including estrogen, progesterone, and testosterone), possibly the most studied and best understood as a resuscitation drug is estrogen. For over 30 years, estrogen resuscitation has been evaluated in numerous injury models, including but not limited to stroke,[12] hemorrhagic shock,[13] sepsis,[14] and burns.[15] Pilot clinical trials of the feasibility and safety of an acute dose of estrogen in patients with hemorrhagic shock and severe traumatic brain injury have been recently completed, with results currently pending.

Through these studies, estrogen's effects on multiple protective mechanisms have been identified that could potentially lead to protection in patients experiencing cardiac arrest. These protective pathways may include decreased inflammation, lessened oxidant injury, and diminished apoptosis. Studies of estrogens in the field of cardiac arrest found estradiol to confer cardioprotection, improve coronary flow, and decrease arrhythmias following ischemic–reperfusion injury in isolated rat hearts[16] and to confer brain and kidney protection following in vivo cardiac arrest.[17–19]

Another sex steroid found to offer protection is progesterone. Progesterone has been studied in the laboratory for many years and has been found to have significant anti-inflammatory properties that decrease cerebral edema and prevent neuronal loss following injury. Clinical studies of the administration of progesterone as an acute resuscitation drug for traumatic brain injury[20] are ongoing.

The least studied of the three major sex steroids as a resuscitation drug, testosterone, has mixed findings in preclinical studies. Multiple studies have noted that testosterone may be harmful for the recently injured brain.[21–23] However, in the heart, testosterone treatment in a cardiac arrest model did improved coronary flow and decrease arrhythmias.[16]

While more data are needed regarding the clinical effects of exogenous sex steroids following cardiac arrest, scientists studying other injury mechanisms are enthusiastically exploring this nascent field of resuscitative endocrinology. Due to the many similarities between other injuries involving ischemia and reperfusion and cardiac arrest, it will be important in the future to expedite studies, both bench and pilot clinical trials, to further evaluate the effects of these exogenous sex steroids on both short-term and long-term survival.

Priority Question

1. Is there a role for sex steroid treatment as an acute resuscitation drug in patients of both sexes in cardiac arrest?

Recommendation 4: Targeted Temperature Management

Targeted temperature management (TTM) has been found neuroprotective in comatose patients who achieve return of spontaneous circulation (ROSC) after cardiac arrest.[24] These landmark trials represent a cohort of comatose survivors of cardiac arrest where women are less represented than men. In the HACA trial, 23% of patients in the hypothermia cohort were women,[25] while in the trial of Bray et al.[26] the hypothermia cohort was 42% female.[24] These two randomized controlled trials enrolled only patients with initial rhythms of ventricular fibrillation, which is less common in women compared to men (9% vs. 22%, respectively). In the TTM trial published in 2013 that included cardiac arrest patients with all initial rhythms, women were still significantly underrepresented in both arms of the trial, with only 17% of the cohort cooled to 33°C being female, versus 21% of the cohort cooled to 36°C.[6]

Similar to TTM clinical trials, there also appears to exist a sex disparity in the use of TTM clinically. There is a paucity of literature that specifically addresses the question of discrepancies in the application of TTM between men and women. One single-center study reported that only 21% of its TTM population was female.[27] In another study of in-hospital cardiac arrests, published from Get-with-the-Guidelines-Resuscitation, investigators found that only 2.0% of the entire cohort received TTM.[28] With respect to sex, 43.8% of the cohort who received standard therapy were female versus 41.0% of the TTM cohort (p = 0.08). No further subgroup analysis was completed to understand the demographics or arrest characteristics of the women who were cooled versus those who were not and if there were changes in trends over time between 2003 and 2009. The authors theorized that patients with initial shockable rhythms would experience higher rates of TTM, while women experience this initial rhythm less frequently than men.

