AGENDA

ICEMA
MEDICAL ADVISORY COMMITTEE

April 23, 2015

1300

Purpose: Information Sharing

Meeting Facilitator: Phong Nguyen

Timekeeper: Danielle Ogaz

Record Keeper: Danielle Ogaz

AGENDA ITEM		PERSON(S)	DISCUSSION/ACTION	TIME
I.	Welcome/Introductions	Phong Nguyen		1300 - 1301
II.	Approval of Minutes	All	Discussion	1301 - 1303
III.	Discussion/Action Items			1303 - 1330
	A. Standing EMS System Updates			
	1. Review of Action Items	1. Phong Nguyen	1. Discussion/Action	
	2. Trauma Program	2. Chris Yoshida-McMath	2. Discussion	
	3. STEMI Program: STEMI Data • Chest Pain Society Accreditation	3. Chris Yoshida-McMath	3. Discussion	
	4. Stroke Program: Stroke Data	4. Chris Yoshida-McMath	4. Discussion	
	5. CQI Report Update • Core Measures	5. Phong Nguyen • Ron Holk	5. Discussion 6. Discussion	
	6. SAC Update	6. Phone Nguyen	7. Discussion	
	7. Literature Review • ACEP - Minus the Neurologists Tempers its tPA Policy • Intravenous Drug Administration During Out-of-Hospital Cardiac Arrest • Prehospital Epinephrine Use and Survival Among Patients With Out-of-Hospital Cardiac Arrest	7. Reza Vaezazizi		
	8. Case Review	8. Reza Vaezazizi	8. Discussion	
	B. EMS Trends			1330 - 1340
	1. TXA Study Update	1. Reza Vaezazizi/Michael Neeki	1. Discussion	
	2. Paramedicine Step I Research Update	2. Michael Neeki	2. Discussion	

	3. Cardiac Arrest Survival Enhancement Project (CARES/ART)	3. Reza Vaezazizi	3. Discussion	
	C. MAC Confidential Case Reviews	Reza Vaezazizi	Discussion	1340 - 1350
	D. Fentanyl/Narcan (Pediatric Dosing)	Chris Yoshida-McMath	Discussion	1350 - 1405
	E. Pediatric Medication Dosing	Reza Vaezazizi	Discussion	1405 - 1420
	F. Appropriate Use of Oxygen	Kevin Parkes	Discussion	1420 - 1430
	G. EZ-IO	Reza Vaezazizi	Discussion/Action	1430 - 1440
	H. Protocol Change Education	Reza Vaezazizi	Discussion	1440 - 1450
V.	Public Comment	All	Discussion	1450 - 1455
VI.	Round Table/Announcements	All	Discussion	1455 - 1457
VII.	Future Agenda Items	All	Discussion	1457 - 1458
VIII.	Next Meeting Date: June 25, 2015	All	Discussion	1458 - 1459
IX.	Adjournment	Phong Nguyen	Action	1459 - 1450

MINUTES

MEDICAL ADVISORY COMMITTEE

February 26, 2015

1300 to 1500

AGENDA ITEM		DISCUSSION/FOLLOW UP	RESPONSIBLE PERSON(S)
I.	WELCOME/INTRODUCTIONS	Meeting called to order at 1310.	Phong Nguyen
II.	APPROVAL OF MINUTES	The December 18, 2014, minutes were approved. Motion to approve. MSC: Michael Neeki/Susie Moss APPROVED Ayes: Debbie Bervel, Lance Brown, Sam Chua, Michael Guirguis, Jeff Grange, Susie Moss, Michael Neeki, Phong Nguyen, Leslie Parham, Kevin Parkes, Stephen Patterson, Joy Peters, Joe Powell, Aaron Rubin, Todd Sallenbach, Joanna Yang	
III.	DISCUSSION ITEMS		
	A. Standing EMS System Updates		
	1. Review of Action Items	Action items incorporated into the agenda.	Phong Nguyen
	2. Trauma Program	There have been no changes to the demographic reports. TSAC/TAC reviewed proposed changes to the Trauma Triage Criteria. The purpose of the change is to align with the CDC/MMWR recommendations from 2011. TSAC/TAC will now be discussing burn issues. Next TSAC/TAC meeting is May 13, 2015, at ICEMA.	Chris Yoshida-McMath
	3. STEMI Program: STEMI Data	ICEMA is continuing to monitor physician attendance at the STEMI meeting. ICEMA will be requiring the Society for Chest Pain Centers Accreditation for all STEMI	Chris Yoshida-McMath

		Receiving Centers. One of the 2015 goals of the STEMI committee is to improve on the capturing of prehospital ECGs. There has already been an improvement from 20 - 30% capture rate to 85% capture rate. Next STEMI meeting is August 6, 2015.	
	4. Stroke Program: Stroke Data	Stroke committee is currently developing an IFT policy between hospitals that have interventional capabilities and those who do not. Next Stroke meeting is July 7, 2015.	Chris Yoshida-McMath
	5. CQI Report Update	The CQI plan is being worked on and should be to the task force for review within the next few months.	Ron Holk
	6. SAC Update	SAC reviewed the Triage Tag Training video. The task force will continue to meet and develop a roll out time line and training. SAC requested Dr. Parkes to ask MAC if it would be possible for ICEMA to provide explanation as to why a protocol has been changed to assist with education. Topic to be discussed at the April 23, 2015, meeting.	Todd Sallenbach
	B. EMS Trends		
	1. TXA Study Update	The official start date of the study is March 9, 2015. The educational video has been completed. Agencies can begin trial as soon as the Condition of Participation form has been submitted and ICEMA has been notified that the education is complete. ICEMA has the TXA Trail Study wristbands for those agencies that have submitted their form and completed the education A monthly conference call will occur the 1st Tuesday of the month. Additional EMS agencies are considering joining the study.	Reza Vaezazizi/ Michael Neeki
	2. Paramedicine Step I Research Update	The educational piece has been completed. Once Rialto Fire and AMR have completed education the study will begin.	Michael Neeki
	3. Cardiac Arrest Survival Enhancement Project (CARES/ART)	CARES registry was reviewed. ICEMA's goal is to get CARES up and running	Reza Vaezazizi

		in order to obtain some baseline data. Then implement ART, to see if there have been any changes in the data since ART was implemented. CARES will begin with the hospitals that are ready to go. Additional hospitals will be added as it progresses. ICEMA is looking for prehospital agencies to champion ART. Interested agencies should notify ICEMA. Goal of after July 1, 2015, to begin.	
	C. Community Paramedicine	The Community Paramedicine Pilot Project policy was presented.	Ron Holk
	D. Amiodarone for IFTs	MAC reviewed the request to consider adding Amiodarone to the list of approved medications. After discussion and consideration of all relevant information, the committee did not recommend addition of Amiodarone to any ICEMA protocol at this time.	Kevin Parkes
	E. Condensed Treatment Protocols	Treatment protocols were presented in their condensed versions. Ron Holk will work with Leslie Parham and Henry Perez to re-write questions that were sent during the first survey and updated survey will be added to the ICEMA website. Results from the new survey to be presented at the April meeting.	Ron Holk
IV.	PUBLIC COMMENT	None	All
V.	ROUND TABLE/ ANNOUNCEMENTS	None	All
VI.	FUTURE AGENDA ITEMS	Appropriate Administration of Oxygen (Kevin Parkes)	Danielle Ogaz
VII.	NEXT MEETING: April 23, 2015		
VIII.	ADJOURNMENT	The meeting adjourned at 1440.	Phong Nguyen

Attendees:

NAME	MAC POSITION	EMS AGENCY STAFF	POSITION
☐ VACANT ☒ Jeff Grange - LLUMC	Trauma Hospital Physicians (2)	☒ Reza Vaezazizi, MD	Medical Director
☒ Phong Nguyen - RDCH ☒ Todd Sallenbach - HDMC (Chair)	Non-Trauma Base Physician s (2)	☒ Tom Lynch	EMS Administrator
☒ Aaron Rubin - Kaiser	Non-Base Hospital Physician	☒ Denice Wicker-Stiles	Assist. Administrator
☒ Michael Neeki - Rialto FD	Public Transport Medical Director	☐ George Stone	Program Coordinator
☒ Sam Chua - AMR	Private Transport Medical Director	☒ Ron Holk	EMS Nurse Specialist
☒ Debbie Bervel - SB City FD	Fire Department Medical Director	☒ Chris Yoshida-McMath	EMS Nurse Specialist
☒ Joy Peters - ARMC	EMS Nurses	☒ Danielle Ogaz	EMS Specialist
☒ Joe Powell - Rialto FD	EMS Officers		
☒ Leslie Parham	Public Transport Medical Rep (Paramedic/RN)		
☒ Susie Moss	Private Transport Medical Rep (Paramedic/RN)		
☒ Lance Brown	Specialty Center Medical Director		
☒ Joanna Yang - LLUMC	Specialty Center Coordinator		
☐ Troy Pennington	Private Air Transport Medical Director		
☒ Stephen Patterson - Sheriff's Air Rescue	Public Air Transport Medical Director		
☒ Micheal Guirguis - SB Comm Center	PSAP Medical Director		
☐ Andrew Stevens	Inyo County Representative		
☐ Rosemary Sachs	Mono County Representative		
☒ Kevin Parkes	SAC Liaison		
☐ Andrea Thorp	Pediatric Critical Care Physician		

