Editors' Note: In "Practice guideline summary: Reducing brain injury following cardiopulmonary resuscitation: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology," the authors concluded that prehospital cooling did not improve neurologic outcome or survival in patients who subsequently underwent in-hospital therapeutic hypothermia. Drs. Machado et al. comment that studies in animals and of accidental hypothermia have shown a benefit to early hypothermia, and that, intuitively, any neuroprotective intervention should be initiated as soon as possible. Authors Geocadin et al. confirm that while animal studies and case reports in support of prehospital cooling exist, multiple human studies failed to demonstrate any benefit. Regarding these same guidelines, Drs. Melegari et al. describe their observation of 32 patients treated with therapeutic hypothermia after an out-of-hospital cardiac arrest over 2 years. They found that patients after a cardiac arrest in which there was a nonshockable rhythm and circulatory instability fared worse due to subsequent cerebral edema. Patients without these factors benefited from the mild therapeutic hypothermia. Authors Geocadin et al. comment that the relationship between these factors (i.e., rhythm during cardiopulmonary resuscitation [CPR] and cerebral edema) and post-CPR management is not clear in the literature and that more research is needed to answer these important questions.

—Megan Alcauskas, MD, and Steven Galetta, MD

**LETTER RE: PRACTICE GUIDELINE SUMMARY:
REDUCING BRAIN INJURY FOLLOWING
CARDIOPULMONARY RESUSCITATION: REPORT
OF THE GUIDELINE DEVELOPMENT,
DISSEMINATION, AND IMPLEMENTATION
SUBCOMMITTEE OF THE AMERICAN ACADEMY
OF NEUROLOGY**

**Calixto Machado, Mario Estevez, Habana, Cuba;
Gerry Leisman, Zichron Ya'acov, Israel:** The American Academy of Neurology guidelines remarked on required recommendations to reduce brain injury after successful cardiopulmonary resuscitation (CPR).¹ Nonetheless, it seems contradictory that prehospital cooling as an adjunct to therapeutic hypothermia (TH) is decidedly ineffectual in further improving neurologic outcome and survival.¹

Safar and Tisherman² documented brain and organ preservation during cardio-circulatory arrest (CCA) in dog experimental models with no-flow durations of up to 90 or 120 minutes. The neuroprotective effect of TH is also supported by reports of patients with accidental hypothermia, combined with CCA. These patients were rewarmed by use of extracorporeal circulation with good outcome in several cases.³ The key point in these cases was that the neuroprotective effect of accidental hypothermia occurred very early, even before a complete CCA had occurred.⁴

Out-of-hospital settings (i.e., the site of accident or inside ambulances) include technical limitations in patients with an absent or unstable blood circulation and possible neurologic complications.^{1,4,5} Any neuroprotective treatment for preventing brain injury after CCA should be initiated as soon as possible and maintained during CPR.⁴

1. Geocadin RG, Wijdicks E, Armstrong MJ, et al. Practice guideline summary: Reducing brain injury following cardiopulmonary resuscitation: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2017;88:2141–2149.
2. Safar PJ, Tisherman SA. Suspended animation for delayed resuscitation. *Curr Opin Anaesthesiol* 2002;15:203–210.
3. Oberhammer R, Beikircher W, Hormann C, et al. Full recovery of an avalanche victim with profound hypothermia and prolonged cardiac arrest treated by extracorporeal re-warming. *Resuscitation* 2008;76:474–480.
4. Machado C. The brain is the target organ in cardiorespiratory reanimation. *Curr Anaesth Crit Care* 2009;20:148.
5. Zafren K. Out-of-hospital evaluation and treatment of accidental hypothermia. *Emerg Med Clin North Am* 2017;35:261–279.