There is paucity of literature regarding the sex differences in response to therapeutic hypothermia. For example, it is unclear whether the time to target temperature varies between men and women. Similarly, there are no studies that have addressed the sex variability in time to awakening after rewarming, differences in drug metabolism during treatment with TTM, or the duration of therapy necessary for neuroprotection. For instance, a study that found shivering during TTM to be associated with a good neurologic outcome reported that 38% of the cohort who did not shiver were women versus 17% of the cohort who did shiver.[29]

Finally, data are lacking regarding potential discrepancies in adverse events between the sexes. Commonly encountered adverse events including arrhythmias, electrolyte shifts, rearrest, infection, skin breakdown, and coagulopathy have not been reported by sex. Many studies have examined adverse events during TTM, and in studies addressing postrewarming pyrexia, women are equally represented in the pyrexia and nonpyrexia groups (32% vs. 27%).[30] In contrast, a second study found that women only accounted for 30% of the pyrexia cohort versus 44% of the cohort who did not record temperatures after rewarming (p = 0.11).[31]

Priority Question

1. Are the adverse events associated with TTM different between men and women?

Recommendation 5: Withdrawal of Care After Cardiac Arrest

Prior studies have examined the demographic trends in the withdrawal of care in acute illness and have established that women often have a higher incidence of withdrawal of life-sustaining therapy (WLST). To date, no published study has answered the question of whether sex disparities exist in withdrawal of care in women who survive cardiac arrest or in prehospital field termination. Additionally, how the two variables of sex and age may interact when establishing a “do not attempt resuscitation” (DNAR) order or WLST is also currently unknown. This concept is further complicated by the fact that the decision to withdraw life-sustaining therapy is being made by a surrogate decision-maker and not by the patient herself. It is not currently known if the sex of the surrogate decision-maker has an effect on WLST.

Currently, literature is lacking regarding when postarrest women have DNAR orders established versus men. In the field of intracerebral hemorrhage (ICH), Nakagawa et al.[32]

found that women had a greater chance of having a DNAR order placed within 24 hours of the event versus men (odds ratio = 3.18). Interestingly, there was no difference in rate of withdrawal of care in women and men with ICH. Similar to cardiac arrest, the decision regarding extent of aggressive care in ICH is often determined by a surrogate decision-maker. Nakagawa et al. further recognized in their discussion that surrogate decision-makers and providers have significant roles in decisions to withdraw therapy and suggest that women have more aggressive implementation of DNAR in the ICH population because women express their desires to family more openly than men do.

In patients hospitalized with acute myocardial infarction, studies have found that advancing age, female sex, and history of diabetes mellitus or stroke increase the use of DNAR orders.[33] This same study indicates that patients who have a DNAR order placed receive different cardiac therapies than the cohort that do not have DNAR orders.

Studies have shown that while women experience what would be thought “more lethal” cardiac arrests, with more frequent nonshockable presenting rhythms, lower incidence of bystander CPR, and advanced age, they have the same rates of ROSC as men. Despite a similar rate of admission to hospital, fewer women survive to hospital discharge. This phenomenon is poorly understood. One hypothesis is that women may have a higher incidence of withdrawal of care postarrest.

Priority Question

- None.

Recommendation 6: CPR Training and Implementation

Resuscitation performance is a key factor in our efforts to improve both neurological outcomes and survival in patients requiring cardiovascular resuscitation. This broad term is made up of multiple different parts that maybe affected by the sex of the provider and/or patient, including, but not limited to, effectiveness of training, willingness to perform CPR, leadership during resuscitation, quality of CPR, and the effect of failed resuscitative efforts on the provider.

Research has demonstrated that testing can enhance knowledge retention related to a particular topic better than additional studying or training. This concept is known as test-enhanced learning.[34] Researchers attribute this phenomenon at least in part to the release of cortisol in response to acute stress. Cortisol is understood to stabilize a memory after the initial acquisition of knowledge.[35,36] A recent study examined this concept of test-enhanced learning as it relates to CPR training and found a significant difference in learning outcomes in the intervention group who were subjected to more testing compared with those in the control group.[34] Following this testing, they also found a significant increase in cortisol in men, with the correlation between learning outcomes medium to large for men, but not for women.[34]

Another important sex-related difference is in the activation of the chain of survival. In a survey of King County, Washington, residents, males reported greater confidence in performing CPR and greater willingness to start CPR. Females surveyed were less likely to have undertaken CPR training.[37] Axelsson et al.[38] reported that in Swedish citizens recently trained in CPR, males were more confident than females in starting CPR and that females were less likely than males to perform CPR on an unkempt person. A Japanese survey on attitudes toward basic life support demonstrated that female respondents were more willing to perform telephone-prompted chest compressions than males, but were less willing to make an emergency call or use an automated external defibrillator.[11]

Good chest compressions save lives, and it has been shown important during CPR to achieve a chest compression depth greater than 38 mm to improve outcomes in ventricular fibrillation cardiac arrest.[39] Several studies have found that females are less likely than males to consistently achieve adequate chest compression depth during CPR.[40,41] In addition to male sex, a higher body mass index is also associated with more consistently achieving adequate chest compression depth.[40,41] Tomlinson et al.,[42] in their study of force–depth relationship during chest compression, concluded that adequate chest compression depth can be achieved by most providers.