GUESTS	AGENCY
Sandy Carnes	Rancho Cucamonga FD
Carly Crews	SB City FD
Patti Eickholt	SACH
Chris Linke	AMR
Pam Martinez	Ontario FD
Sara Morning	RCH
Leigh Overton	SB County FD
Shane Panto	CHP
Henry Perez	Colton FD
Shawn Reynolds	LLUMC
Art Rodriguez	Desert Ambulance
Bob Tyson	Redlands FD

CM	Core Measure	2012	2013	2014	Question
01-TRA-1	Scene Time for Trauma Patients	0:27:00	0:26:30	0:26:16	What is the 90th percentile for on scene time value for trauma patients (as defined by the 2011 Guidelines for Field Triage of Injured Patients) who were transported from the scene by ground ambulance?
01-TRA-2	Direct Transport to Trauma Center	60%	52%	50%	What is the percentage of trauma patients who were transported from the scene directly to a trauma center by a ground ambulance?
02-ACS-1	ASA Admin for CP	51%	44%	46%	What is the percent of patients age 35 and older with suspected cardiac chest pain who received aspirin prior to hospital by pre-hospital personnel?
02-ACS-2	12 lead EKG Performed	78%	87%	91%	What is the percentage of patients with cardiac chest pain discomfort who received 12 lead ECG by paramedics?
02-ACS-3	Scene time for suspected HA	0:23:00	0:26:00	0:23:36	What is the 90th percentile for ground ambulance scene time of STEMI patients?
02-ACS-5	Direct transport to STEMI Center	83%	86%	82%	What percentage of suspected STEMI patients are transported by ground ambulance directly to a designated STEMI receiving center?
03-CAR-2	Out of hospital Cardiac Arrest ROSC	21%	20%	19%	Per Utstein definition of ROSC (see references section): What is the percentage of patients experiencing cardiac origin cardiac arrest who have ROSC?
03-CAR-3	Survival to Hospital Discharge	NA	NA	NA	Per Utstein definition of ROSC (see references section): What is the percentage of patients experiencing cardiac origin cardiac arrest, where resuscitation was attempted, who survived to ED discharge?
03-CAR-4	Out of hospital survival to discharge	NA	NA	NA	Per Utstein definition of ROSC (see references section): What is the percentage of patients experiencing cardiac origin cardiac arrest, where resuscitation was attempted, who survived to hospital discharge?
04-STR-2	Glucose Testing for Stroke	76%	82%	81%	What is the percentage of suspected acute stroke patients meeting local criteria who received a glucose test in a pre-hospital setting?
04-STR-3	Scene time for suspected Stroke	0:23:03	0:24:23	0:24:57	What is the 90th percentile for on scene time value for suspected acute stroke patients meeting local criteria who were transported from the scene by ground ambulance?
04-STR-5	Direct Transport to Stroke Center	69%	76%	76%	What percent of suspected acute stroke patients meeting local criteria were transported from the scene by ground ambulance directly to a designated stroke center?

05-RES-2	Beta 2 agonist admin	33%	32%	31%	What is the percentage of beta2 agonist (bronchodilator or Ipratropium) administration by EMS personnel for patients older than 14 years old with signs and symptoms of suspected bronchospasm?
06-PED-1	Pediatric who received bronchodilators	30%	28%	27%	What is the percentage of beta2 agonist (bronchodilator or Ipratropium) administration by EMS personnel for pediatric patients younger than 14 years old with signs and symptoms of suspected bronchospasm?
07-PAI-1	Pain Intervention	89%	90%	91%	What is the percentage of adult patients with pain (value of 7 or greater on a 10 point scale) that received a pain intervention by EMS personnel? Adjustment for change in measurement matrix
08-SKL-1	ET Success rate	79%	63%	61%	What is the percentage of patients who received successful endotracheal intubation within two attempts in a pre-hospital setting?
08-SKL-2	Capnography performed	20%	19%	17%	What is the percentage of intubated patients where capnography measurement is performed?
09-RST-1	Emergency Response Time				What is the 90th percentile time value of the Ambulance Response time in Ground Ambulance Transport Zone as defined by the EMS Plan?
09-RST-2	Non-Emergency Response Time				What is the 90th percentile time value of the ambulance response time in Ground Ambulance Transport Zone as defined by the EMS Plan?
09-RST-3	Hospital Transport Rate				What is the percentage of EMS Patients transported to a General Acute Care Hospital with a Basic Permit for emergency services?

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Wolters Kluwer

ACEP — Minus the Neurologists — Tempers its tPA Policy

BY GINA SHAW

A draft of a new clinical policy from the American College of Emergency Physicians (ACEP) takes a much more conservative approach on using intravenous tPA for managing acute ischemic stroke in the emergency department than the current guidelines, which were approved in 2012.

Those guidelines provoked a fair amount of controversy, with some emergency physicians saying the treatment was too risky and had little potential for benefit. ("The 'Biggest, Baddest' Controversy in EM," *EMN* 2013;35[4]:1; http://bit.ly/EMN12.)

Marino's The ICU Book, Lippincott Williams & Wilkins, 2013.

A year later, an article in the *British Medical Journal* questioned the reliability of the guidelines, calling them more industry marketing than tools of evidence-based medicine. (2013;346:f3830.) That report also questioned some of the committee members' conflicts of interest, some undeclared, and the "committee stacking" of the joint American Academy of Neurology-ACEP panel with experts with known viewpoints on a particular side of an issue. Seven of eight members of the AAN-ACEP committee, the *BMJ* article said, had previously spoken or written on the benefits of tPA for stroke, and "[n]ot one skeptic

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ACLS Drugs Provide No Benefit for Out-of-Hospital Cardiac Arrest

BY JAMES R. ROBERTS, MD

It may sound like medical heresy, but the decades-long use of ACLS drugs does not appear to favorably affect the outcome of out-of-hospital cardiac arrest. Their use, in fact, may be detrimental to long-term survival. Despite a growing number of studies supporting this concept, prehospital ACLS drugs are still recommended by national societies and guidelines, and they are frequently, if not universally, used in our EMS system. The number of ACLS recommended drugs has decreased over the years, specifically eschewing calcium, atropine, magnesium, lidocaine,

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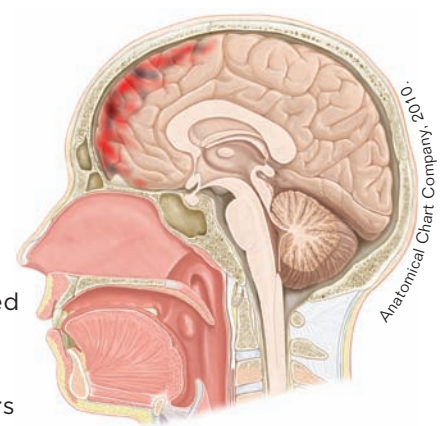
Promising Biomarker May ID Long-Term Concussion Damage

BY GINA SHAW



Anatomical Chart Company, 2010.

A new blood biomarker accurately predicted which concussion victims would have persistent cognitive dysfunction after a mild traumatic brain injury, according to researchers from the Perelman School of Medicine at the

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PERIODICALS

ACLS Drugs

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and bicarbonate, but the current CPR guidelines from the American Heart Association (2010) still recommend the use of epinephrine/vasopressin or amiodarone as empiric therapy for cardiac arrest. EMS personnel will tell you that ACLS drugs result in an increase in return of spontaneous circulation in the field, but this is not a parameter associated with better long-term survival after hospital arrival.

This month's column discusses two articles, both quite well done, that indicate that intravenous drug administration during out-of-hospital cardiac arrest has no proven benefit, and their use may actually be detrimental. This may seem like an outrageous contradiction to current practice, but the widespread use of ACLS drugs was adopted on theoretical grounds or animal studies without any controlled studies or verified supporting data. Apparently, it's easier to get a drug into ACLS guidelines than it is to get it out.