© 2017 American Academy of Neurology

**LETTER RE: PRACTICE GUIDELINE SUMMARY:
REDUCING BRAIN INJURY FOLLOWING
CARDIOPULMONARY RESUSCITATION: REPORT
OF THE GUIDELINE DEVELOPMENT,
DISSEMINATION, AND IMPLEMENTATION
SUBCOMMITTEE OF THE AMERICAN ACADEMY
OF NEUROLOGY**

Gabriele Melegari, Alberto Barbieri, Antonio Manenti, Elisabetta Bertellini, Enrico Giuliani, Modena, Italy: We read with interest the article by Geocadin et al.¹ and found the conclusion of

importance. Over the last 2 years, we observed a group of 32 patients treated with mild therapeutic hypothermia after an out-of-hospital nontraumatic cardiac arrest. When considering the effect of the cardiac arrest on the patients' subsequent outcomes in the short and middle term, a sharp difference between 2 conditions was observed. A cardiac arrest complicated by a not-shockable rhythm and a circulatory instability is usually accompanied by a worsening cerebral edema. These 2 signs, clearly connected to each other, are strong predictors of short survival and of poor neurologic outcome, independent from any treatment. On the contrary, in the case of cardiac arrest followed by a shockable rhythm, mild therapeutic hypothermia is directly indicated for the greater possibility of a good outcome.²⁻⁴ In these patients, any early invasive treatment of the acute cardiac pathology, or of any other intervening complication, is not contraindicated.

1. Geocadin RG, Wijdicks E, Armstrong MJ, et al. Practice guideline summary: Reducing brain injury following cardiopulmonary resuscitation: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2017; 88:2141–2149.
2. Zheng R, Luo S, Liao J, et al. Conversion to shockable rhythms is associated with better outcomes in out-of-hospital cardiac arrest patients with initial asystole but not in those with pulseless electrical activity. *Resuscitation* 2016;107:88–93.
3. Wah W, Wai KL, Pek PP, et al. Conversion to shockable rhythms during resuscitation and survival for out-of-hospital cardiac arrest. *Am J Emerg Med* 2017;35: 206–213.
4. Granau B, Reynolds JC, Sheuermeyer FX, et al. Comparing the prognosis of those with initial shockable and non-shockable rhythms with increasing durations of CPR: informing minimum durations of resuscitation. *Resuscitation* 2016;101:50–56.

© 2017 American Academy of Neurology

AUTHOR RESPONSE: PRACTICE GUIDELINE SUMMARY: REDUCING BRAIN INJURY FOLLOWING CARDIOPULMONARY RESUSCITATION: REPORT OF THE GUIDELINE DEVELOPMENT, DISSEMINATION, AND IMPLEMENTATION SUBCOMMITTEE OF THE AMERICAN ACADEMY OF NEUROLOGY

Romergrzyko G. Geocadin, Baltimore; **Eelco Wijdicks,** Rochester, MN; **Richard M. Dubinsky,** Kansas City, KS; **Joseph P. Ornato,** Richmond, VA; **Michael T. Torbey,** Columbus, OH; **Jose I. Suarez,** Houston: We appreciate the comments of Machado et al. and Melegari et al. on our guideline, which provided recommendations to reduce brain injury following cardiopulmonary resuscitation (CPR).¹

Despite the promising results in animal studies (many used hypothermia during resuscitation

or minutes thereafter in controlled circumstances) with the early initiation of therapeutic hypothermia (TH), as mentioned by Machado et al., multiple human studies (5 Class I and 1 Class II) failed to demonstrate any benefit of prehospital TH followed by TH in-hospital vs only TH in-hospital for comatose survivors of out-of-hospital cardiac arrest (OHCA).²⁻⁷ Many factors may have contributed to the difference in outcomes between animal studies and human trials, including the difference in time of initiation, methods, and application consistency of TH in relation to CPR. While case reports exist of good survival of people who had extreme accidental hypothermia followed by cardiac arrest, the pathophysiologic mechanism is quite different from the controlled clinical trials of TH after OHCA included in the practice guideline.¹