Limited literature currently exists on the effect of sex on the leadership of a code team. One study demonstrated that female medical students exhibited less leadership behavior and less hands-on time than male students.[43,44] Female students did not differ from their male counterparts in terms of level of knowledge or communications, but made significantly fewer leadership statements.[43,44] It is important to note that sex differences in leadership and hands-on time in other arenas may differ greatly than these findings. For example, different occupations and venues may select for more naturally dominant females, such as firefighters and paramedics.

Finally, CPR resuscitations that do not go well are known to have physiologic effects on an individual, such as elevated heart rate, blood pressure, and salivary cortisol level. However, there is paucity of literature related to the psychological effects of a failed resuscitation in the literature on either sex.

Priority Question

1. Could CPR teaching and techniques be modified for men and women to maximize chest compression effectiveness?

CONCLUSIONS

We believe that gender- and sex-related differences in resuscitation are important and that research designed to both better understand and better treat these differences may significantly improve outcomes in the near future. We have made six specific research recommendations, each focusing on a piece of this nascent yet important field, and posed questions that identify major gaps in knowledge pertaining to each subject area. It is significant to note that while these research questions and topic areas have been identified as potential priorities, they in no way exhaust the investigative opportunities to contribute to a better understanding of the effect of sex and gender in resuscitation. It is our hope that this effort will inspire many future fertile discussions involving these topics.

Acknowledgments

The consensus conference was supported by grant 1R13NS087861–01 from the National Institute of Neurological Disorders and Stroke and the Office of Research on Women's Health at the National Institutes of Health. Additional funding was provided by several organizational, institutional, and individual donors. Non-CME events were supported by Janssen Pharmaceuticals and Besins Critical Care/BH Pharma. See the executive summary elsewhere in this issue for full funding information.