Despite great advances in prehospital care, the routine use of currently recommended ACLS medications has not significantly changed long-term survival rates from out-of-hospital cardiac arrest. Current ACLS drug protocols may result in an initial heart beat/blood pressure, but this does not translate into a better outcome. The counterintuitive observation is that ACLS drugs may actually worsen long-term survival. When the initial observed rhythm is asystole (even if preceded by ventricular tachycardia or ventricular fibrillation), the likelihood of successful resuscitation is low. Only 10 percent of patients with out-of-hospital arrest and initial asystole survive until hospital admission and only up to two percent until hospital discharge.

Intravenous Drug Administration during Out-of-Hospital Cardiac Arrest: A Randomized Trial
Olasveengen TM, Sunde K, et al.
JAMA
2009;302(20):2222

This study prefaces its data by emphasizing a poorly disseminated concept: Intravenous drug administration in cardiac arrest is included in ACLS guidelines despite the lack of evidence of improved outcomes. Millions of patients worldwide have received and continue to receive ACLS medications, particularly epinephrine, with little or no evidence of improved survival to hospital discharge. It is known that epinephrine will rapidly increase cerebral and coronary perfusion by redirecting peripheral blood flow, but the initial drug benefit may quickly wane, resulting in an increased concern for myocardial dysfunction and disturbed or truncated cerebral microcirculation after the cardiac arrest patient has been resuscitated. The relatively low chance of survival among patients receiving epinephrine after out-of-hospital cardiac arrest was noted more than 10 years ago. (*Resuscitation* 2002;54[1]:37.)

As reported in nonrandomized studies and similar to other ACLS caveats in the literature, resuscitation drugs were never tested in any randomized controlled human studies or involved in any non-drug comparison group before they were incorporated into ACLS protocols. It may also be possible that inadequate CPR quality, often associated with stopping pristine CPR during drug administration, may also influence long-term outcome. Using data from this prospective randomized controlled trial of drug administration during out-of-hospital cardiac arrest, the authors compared outcomes for patients receiving standard ACLS interventions with patients receiving similar ACLS but not intravenous drug administration.

The study was conducted in Oslo, Norway, and such a study would not likely be allowed in the United States currently because of the strong support for ACLS drugs for cardiac arrest. Out-of-hospital resuscitation in Norway was relatively sophisticated, often run by two paramedics and an anesthesiologist. CPR was performed in those with ventricular fibrillation for three minutes prior to the administration of electrical shock, and all patients were intubated during the study. Following hospital arrival post-resuscitation, therapeutic hypothermia was instituted regardless of the initial rhythm or arrest etiology. Those with a prehospital 12-lead EKG that suggested the possible need for coronary artery intervention were directly transferred for angiographic intervention.

Effect of Epinephrine on Out-of-Hospital Cardiac Arrest

	With Epinephrine	Without Epinephrine
Return of spontaneous circulation	18.3%	10.5%
Survival at one month	5.1%	7%
Survival with good or moderate cerebral performance	15.4%	21.3%
Survival with no or mild neurologic disability	6.2%	13.5%

Source: *JAMA* 2012;307(11):1161.

Patients were randomly placed into the intravenous versus no intravenous drug group just before resuscitation. Exclusion criteria included those who had an arrest witnessed by the ambulance crew, those whose resuscitation was initiated by physicians outside the ambulance team, or cardiac arrest because of asthma or anaphylactic shock. The primary outcome was survival to hospital discharge. A secondary outcome was one-year survival with a favorable neurological status.

The study included 851 randomized patients collected from 2003 to 2008. The rate of survival to hospital discharge was 10.5 percent for the intravenous drug and 9.2 percent for the non-drug administration group (P=0.61). Survival with a favorable neurologic outcome was likewise not statically significant, 9.8 percent for the drug treated group, 8.1 percent for the non-drug group (P=0.45). The rate of initial return of spontaneous circulation was statistically significant at 32 percent for the drug-treated group versus 21 percent for the non-drug group (P=0.001). The authors said CPR quality was comparable and within recommended guidelines for both groups. The authors also attempted to adjust for the presence or absence of ventricular fibrillation, the response time interval, witnessed versus unwitnessed arrest, or arrest in a public location. No significant difference in survival to hospital discharge was seen for any of these subgroups.

The authors concluded that those given drugs had a higher rate of short-term survival for patients who received no ACLS intravenous drug administration following outpatient cardiac arrest versus patients with standard intravenous drug administration. But no significant improvement was shown between the two groups in survival to hospital discharge or long-term survival. These two factors were inconsequential because there was an equal distribution of therapeutic hypothermia and coronary intervention. Most of the deaths were caused by persistent brain damage.

No difference was seen in short-term or long-term outcomes in patients with an initial rhythm of ventricular fibrillation or pulseless ventricular tachycardia. There

was, however, a higher rate of return of spontaneous circulation in those with asystole or pulseless electrical activity with medications but no difference in long-term outcomes.

Comment: It is difficult to control for all of the variables present in any ACLS study. The downtime is always most difficult to determine, and prolonged downtime has always been associated with a poorer outcome. These authors said their study was the first attempt to scientifically evaluate the effects of intravenous drug administration on the outcome of patients with out-of-hospital cardiac arrest. They attempted to determine if removing ACLS drug therapy would improve survival to discharge. They concluded that short-term survival was higher following use of intravenous ACLS drugs, but the universally applied drug interventions did not result in statistically significant improvement in final outcome.

Unlike some other reports of a worsened final outcome with epinephrine, this study did not conclude that epinephrine was an independent predictor of a poor outcome, but the researchers said their study was consistent with other reports that found no difference in survival after implementation of standard ACLS drugs during out-of-hospital cardiac arrest. Apparently, the only drugs used were epinephrine, atropine, and amiodarone. The drugs currently suggested by the American Heart Association are only epinephrine/vasopressin or amiodarone. Epinephrine and vasopressin, both arterial vasoconstrictors, have similar results, and are interchangeable per the guidelines.

It's always heartening to see an initial return of spontaneous circulation (ROSC), but it has been suggested that the negative resuscitation effects of epinephrine negate any short-term benefit of ROSC produced by this medication. The authors do note, like many others, that epinephrine does have substantial downsides following cardiac arrest, particularly on cerebral microcirculation.

This study is relatively good evidence to negate the previously accepted axiom that the routine use of empiric medications during prehospital cardiac arrest is helpful and not harmful. No prior prospective data show that ACLS drugs are helpful, and this study, which actually looked at long-term outcomes, indicates that epinephrine, in particular, is of no benefit to long-term survival.

One usually feels that ROSC signifies a better outcome or at least a better chance that the patient will have long-term survival. ROSC in the ED or ambulance, however, does not actually mean much. It appears to be easily accomplished with ACLS and medications. Long-term survival can't be achieved without first restoring circulation, but current drugs used to obtain this may produce subsequent irreversible cerebral damage.

This study had a few problems, but likely the perturbations will be of no significance. The ambulance personnel were not blinded to the randomization, and the use of medications may have been dictated by EMS preference. The quality of CPR could not be universally assessed, but the authors said there was no significant difference between the CPR data that were available for analysis. The study also lacked reliable timing for drug administration, so the time from cardiac arrest to intervention was not investigated because many of the cases were unwitnessed cardiac arrest.

De-emphasis on Devices and ACLS Drugs during Cardiac Arrest

"At the time of the 2010 International Consensus Conference, there were still insufficient data to demonstrate that any drugs or mechanical CPR devices improve long-term outcome after cardiac arrest. Clearly further studies, adequately powered to detect clinically important outcome differences with these interventions, are needed."

Source: *Circulation* 2010;122(18 Suppl 3):S640.

Prehospital Epinephrine Use and Survival among Patients with Out-of-Hospital Cardiac Arrest
Hagihara A, Hasegawa M, et al.
JAMA
2012;307(11):1161

This article is similar to the previous one in evaluating the association between epinephrine use before hospital arrival and short- and long-term mortality in patients with cardiac arrest. It was done in Japan, and analyzed data from more than 400,000 patients during a three-year period. The EMS time-to-arrival from first call averaged about seven minutes, and the average patient age was 72 years. The authors could not control for a variety of parameters, but they could assess the effectiveness of epinephrine use during CPR. Similar to the previous reports, they concluded that epinephrine is not beneficial for one-month survival, even though there was a significant improved likelihood of achieving ROSC in those given the drug. Epinephrine was given in this study for all causes of cardiac arrest after verifying the absence of a pulse in the carotid artery. The parameters studied were the return of spontaneous circulation before hospital arrival, survival at one-month post-arrest, survival with good or moderate cerebral performance, and survival with no, mild, or moderate CNS adverse outcomes.