The comments of Melegari et al. are based on their observation of 32 patients post CPR who were treated with mild TH. A population-based cardiac arrest study showed the associations of nonshockable cardiac rhythm to preexisting noncardiovascular diseases and shockable cardiac rhythms to preexisting cardiovascular diseases.⁸ Although some association has been attributed to preexisting conditions (e.g., cardiac disease and lung disease) and measures during CPR (e.g., cardiac rhythm and arrest time) to the outcomes after successful CPR, these conditions were found less reliable as predictors of neurologic outcome.⁹⁻¹¹ Some post-CPR measures, such as neurologic examination and somatosensory evoked potentials, are deemed reliable as predictors of neurologic outcome⁹⁻¹¹; however, neuroimaging (e.g., CT scan and MRI) after CPR to detect extent of brain injury (e.g., brain edema) is not considered reliable as a predictor of outcome.^{9,11,12} After a careful literature review, the effects of factors (i.e., cardiac rhythm during CPR and cerebral edema) provided by Melegari et al. to post-CPR management remain unclear. Furthermore, no studies have shown the precise link of cardiac arrest and brain edema. More research is needed. Until better data are available, the recommendations remain as provided in the guideline.¹

1. Geocadin RG, Wijdicks E, Armstrong MJ, et al. Practice guideline summary: Reducing brain injury following cardiopulmonary resuscitation: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2017;88:2141–2149.
2. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. *JAMA* 2014;311:45–52.
3. Castren M, Nordberg P, Svensson L, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). *Circulation* 2010;122:729–736.

4. Bernard SA, Smith K, Cameron P, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. *Circulation* 2010;122:737–742.
5. Bernard SA, Smith K, Cameron P, et al. Induction of pre-hospital therapeutic hypothermia after resuscitation from nonventricular fibrillation cardiac arrest. *Crit Care Med* 2012;40:747–753.
6. Kamarainen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silvast T. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: a randomized controlled trial. *Acta Anaesthesiol Scand* 2009;53:900–907.
7. Debaty G, Maignan M, Savary D, et al. Impact of intra-arrest therapeutic hypothermia in outcomes of prehospital cardiac arrest: a randomized controlled trial. *Intensive Care Med* 2014;40:1832–1842.
8. Granfeldt A, Wissenberg M, Hansen SM, et al. Clinical predictors of shockable versus non-shockable rhythms in patients with out-of-hospital cardiac arrest. *Resuscitation* 2016;108:40–47.
9. Wijdicks EF, Hijdra A, Young GB, et al. Practice parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;67:203–210.
10. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication: a consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. *Circulation* 2008;118:2452–2483.
11. Callaway CW, Donnino MW, Fink EL, et al. Part 8: Post-cardiac arrest care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2015;132:S465–S482.
12. Hahn DK, Geocadin RG, Greer DM. Quality of evidence in studies evaluating neuroimaging for neurologic prognostication in adult patients resuscitated from cardiac arrest. *Resuscitation* 2014;85:165–172.

© 2017 American Academy of Neurology

CORRECTION

Meta-analysis of pharmacogenetic interactions in amyotrophic lateral sclerosis clinical trials

In the article “Meta-analysis of pharmacogenetic interactions in amyotrophic lateral sclerosis clinical trials” by R.P.A. van Eijk et al.,¹ there was an error in figure 2 of the version published online on October 4, 2017. The key in figure 2 should have labeled the green line “*UNC13A* carriers – Lithium” and the purple line “*UNC13A* carriers – Control.” In subsequent versions of the article (republished online on October 11, 2017, and in the issue dated October 31, 2017), figure 2 is correct. The editorial staff regret the error in the first version.

REFERENCE

1. van Eijk RPA, Jones AR, Sproviero W, et al. Meta-analysis of pharmacogenetic interactions in amyotrophic lateral sclerosis clinical trials. *Neurology* 2017;89:1915–1922.

Neurology[®]

Meta-analysis of pharmacogenetic interactions in amyotrophic lateral sclerosis clinical trials

Neurology 2017;89:2303
DOI 10.1212/WNL.0000000000004727

This information is current as of November 27, 2017

Updated Information & Services

including high resolution figures, can be found at:
<http://n.neurology.org/content/89/22/2303.full>

References

This article cites 1 articles, 1 of which you can access for free at:
<http://n.neurology.org/content/89/22/2303.full#ref-list-1>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints

Information about ordering reprints can be found online:
<http://n.neurology.org/subscribers/advertise>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2017 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.