References

1. Safdar B, Greenberg MR. Conference on gender-specific research in emergency care – an executive summary. Acad Emerg Med 2014;
2. Safdar B, Nagurney JT, Anise A, et al. Gender-specific research for emergency diagnosis and management of ischemic heart disease: proceedings from the 2014 AEM consensus conference cardiovascular research workgroup. Acad Emerg Med 2014;
3. Adabag AS, Luepker RV, Roger VL, Gersh BJ. Sudden cardiac death: epidemiology and risk factors. Nat Rev Cardiol 2010;7:216–25. [PubMed: 20142817]
4. Kim C, Fahrenbruch CE, Cobb LA, Eisenberg MS. Out-of-hospital cardiac arrest in men and women. Circulation 2001;104:2699–703. [PubMed: 11723022]
5. Wigginton JG, Pepe PE, Bedolla JP, DeTamble LA, Atkins JM. Sex-related differences in the presentation and outcome of out-of-hospital cardiopulmonary arrest: a multiyear, prospective, population-based study. Crit Care Med 2002;30:S131–6. [PubMed: 11940787]
6. Akahane M, Ogawa T, Koike S, et al. The effects of sex on out-of-hospital cardiac arrest outcomes. Am J Med 2011;124:325–33. [PubMed: 21435423]
7. Johnson MA, Haukoos JS, Larabee TM, et al. Females of childbearing age have a survival benefit after out-of-hospital cardiac arrest. Resuscitation 2013;84:639–44. [PubMed: 22986061]
8. Topjian AA, Localio AR, Berg RA, et al. Women of child-bearing age have better inhospital cardiac arrest survival outcomes than do equal-aged men. Crit Care Med 2010;38:1254–60. [PubMed: 20228684]
9. Airaksinen KE, Ikaheimo MJ, Linnaluoto M, Tahvanainen KU, Huikuri HV. Gender difference in autonomic and hemodynamic reactions to abrupt coronary occlusion. J Am Coll Cardiol 1998;31:301–6. [PubMed: 9462571]
10. Wing LM, Miners JO, Birkett DJ, Foenander T, Lillywhite K, Wanwimolruk S. Lidocaine disposition--sex differences and effects of cimetidine. Clin Pharmacol Ther 1984;35:695–701. [PubMed: 6713782]
11. Kitamura T, Iwami T, Nichol G, et al. Reduction in incidence and fatality of out-of-hospital cardiac arrest in females of the reproductive age. Eur Heart J 2010;31:1365–72. [PubMed: 20231155]
12. Liu R, Wang X, Liu Q, Yang SH, Simpkins JW. Dose dependence and therapeutic window for the neuroprotective effects of 17beta-estradiol when administered after cerebral ischemia. Neurosci Lett 2007;415:237–41. [PubMed: 17331646]
13. Kozlov AV, Duvigneau JC, Hyatt TC, et al. Effect of estrogen on mitochondrial function and intracellular stress markers in rat liver and kidney following trauma-hemorrhagic shock and prolonged hypotension. Mol Med 2010;16:254–61. [PubMed: 20379612]
14. Yokoyama Y, Schwacha MG, Bland KI, Chaudry IH. Effect of estradiol administration on splanchnic perfusion after trauma-hemorrhage and sepsis. Curr Opin Crit Care 2003;9:137–42. [PubMed: 12657977]
15. Gatson JW, Maass DL, Simpkins JW, Idris AH, Minei JP, Wigginton JG. Estrogen treatment following severe burn injury reduces brain inflammation and apoptotic signaling. J Neuroinflammation 2009;6:30. [PubMed: 19849845]
16. Kuhar P, Lunder M, Drevensek G. The role of gender and sex hormones in ischemic-reperfusion injury in isolated rat hearts. Eur J Pharmacol 2007;561:151–9. [PubMed: 17335799]
17. Hutchens MP, Nakano T, Kosaka Y, et al. Estrogen is renoprotective via a nonreceptor-dependent mechanism after cardiac arrest in vivo. Anesthesiology 2010;112:395–405. [PubMed: 20068453]