Like other studies, ROSC before hospital arrival was observed more commonly in patients given epinephrine than in the non-epinephrine group (18.5% versus 5.7%, $P < 0.001$). Importantly, in all of the other parameters studied, the use of epinephrine resulted in a statistically significant decrease in patients with one-month survival, those with survival with mild to moderate cerebral performance, and those who survived with no and mild neurological disability. Epinephrine administration also had a negative effect in all final outcome parameters studied. The negative association between prehospital epinephrine and long-term outcome variables suggests that there was a decreased chance of ultimate survival and good functional outcome despite an increased chance of ROSC with epinephrine.

Comment: This is another study indicating that epinephrine might make medical providers feel better during the initial evaluation and treatment of cardiac arrest, but worse in the long run because it has no proven value. That by itself is not a catastrophic effect, but epinephrine was actually associated with worse neurological outcome. Per the AHA, no drug has been proven to increase survival rates in cardiac arrest. Although downsides and lack of benefit of drugs are mentioned in the 2010 CPR guidelines, one wonders why the American Heart Association has not focused on these studies, and amended its recommendation that still includes empiric epinephrine/vasopressin or amiodarone.

I remember giving very high doses of epinephrine with a better initial ROSC more than 20 years ago. It was not uncommon to give 5 mg/5 amps of epinephrine to someone in asystole, and see at least an initial return of circulation in many. When this was followed up, it did not have any beneficial

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Learning Objectives for This Month's CME Activity: After participating in this CME activity, readers should be better able to identify the pitfalls of ACLS drugs during out-of-hospital cardiac arrest.

ACLS Drugs

Continued from previous page

effect on long-term survival and was subsequently abandoned. Likewise, any benefit from bicarbonate, lidocaine, atropine, calcium, and glucocorticoids has not been demonstrated.

These two articles, and a number of others, are unsettling. It appears that there are significant data suggesting that the use of epinephrine in cardiac arrest is detrimental, even though drugs may result in a transient pulse and a heartbeat. A worsened final outcome, despite an initial benefit, may be reversed with some yet to be suggested interventions provided post-arrest. Perhaps some cerebral vasodilator may prove useful in derailing the subsequent adverse effects of epinephrine used in resuscitation. Given the tremendous time, effort, and expense required for patients resuscitated from cardiac arrest, a good neurological outcome is still in the single percentage numbers. Overall, only about 10 percent of prehospital cardiac arrest patients are ever discharged, many of whom are markedly impaired neurologically.

Time-to-treatment is probably the most sensitive predictor of a good outcome. There is at least a three-to-five percent drop in survival rate for each minute of untreated VF. The best scenario is for someone to have VT/VF, immediate CPR, only a few minutes for EMS response time, and rapid defibrillation.

I remember a malpractice case where an emergency physician was found to have committed malpractice because he delayed epinephrine use in an in-house cardiac arrest. Having to respond from the ED to in-hospital arrests is bad enough, but that was an absurd verdict then. Now data indicate that the outcome would likely have been better had no epinephrine been used.

Whether recent information will change the American Heart Association recommendations is questionable, but one can certainly not be faulted for failing to routinely administer epinephrine in patients who have had lack of ROSC from paramedic interventions. Patients who arrive in asystole are probably best left alone unless there are extenuating circumstances, such as hypothermia, drowning, young child, or lack of any ACLS interventions. It does no good to resuscitate an 80-year-old nursing home patient who hangs on for three to five days while the family is offered false hope, and many thousands of dollars are spent on useless interventions with no hope of viable long-term outcome. **EMN**

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Dr. Roberts *is a professor of emergency medicine and toxicology at the Drexel University College of Medicine in Philadelphia. Read the Procedural Pause, a blog by Dr. Roberts and his daughter, Martha Roberts, ACNP, CEN, at* http://bit.ly/ProceduralPause, *and read his past columns at* http://bit.ly/RobertsInFocus.

In Brief

Public Housing Type Predicts Kids' ED Use

Children living in San Francisco public housing that has not been redeveloped are 39 percent more likely to visit EDs repeatedly, according to new research from UC-San Francisco and UC-Berkeley.

Researchers looked at the number of children under 18 with public insurance who sought emergency care from any of three large San Francisco medical systems —San Francisco General Hospital, UCSF Medical Center, and Sutter Health — and linked that information to whether they lived in public housing that had not been redeveloped, in redeveloped HOPE VI public housing, or in nonpublic housing in the same neighborhood as public housing. HOPE VI, an initiative by the U.S. Department of Housing and Urban Development, is revitalizing the worst public housing projects in the country into mixed-income developments.

The study found that low-income children in redeveloped HOPE IV public housing were less likely to have repeat ED visits than peers living in older public housing, which suggests that investing in physical infrastructure may foster better health and reduce spending on acute care services.

Researchers weren't able to tell what aspects of housing were factors for children seeking emergency care, but they are currently doing more in-depth analysis to better understand how health conditions differ by housing type. Read the abstract: http://bit.ly/1uIGFzo.

Reader Feedback: Readers are invited to ask specific questions and offer personal experiences, comments, or observations on InFocus topics. Literature references are appreciated. Pertinent responses will be published in a future issue. Please send comments to emn@lww.com.

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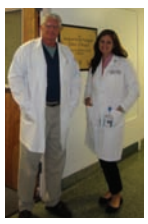
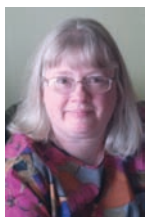


New Blog Post! By James R. Roberts, MD, & Martha Roberts, ACNP, CEN
This month in the Procedural Pause blog: **Abscess Drainage, Part 2**

New Podcast! By Ryan Stanton, MD
This month in the Everyday Medicine for Physicians Podcast: **How to be Media Savvy**

New Videos! By Larry Mellick, MD
This month in M2E Too! Mellick's Multimedia Edublog with Video: **Emergency Medicine Procedures You Should Know**

New Blog Post! By Rick Pescatore, DO
Read Little White Coats to follow Dr. Pescatore as he starts his emergency medicine residency.



New Blog Post! By Loice Swisher, MD
Don't think zebras; think Lions and Tigers and Bears, a new blog that exposes the cases out there ready to bite. This month: **We All Fall Down**

New Blog Post! By Gregory S. LaSala, MD, Rita G. McKeever, MD, & Jolene Okaneku, MD
Case reports from The Tox Cave by three EPs doing medical toxicology fellowships.

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Intravenous Drug Administration During Out-of-Hospital Cardiac Arrest

A Randomized Trial

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Context Intravenous access and drug administration are included in advanced cardiac life support (ACLS) guidelines despite a lack of evidence for improved outcomes. Epinephrine was an independent predictor of poor outcome in a large epidemiological study, possibly due to toxicity of the drug or cardiopulmonary resuscitation (CPR) interruptions secondary to establishing an intravenous line and drug administration.

Objective To determine whether removing intravenous drug administration from an ACLS protocol would improve survival to hospital discharge after out-of-hospital cardiac arrest.

Design, Setting, and Patients Prospective, randomized controlled trial of consecutive adult patients with out-of-hospital nontraumatic cardiac arrest treated within the emergency medical service system in Oslo, Norway, between May 1, 2003, and April 28, 2008.

Interventions Advanced cardiac life support with intravenous drug administration or ACLS without access to intravenous drug administration.

Main Outcome Measures The primary outcome was survival to hospital discharge. The secondary outcomes were 1-year survival, survival with favorable neurological outcome, hospital admission with return of spontaneous circulation, and quality of CPR (chest compression rate, pauses, and ventilation rate).

Results Of 1183 patients for whom resuscitation was attempted, 851 were included; 418 patients were in the ACLS with intravenous drug administration group and 433 were in the ACLS with no access to intravenous drug administration group. The rate of survival to hospital discharge was 10.5% for the intravenous drug administration group and 9.2% for the no intravenous drug administration group ($P=.61$), 32% vs 21%, respectively, ($P<.001$) for hospital admission with return of spontaneous circulation, 9.8% vs 8.1% ($P=.45$) for survival with favorable neurological outcome, and 10% vs 8% ($P=.53$) for survival at 1 year. The quality of CPR was comparable and within guideline recommendations for both groups. After adjustment for ventricular fibrillation, response interval, witnessed arrest, or arrest in a public location, there was no significant difference in survival to hospital discharge for the intravenous group vs the no intravenous group (adjusted odds ratio, 1.15; 95% confidence interval, 0.69-1.91).

Conclusion Compared with patients who received ACLS without intravenous drug administration following out-of-hospital cardiac arrest, patients with intravenous access and drug administration had higher rates of short-term survival with no statistically significant improvement in survival to hospital discharge, quality of CPR, or long-term survival.

Trial Registration clinicaltrials.gov Identifier: NCT00121524

JAMA. 2009;302(20):2222-2229 www.jama.com

INTRAVENOUS ACCESS AND DRUG ADministration are integral parts of cardiopulmonary resuscitation (CPR) guidelines.[1] Millions of patients have received epinephrine during advanced cardiac life support (ACLS) with little or no evidence of improved survival to hospital discharge.[1,2] The use of epinephrine is based on preclinical evidence of increased cerebral and coronary perfusion by redirected peripheral blood flow.[1,2] Beneficial short-term effects of epinephrine have been shown in animal studies,[3-5] but there is increasing concern for increased myocardial dysfunction[6,7] and disturbed cerebral microcirculation after cardiac arrest.[8] Epinephrine was an independent predictor of poor outcome in a large retrospective registry study,[9] but this observational, nonrandomized study cannot prove a causal relationship. Despite its near-universal use, epinephrine has, to our knowledge, not been tested in a randomized controlled study with a no-drug comparison group.

If a negative association between epinephrine and survival is causal, it may be due to the drug or to inadequate CPR quality associated with drug adminis-

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tration. Drug administration includes time-consuming factors like establishing intravenous access, preparation, and administration of drugs and saline, thereby potentially removing focus from good-quality CPR. There are recent reports of poor-quality CPR and protocol adherence among professional CPR providers,[10,11] and some consider intubation and intravenous access more important than giving good-quality chest compressions.[12] With inadequate CPR quality, effects of drugs administered peripherally also may be diminished or absent.[13] Because there are no randomized controlled studies showing improved survival to hospital discharge with any drugs routinely administered during CPR, we concluded such a study was warranted.

In this prospective, randomized controlled trial of intravenous drug administration during out-of-hospital cardiac arrest, we compared outcomes for patients receiving standard ACLS with intravenous drug administration (control) and patients receiving ACLS without intravenous drug administration (intervention).

METHODS

The city of Oslo has a single-tiered emergency medical service system administered by the Oslo University Hospital for a population of 540 000. On weekdays between 7:30 AM and 10:00 PM, an ambulance staffed by 2 paramedics and an anesthesiologist functions on the same level as the regular paramedic-staffed ambulances. Until January 2006, ACLS was performed according to the International Guidelines 2000,[14] with the modification that patients with ventricular fibrillation received 3 minutes of CPR before the first shock and between unsuccessful series of shocks.[15] The European Resuscitation Council Guidelines for Resuscitation 2005[16] were implemented in January 2006, incorporating this same modification of 3-minute periods of CPR. Defibrillators in manual mode are used and endotracheal intubation is standard for securing the airways. Two ambulances are routinely dispatched for suspected cardiac arrest. The physician-staffed ambulance is dispatched whenever available.

All hospitals in Oslo have goal-directed postresuscitation protocols including therapeutic hypothermia regardless of initial rhythm or arrest etiology.[17] A prehospital 12-lead electrocardiogram is routinely transmitted to the cardiologist on call after return of spontaneous circulation (ROSC). If coronary angiography is indicated for possible percutaneous coronary intervention, patients are transported directly from the scene to 1 of 2 university hospitals (Oslo University Hospital, Ullevaal and Rikshopitalet) with this capacity 24 hours per day.

Study Design and Recruitment

All patients older than 18 years with nontraumatic, out-of-hospital cardiac arrests between May 1, 2003, and April 28, 2008, were randomized by ambulance personnel on-site. Simple randomization occurred directly after ambulance personnel confirmed the cardiac arrest and then opened the sealed envelopes provided by the investigators. Patients were randomized to receive either ACLS with access to intravenous drug administration (intravenous group) or ACLS without access to intravenous drug administration (no intravenous group). In the no intravenous group, intravenous access was to be established 5 minutes after ROSC, and drugs could then be given if indicated.

Exclusion criteria were (1) cardiac arrest witnessed by ambulance crew because these patients almost always have an intravenous needle in place at the time of the cardiac arrest, (2) resuscitation initiated or interrupted by physicians outside of the ambulance team, or (3) cardiac arrest induced by asthma or anaphylactic shock (which were the last criteria added in October 2006). The study was approved by the regional ethics committee. Informed consent for inclusion was waived as decided by this committee, but was required from survivors with 1-year follow-up.

Equipment and Data Collection

Standard defibrillators (LIFEPAK 12 Physio-Control, Medtronic, Redmond, Washington) were used. Electrocardiograms with transthoracic impedance signals from these defibrillators were routinely transferred to a server at the National Competence Center for Emergency Medicine (Oslo, Norway) following cardiac arrest. Utstein cardiac arrest forms[18] routinely completed by paramedics were submitted to the study supervisor along with a copy of the ambulance run sheet. Automated, computer-based dispatch center time records supplemented ambulance run sheets with regard to response intervals. For admitted patients, additional hospital records were obtained.

All trial data were documented according to the Utstein style.[18] The primary end point was survival to hospital discharge. Secondary outcomes were 1-year survival, survival with favorable neurological outcome (using cerebral performance categories from 1 to 4),[18] hospital admission with ROSC, and quality of CPR (ie, chest compression rate, pauses, and ventilation rate). The study was monitored annually with interim analysis by an external researcher who did not reveal any results to the investigators.

Data Processing

Data from each case were viewed and annotated using CODE-STAT 7.0 (Physio-Control, Medtronic) for detection of ventilations and chest compressions by changes in transthoracic impedance. Written information from patient report forms and locally adapted Utstein style forms were compared with typical changes in CPR patterns as shown using CODE-STAT 7.0. Initial rhythm assessment registered on patient report forms were confirmed by these electrocardiographic recordings if possible. Time without spontaneous circulation, time without compressions during time without spontaneous circulation (hands-off time), preshock pauses, compression rate and actual number of compressions, and ventilations per minute were calcu-

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lated for each episode. Hands-off ratio is defined as hands-off time divided by total time without ROSC. Electrocardiographic analysis was performed by 1 researcher (T.M.O.).

Statistical Analysis

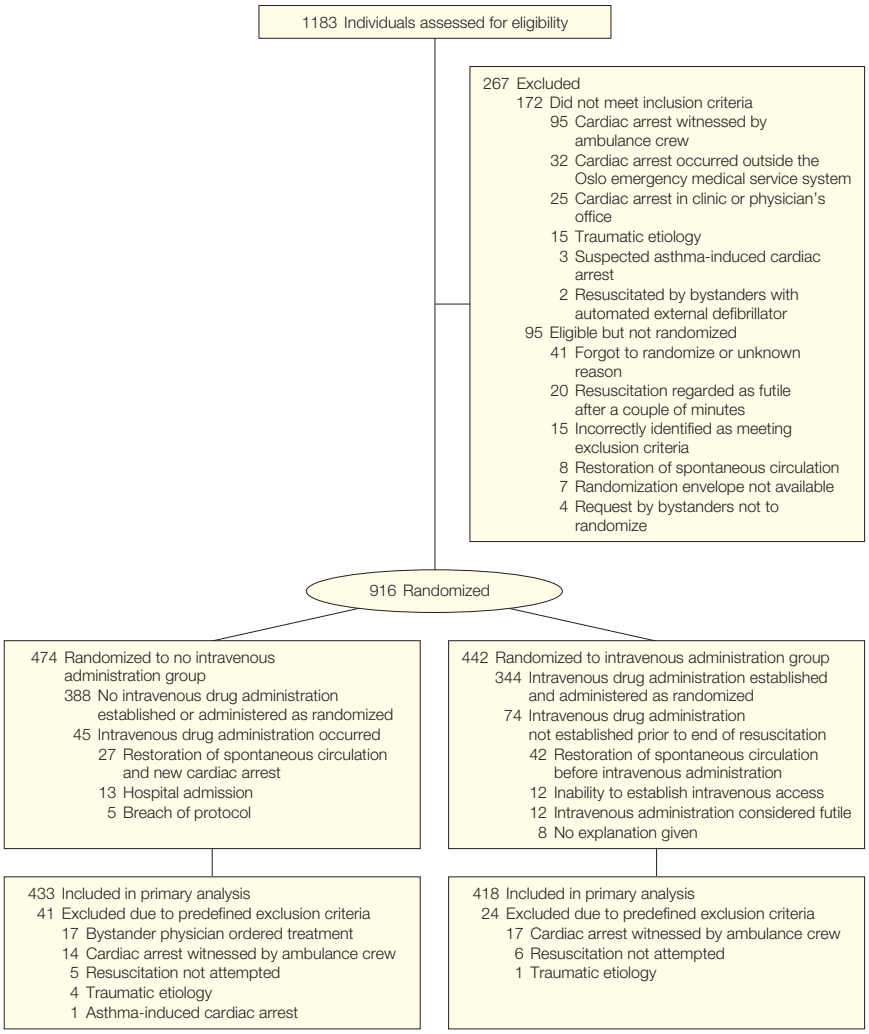
Initial power analysis was based on survival statistics for the Oslo emergency medical service system and assumed that the survival rate would be doubled among patients not receiving epinephrine, as described previously in an observational study.[9] With a projected survival rate of 7% in the intravenous group and 14% in the no intravenous group, 900 patients provided a power level of 91.4% with a type I error of 5%.[19]

Analysis was performed on an intention-to-treat basis regardless of which treatment was actually given. Patients who were initially randomized, but were later found to meet predefined exclusion criteria were not included in the intention-to-treat analysis. Demographic and clinical data are presented as means with 95% confidence intervals (CIs), medians with ranges, or proportions. Crude effects between the 2 trial groups and survival were quantified by odds ratios (ORs) with 95% CIs. The χ^2 test for contingency tables with different degrees of freedom was used to detect associations between categorical independent variables. For continuous variables, the *t* test was used for normally distributed data and the Mann-Whitney test was used for nonnormally distributed data.