18. Noppens RR, Kofler J, Grafe MR, Hurn PD, Traystman RJ. Estradiol after cardiac arrest and cardiopulmonary resuscitation is neuroprotective and mediated through estrogen receptor-beta. J Cereb Blood Flow Metab 2009;29:277–86. [PubMed: 18957991]
19. Noppens RR, Kofler J, Hurn PD, Traystman RJ. Dose-dependent neuroprotection by 17beta-estradiol after cardiac arrest and cardiopulmonary resuscitation. Crit Care Med 2005;33:1595–602. [PubMed: 16003068]
20. Wright DW, Kellermann AL, Hertzberg VS, et al. ProTECT: a randomized clinical trial of progesterone for acute traumatic brain injury. Ann Emerg Med 2007;49:391–402, [PubMed: 17011666]
21. Nakano T, Hurn PD, Herson PS, Traystman RJ. Testosterone exacerbates neuronal damage following cardiac arrest and cardiopulmonary resuscitation in mouse. Brain Res 2010;1357:124–30. [PubMed: 20709035]
22. Yang SH, Perez E, Cutright J, et al. Testosterone increases neurotoxicity of glutamate in vitro and ischemia-reperfusion injury in an animal model. J Appl Physiology 2002;92:195–201.
23. Cheng J, Alkayed NJ, Hurn PD. Deleterious effects of dihydrotestosterone on cerebral ischemic injury. J Cerebral Blood Flow Metab 2007;27:1553–62.
24. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557–63. [PubMed: 11856794]
25. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–56. [PubMed: 11856793]
26. Bray JE, Stub D, Bernard S, Smith K. Exploring gender differences and the “oestrogen effect” in an Australian out-of-hospital cardiac arrest population. Resuscitation 2013;84:957–63. [PubMed: 23246988]
27. Herzog E, Tamis J, Aziz EF, Shapiro JM. A novel program focused on women survivors who were enrolled in a cardiac arrest pathway. Crit Pathw Cardiol 2013;12:28–30. [PubMed: 23411605]
28. Mikkelsen ME, Christie JD, Abella BS, et al. Use of therapeutic hypothermia after in-hospital cardiac arrest. Crit Care Med 2013;41:1385–95. [PubMed: 23518870]
29. Nair SU, Lundbye JB. The occurrence of shivering in cardiac arrest survivors undergoing therapeutic hypothermia is associated with a good neurologic outcome. Resuscitation 2013;84:626–9. [PubMed: 23201502]
30. Cocchi MN, Boone MD, Giberson B, et al. Fever after rewarming: incidence of pyrexia in postcardiac arrest patients who have undergone mild therapeutic hypothermia. J Intensive Care Med 2013;doi 0885066613491932.
31. Leary M, Grossestreuer AV, Iannacone S, et al. Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest. Resuscitation 2013;84:1056–61. [PubMed: 23153649]
32. Nakagawa K, Vento MA, Seto TB, et al. Sex differences in the use of early do-not-resuscitate orders after intracerebral hemorrhage. Stroke 2013;44:3229–31. [PubMed: 23982712]
33. Jackson EA, Yarzebski JL, Goldberg RJ, et al. Do-not-resuscitate orders in patients hospitalized with acute myocardial infarction: the Worcester Heart Attack Study. Arch Intern Med 2004;164:776–83. [PubMed: 15078648]
34. Kromann CB, Jensen ML, Ringsted C. Test-enhanced learning may be a gender-related phenomenon explained by changes in cortisol level. Med Educ 2011;45:192–9. [PubMed: 21208264]
35. de Kloet ER, Oitzl MS, Joels M. Stress and cognition: are corticosteroids good or bad guys? Trends Neurosci 1999;22:422–6. [PubMed: 10481183]
36. McGaugh JL, Roozendaal B. Role of adrenal stress hormones in forming lasting memories in the brain. Curr Opin Neurobiol 2002;12:205–10. [PubMed: 12015238]
37. Sipsma K, Stubbs BA, Plorde M. Training rates and willingness to perform CPR in King County, Washington: a community survey. Resuscitation 2011;82:564–7. [PubMed: 21257253]
38. Axelsson A, Thoren A, Holmberg S, Herlitz J. Attitudes of trained Swedish lay rescuers toward CPR performance in an emergency. A survey of 1012 recently trained CPR rescuers. Resuscitation 2000;44:27–36. [PubMed: 10699697]

39. Edelson DP, Abella BS, Kramer-Johansen J, et al. Effects of compression depth and pre-shock pauses predict defibrillation failure during cardiac arrest. Resuscitation 2006;71:137–45. [PubMed: 16982127]

40. Ashton A, McCluskey A, Gwinnutt CL, Keenan AM. Effect of rescuer fatigue on performance of continuous external chest compressions over 3 min. Resuscitation 2002;55:151–5. [PubMed: 12413752]

41. Peberdy MA, Silver A, Ornato JP. Effect of caregiver gender, age, and feedback prompts on chest compression rate and depth. Resuscitation 2009;80:1169–74. [PubMed: 19674826]

42. Tomlinson AE, Nysaether J, Kramer-Johansen J, Steen PA, Dorph E. Compression force-depth relationship during out-of-hospital cardiopulmonary resuscitation. Resuscitation 2007;72:364–70. [PubMed: 17141936]

43. Streiff S, Tschan F, Hunziker S, et al. Leadership in medical emergencies depends on gender and personality. Simul Healthc 2011;6:78–83. [PubMed: 21358565]

44. Wayne NL, Vermillion M, Uijtdehaage S. Gender differences in leadership amongst first-year medical students in the small-group setting. Acad Med 2010;85:1276–81. [PubMed: 20671452]

Table 1

Rank Order of Consensus-driven Research Questions

Rank	Consensus-based Questions*	Mean Likert Score
1	Why do young men die more frequently than comparably aged women despite men having more favorable predictors of survival?	4.54
2	Are there sex disparities in withdrawal of care after cardiac arrest?	4.48
3	Do women have earlier advancement of code status (DNAR order) than men following cardiac arrest?	4.33
4	Do women respond to TTM similarly to their male counterparts?	4.31
5	Do women have improved neurological outcomes after TIM and is there an additive effect between TTM and endogenous sex steroids?	4.00

TTM = targeted temperature management.

*Voted in degree of importance from highest (5) to lowest (1).