Confounders were identified and quantified by using the Mantel-Haenszel test for both short-term and long-term survival, and subsequent manual backward-elimination procedures were performed. Correlations between potential confounders were investigated. Comparison of Kaplan-Meier survival curves was obtained using the Breslow and log-rank test statistics for short-term and long-term survival, respectively.[20,21]

Two-sided *P* values of less than .05 were considered significant. The statistical analyses were performed using the software packages SPSS version 15.0 and SamplePower version 2.0 (SPSS Inc, Chicago, Illinois) and Egret version 2.0.31 (Cytel Software Corporation, Cambridge, Massachusetts).

Figure 1. Randomization Profile



RESULTS

Resuscitation was attempted in 1183 patients who experienced cardiac arrest during the study period, and 851 of 946 eligible patients were successfully randomized with 418 patients in the intravenous group and 433 patients in the no intravenous access group. For reasons listed in FIGURE 1, 95 eligible patients were not randomized and further randomization and inclusion details are illustrated. Eligible, nonrandomized patients did not differ significantly from randomized patients with regard to demographic characteristics and outcomes.

Baseline demographic characteristics and CPR-quality parameters are listed in TABLE 1. Defibrillation was attempted in more patients in the intravenous group compared with the no intravenous group (47% vs 37%, respectively; OR, 1.16 [95% CI, 0.74-1.82]). More defibrillation shocks were delivered to those who received defibrillation in the intravenous group compared with the no intravenous group

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(median, 3 [range, 1-22] vs 2 [range, 1-26], respectively; $P=.008$). Both groups had adequate and similar CPR quality with few chest compression pauses (median hands-off ratio, 0.15 for the intravenous group and 0.14 for the no intravenous group) and the compression and ventilation rates were within the guideline recommendations (Table 1).

In the intravenous group, 44 of 418 patients (10.5%) survived to hospital discharge vs 40 of 433 (9.2%) in the no intravenous group (OR, 1.16; 95% CI, 0.74-1.82; $P=.61$). Survival with favorable neurological outcome was 9.8% for the intravenous group and 8.1% for the no intravenous group (OR, 1.24; 95% CI, 0.77-1.98; $P=.45$). Short-term survival was significantly better in the intravenous group than in the no intravenous group with 40% vs 25%, respectively, achieving ROSC (OR, 1.99; 95% CI, 1.48-2.67; $P<.001$), 43% vs 29% admitted to the hospital (OR, 1.81; 95% CI, 1.36-2.40; $P<.001$), and 30% vs 20% admitted to the intensive care unit (ICU) (OR, 1.67; 95% CI, 1.22-2.29; $P=.002$) (TABLE 2). In-hospital treatments, including therapeutic hypothermia and percutaneous coronary intervention, were equally distributed between the 2 groups. There were no differences in cause of death among patients admitted to the ICU and most deaths were due to brain damage (Table 2).

Patients were divided into 2 predefined subgroups based on their initial rhythms (TABLE 3). In patients with an initial rhythm of ventricular fibrillation or pulseless ventricular tachycardia, there were no differences in short-term or long-term outcomes. In the subgroup with nonshockable rhythms (initial rhythm of asystole or pulseless electrical activity), the ROSC rate was 3-fold higher with intravenous treatment ($P<.001$), but there was no difference in long-term outcome because the survival rate among those admitted to the ICU tended to be almost 3 times higher in the no intravenous group ($P=.07$; Table 3).

A public cardiac arrest location, response interval, and initial ventricular fibrillation were identified as potential confounders and were included in the logistic regression analysis. Multivariate logistic regression analyses for short-term survival (admitted to the ICU) and long-term survival (discharged from the hospital) were performed. After adjustment for confounders, patients in the intravenous group had a nonsignificant 15% increased chance of surviving to hospital discharge (adjusted OR [AOR], 1.15; 95% CI, 0.69-1.91) compared with patients in the no intravenous group. Patients with ventricular fibrillation or pulseless ventricular tachycardia as the initial rhythm had a 10-fold improvement in long-term survival (AOR, 10.47; 95% CI, 5.47-20.03). Patients with bystander-witnessed cardiac arrests or cardiac arrests in public places had a 2-fold improvement in long-term survival (AOR, 2.13 [95% CI, 1.02-4.45] and AOR, 2.03 [95% CI, 1.19-3.44], respectively), whereas the odds of long-term survival decreased by

Table 1. Demographics and Quality of Cardiopulmonary Resuscitation (CPR)[a]

	No Intravenous (n = 433)	Intravenous (n = 418)	*P* Value[b]
Age, mean (SD), y	64 (17)	64 (18)	.85
Male sex, No. (%)	303 (70)	302 (72)	.51
Cardiac etiology, No. (%)	305 (70)	300 (72)	.72
Location of arrest, No. (%)			
Home	238 (55)	237 (57)	.72
Public	159 (37)	144 (34)	.50
Other	34 (8)	37 (9)	.70
Bystander witnessed, No. (%)	273 (63)	283 (68)	.18
Bystander basic life support, No. (%)	274 (63)	261 (62)	.86
Initial rhythm, No. (%)			
Ventricular fibrillation or pulseless ventricular tachycardia	142 (33)	144 (34)	.66
Asystole	228 (53)	192 (46)	.06
Pulseless electrical activity	63 (15)	82 (20)	.06
Physician-staffed ambulance present	160 (37)	157 (38)	.91
Response interval, mean (95% CI), min	10 (9-10)	10 (9-10)	.28
Intubation, No. (%)	363 (84)	368 (88)	.10
Intravenous drugs during resuscitation, No. (%)	42 (10)	343 (82)	<.001
Epinephrine	37 (9)	330 (79)	<.001
Atropine	20 (5)	194 (46)	<.001
Amiodarone	17 (4)	69 (17)	<.001
Defibrillation	160 (37)	194 (46)	.005
No. of shocks when defibrillated, median (range)	2 (1-22)	3 (1-26)	.008
Electrocardiogram available for analysis, No. (%)	329 (76)	314 (75)	.83
CPR duration, mean (95% CI), min	18 (17-19)	22 (20-23)	<.001
Hands-off ratio, median (range)[c]	0.14 (0.01-0.59)	0.15 (0.02-0.89)	.16
Compression rate, mean (95% CI)[d]	116 (115-117)	117 (116-119)	.12
Compressions, mean (95% CI), min^{-1} [e]	94 (93-96)	94 (92-96)	.90
Ventilations, mean (95% CI), min^{-1} [e]	11 (10-11)	11 (11-11)	.48
Preshock pause, median (range), s	11 (1-74)	12 (1-82)	.58

Abbreviation: CI, confidence interval.
[a] Data are missing for 80 patients in the group with advanced cardiac life support without intravenous access or administration (no intravenous) and 79 patients in the group with advanced cardiac life support and intravenous access and administration of drugs (intravenous).
[b] The differences between groups were analyzed using the χ^2 test with continuity correction for categorical data and the *t* test or Mann-Whitney test for continuous data as appropriate.
[c] Indicates the proportion of time without chest compressions during the resuscitation effort.
[d] Indicates the rate of compressions when delivered.
[e] Indicates the average number of compressions actually given per minute during the resuscitation effort.

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17% for each minute of prolonged response interval (AOR, 0.83; 95% CI, 0.77-0.90). When adjusted for the same confounding factors, survival to ICU admission was higher for patients in the intravenous group (AOR, 1.78; 95% CI, 1.26-2.51).

The cumulative postcardiac arrest survival rate at 7 days was 14.6% (95% CI, 11.3%-17.9%) for patients in the intravenous group vs 12.8% (95% CI, 9.7%-15.9%) for patients in the no intravenous group, 11.3% (95% CI, 8.4%-14.2%) vs 8.8% (95% CI, 6.1%-11.5%), respectively, at 1 month, and 9.8% (95% CI, 6.9%-12.7%) vs 8.4% (95% CI, 5.9%-10.9%) at 1 year (FIGURE 2). Short-term survival was significantly higher for patients in the intravenous group compared with patients in the no intravenous group (Breslow $P = .004$), although there was no difference in long-term survival (log-rank $P = .23$)

COMMENT

Our results represent the first attempt, to our knowledge, to evaluate the effect of intravenous access and intravenous drug administration on outcome in patients with an out-of-hospital cardiac arrest. Short-term survival was higher in the intravenous group, but these nearly universally applied interventions were not associated with a statistically significant improvement in survival to hospital discharge.

Administration of intravenous drugs did not appear to interfere with the quality of CPR. Ambulance personnel delivered good-quality CPR with few pauses and with rates within guideline recommendations[1] in both groups. This is important because potential improvements in intravenous medication administration during ACLS will not need to overcome an intrinsic tendency to degrade CPR.

We did not confirm the previous observational finding that intravenous epinephrine was an independent predictor for poor outcome.[9] Our results are consistent with a multicenter study by Stiell et al[22] that found no difference in survival after implementing intravenous drug administration during out-of-hospital cardiac arrest (OR, 1.1; 95% CI, 0.8-1.5).

Without differences in the predefined primary outcome, patients in the intravenous group received more defibrillations, were resuscitated for a longer period, and more frequently had ROSC. With similar and adequate CPR quality, this is likely due to the pharmacological effects of the drugs used (epinephrine, atropine, and/or amiodarone). This finding is consistent with previous animal studies with epinephrine,[6,7] and clinical studies evaluating the effects of amiodarone,[23] atropine,[24] and even high-dose epinephrine,[25] all of which documented improved short-term effects without improving long-term outcomes. While epinephrine can produce more spontaneously beating hearts in animal models, it is also associated with increased postresuscitation myocardial dysfunction that might partly explain these clinical observations.[6,7] Negative postresuscitation effects of epinephrine also are reported to be more prominent after longer, more clinically relevant cardiac arrest periods (eg, 4-6 minutes) than short cardiac arrest periods (eg, 2 minutes).[7] Moreover, an experimental study has recently documented detrimental effects of epinephrine on cerebral microcirculation.[8]

The clinical implications of an increased ROSC rate in the intravenous group are difficult to interpret. Should improved short-term outcome be regarded as unfulfilled potential that

Table 2. In-Hospital Treatment and Outcome

	No Intravenous (n = 433)	Intravenous (n = 418)	*P* Value[a]
Any ROSC during resuscitation	107 (25)	165 (40)	<.001
Admitted to hospital	126 (29)	178 (43)	<.001
ROSC	89 (21)	133 (32)	<.001
Ongoing CPR	37 (9)	45 (11)	.33
Admitted to ICU[b]	88 (20)	125 (30)	.002
Awake at ICU admission	8 (9)	7 (6)	.48
Therapeutic hypothermia	62 (70)	90 (72)	.93
Angiography or PCI	43 (49)	50 (40)	.33
Time in ICU, median (range), d[c]	6 (1-31)	4 (1-44)	.05
Cause of death in ICU[d]			
Brain	29 (69)	52 (70)	>.99
Cardiac	8 (19)	12 (16)	.90
Multiorgan failure	5 (12)	10 (14)	>.99
Discharged alive	40 (9.2)	44 (10.5)	.61
Cerebral performance score at discharge			
1 (good cerebral performance)	30 (7.0)	37 (8.9)	.31
1-2 (good cerebral performance to moderate cerebral disability)	35 (8.1)	41 (9.8)	.45
2 (moderate cerebral disability)	5 (1.2)	4 (1.0)	>.99
3 (severe cerebral disability)	3 (1.0)	3 (1.0)	>.99
4 (coma or vegetative state)	2 (<1.0)	0	.50
Discharged from hospital if admitted to ICU	40 (45)	44 (35)	.17
Alive 1 y after cardiac arrest[e]	36 (8)	41 (10)	.53

Abbreviations: CPR, cardiopulmonary resuscitation; ICU, intensive care unit; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation.

[a] The differences between groups were analyzed using the χ^2 test with continuity correction for categorical data and the Mann-Whitney test for number of days in the ICU.

[b] Includes patients admitted to the ICU only.

[c] Data are missing for 3 patients in each group.

[d] Includes patients who died in the ICU only. Data are missing for 6, leaving 42 as the denominator in the group with advanced life support without intravenous accss or drug administration (no intravenous), and 7, leaving 74 as the denominator in the group with advanced cardiac life support and intravenous access and administration of drugs (intravenous).

[e] Two patients in the no intravenous group and 1 patient in the intravenous group were lost to 1-year follow-up.

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Table 3. Outcome for Subgroups With and Without Ventricular Fibrillation or Pulseless Ventricular Tachycardia Rhythms

	With Rhythms, No. (%)			Without Rhythms		
	No Intravenous (n = 142)	Intravenous (n = 144)	*P* Value[a]	No Intravenous (n = 291)	Intravenous (n = 274)	*P* Value[a]
Any ROSC during resuscitation	75 (53)	85 (59)	.35	32 (11)	80 (29)	<.001
Admitted to hospital	79 (56)	94 (65)	.12	47 (16)	84 (31)	<.001
Admitted to ICU	60 (42)	74 (51)	.15	28 (10)	51 (19)	.003
Discharged alive	32 (23)	39 (27)	.45	8 (3)	5 (2)	.65
Discharged with CPC score of 1-2	29 (20)	37 (26)	.36	6 (2)	4 (2)	.82
Discharged if admitted to ICU	32 (53)	39 (53)	>.99	8 (29)	5 (10)	.07

Abbreviations: CPC, cerebral performance score; ICU, intensive care unit; ROSC, return of spontaneous circulation.
[a]The differences between the groups were analyzed using the χ^2 test with continuity correction.

might be addressed with better post-ROSC care, or unproductive resuscitation of patients whose vital organ injury makes them unlikely candidates for long-term survival? In the present study, most patients who died in the hospital after initial successful resuscitation in both groups had severe cerebral damage. If present pharmacological interventions only facilitate cardiac resuscitation in patients who will ultimately experience irreversible cerebral damage, this may cause an additional burden on already overburdened ICUs.

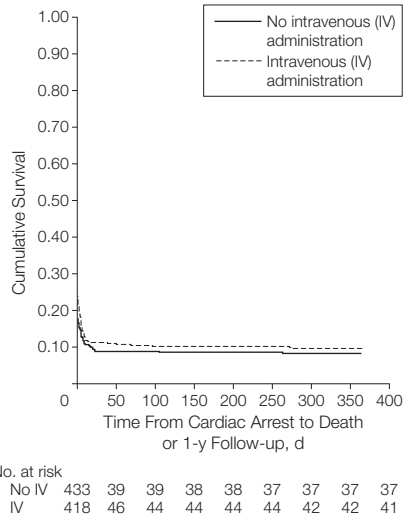
However, long-term survival cannot be achieved without first restoring circulation. Improved brain-directed postresuscitation treatment might at some point prevent irreversible cerebral damage and increase survival. At present, the only established brain-directed treatment is therapeutic hypothermia,[26,27] and the rate of which was high in both groups (71% and 72%). It is possible that for some patients in our study with early postresuscitation cardiac death, advanced options such as mechanical chest compression devices,[28] extracorporeal membrane oxygenation,[29] or left ventricular assist devices[30] could enable corrective treatment of underlying causes and theoretically improve survival.

The results of our study highlight the question of whether patients presenting with initial shockable rhythms and nonshockable rhythms should be treated differently. Initial shockable rhythm was a potential effect modifier in our statistical analysis, indicating that the degree of benefit or harm of intravenous drug administration during cardiac arrest may depend on the presenting rhythm. No differences in outcome were found for patients with shockable rhythms, while patients with nonshockable rhythms had higher rates of ROSC in the intravenous group, but an opposite tendency toward a lower rate of survival to hospital discharge among those admitted to the hospital. This suggests that late toxicity after intravenous drug administration contributes importantly to the poor outcomes of these patients.

Several studies have identified dissimilar etiologies in subgroups with shockable and nonshockable rhythms,[31-33] and it seems reasonable that differences in treatment strategies will emerge.[34] Retrospective subgroup analysis for cardiac arrest times (<5 minutes, 5-10 minutes, or >10 minutes) did not reveal any suggestive information either alone or combined with initial rhythm (data not presented but available from authors upon request). However, our study was not powered for formal subgroup analysis and no conclusions should be drawn.

The present data indicating good-quality CPR in both groups suggest that the lack of improved long-term outcome with ACLS with intravenous drug administration cannot be explained by poor-quality CPR.[13] This does not exclude the possibility that other drug regimens might improve outcome. Early administration, as recently advocated,[35,36] must be evaluated in systems with shorter ambulance response intervals or other intravenous drug regimens and priorities that are different from the present guidelines.

Figure 2. Cumulative Survival for Up to 1 Year After Cardiac Arrest



Our study has several limitations. First, ambulance personnel could not be blinded to the randomization. Closely related to this, only patients who were randomized to the no intravenous group could be monitored with regard to protocol compliance. If intravenous drugs were administered to a patient in the no intravenous group, violation of the study protocol could be documented. If intravenous drugs were not administered to a patient in the intravenous group, several valid reasons could exist, such as rapid ROSC. We have no reason to believe that personnel refrained from establishing intra-

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venous access under the pretense that the procedure was unsuccessful. The ambulance personnel involved were strongly committed to testing the hypothesis presented, but we cannot totally rule out possible bias toward procedures such as intravenous access and administration of drugs, which have been important in Norwegian culture for decades.

Second, quality of CPR could only be assessed in 75% of cases. Still, this is, to our knowledge, the first clinical intervention study reporting CPR quality data, and no significant differences were found between these data and those unavailable for analysis. Also, we do not have reliable time points for drug administration. Paramedics in the Oslo emergency medical service system are highly trained and both the guidelines and training emphasize early intravenous access and drug administration and intubation with the shortest possible pauses in chest compressions.

Third, this is a single center study and the results may not be generalized to systems with different training, infrastructure, treatment protocols, or quality of CPR. Fourth, while time from cardiac arrest to the initiation of ACLS is important for patient survival, the estimated time of cardiac arrest is imprecise and one-third of the cardiac arrests were unwitnessed. This variable is therefore not included in the anlysis. Only the emergency medical service response interval was included.

Finally, a type II error cannot be ruled out. Although based on the best available evidence at the time,[9] the power analysis was, in retrospect, optimistic in assuming a doubling in survival for the patients in the no intravenous group. For the observed difference between the groups to be statistically significant, a sample size of 14 000 patients would be needed. Because this sample size has not been considered inappropriate in cardiovascular interventions, our results could be background for such a large study that could be positive for intravenous access and drug administration. At a minimum, our results indicate that clinical equipoise exists on the efficacy of intravenous drugs in the treatment of cardiac arrest and that more definitive trials could be ethically undertaken. Alternatively, the poor survival rates after cardiac arrest, which do not seem to be significantly improved by intravenous drug administration, indicate that research should be directed at new pharmacological interventions that hold promise of greater effect.

CONCLUSION

Despite improved short-term survival among patients randomized to receive intravenous access and drug administration, these nearly universal interventions were not associated with a statistically significant improvement in survival to hospital discharge. Larger trials examining resuscitation without intravenous access and drug administration, as well as of existing or new drugs, appear to be justified.

Author Contributions: Dr Olasveengen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Thowsen, Steen, Wik.
Acquisition of data: Olasveengen, Thowsen, Wik.
Analysis and interpretation of data: Olasveengen, Sunde, Brunborg, Steen.
Drafting of the manuscript: Olasveengen, Sunde, Steen.
Critical revision of the manuscript for important intellectual content: Brunborg, Thowsen, Wik.
Statistical analysis: Olasveengen, Brunborg.
Obtained funding: Steen.
Administrative, technical, or material support: Thowsen, Wik.
Study supervision: Sunde, Brunborg, Steen, Wik.
Financial Disclosures: Dr Olasveengen reported receiving speakers' fees from Medtronic (Oslo, Norway) and research support from Laerdal Medical Corporation (Stavanger, Norway). Dr Steen reported being a member of the board of directors for Laerdal Medical and the Norwegian Air Ambulance. Dr Wik reported being on a medical advisory board for Physio-Control, consulting for Laerdal, Zoll, and Jolife, and being a principle investigator for a multicenter mechanical chest compression device study sponsored by Zoll. Dr Sunde, Ms Brunborg, and Mr Thowsen did not report any financial disclosures.
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Additional Contributions: Martin Samdal assisted in data collection as required research exposure as a medical student at the University of Oslo and did not receive any financial compensation for his work. Andres Neset is enrolled in a combined MD/PhD program at the University of Oslo and assisted with data analysis and did not receive any financial compensation for his work. Morten Pytte, MD, PhD, provided useful feedback in preparing the manuscript and did not receive any financial compensation for his work. Knut Arvid Kirkebøen, MD (University of Oslo), provided useful feedback in preparing the manuscript and did not receive any financial compensation for his work. Norman Paradis, MD (vice president and chief medical officer at Zoll Circulation), provided useful feedback and advice in preparing the manuscript and did not receive any financial compensation for his work. We thank all of the physicians and paramedics working in the Oslo emergency medical service system.

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I have learned throughout my life as a composer chiefly through my mistakes and pursuits of false assumptions, not by my exposure to founts of wisdom and knowledge.

—Igor Stravinsky (1882-1971)

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Prehospital Epinephrine Use and Survival Among Patients With Out-of-Hospital Cardiac Arrest

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Context Epinephrine is widely used in cardiopulmonary resuscitation for out-of-hospital cardiac arrest (OHCA). However, the effectiveness of epinephrine use before hospital arrival has not been established.

Objective To evaluate the association between epinephrine use before hospital arrival and short- and long-term mortality in patients with cardiac arrest.

Design, Setting, and Participants Prospective, nonrandomized, observational propensity analysis of data from 417 188 OHCAs occurring in 2005-2008 in Japan in which patients aged 18 years or older had an OHCA before arrival of emergency medical service (EMS) personnel, were treated by EMS personnel, and were transported to the hospital.

Main Outcome Measures Return of spontaneous circulation before hospital arrival, survival at 1 month after cardiac arrest, survival with good or moderate cerebral performance (Cerebral Performance Category [CPC] 1 or 2), and survival with no, mild, or moderate neurological disability (Overall Performance Category [OPC] 1 or 2).

Results Return of spontaneous circulation before hospital arrival was observed in 2786 of 15 030 patients (18.5%) in the epinephrine group and 23 042 of 402 158 patients (5.7%) in the no-epinephrine group ($P<.001$); it was observed in 2446 (18.3%) and 1400 (10.5%) of 13 401 propensity-matched patients, respectively ($P<.001$). In the total sample, the numbers of patients with 1-month survival and survival with CPC 1 or 2 and OPC 1 or 2, respectively, were 805 (5.4%), 205 (1.4%), and 211 (1.4%) with epinephrine and 18 906 (4.7%), 8903 (2.2%), and 8831 (2.2%) without epinephrine (all $P<.001$). Corresponding numbers in propensity-matched patients were 687 (5.1%), 173 (1.3%), and 178 (1.3%) with epinephrine and 944 (7.0%), 413 (3.1%), and 410 (3.1%) without epinephrine (all $P<.001$). In all patients, a positive association was observed between prehospital epinephrine and return of spontaneous circulation before hospital arrival (adjusted odds ratio [OR], 2.36; 95% CI, 2.22-2.50; $P<.001$). In propensity-matched patients, a positive association was also observed (adjusted OR, 2.51; 95% CI, 2.24-2.80; $P<.001$). In contrast, among all patients, negative associations were observed between prehospital epinephrine and long-term outcome measures (adjusted ORs: 1-month survival, 0.46 [95% CI, 0.42-0.51]; CPC 1-2, 0.31 [95% CI, 0.26-0.36]; and OPC 1-2, 0.32 [95% CI, 0.27-0.38]; all $P<.001$). Similar negative associations were observed among propensity-matched patients (adjusted ORs: 1-month survival, 0.54 [95% CI, 0.43-0.68]; CPC 1-2, 0.21 [95% CI, 0.10-0.44]; and OPC 1-2, 0.23 [95% CI, 0.11-0.45]; all $P<.001$).

Conclusion Among patients with OHCA in Japan, use of prehospital epinephrine was significantly associated with increased chance of return of spontaneous circulation before hospital arrival but decreased chance of survival and good functional outcomes 1 month after the event.

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EPINEPHRINE IS WIDELY USED IN cardiopulmonary resuscitation (CPR) for patients with out-of-hospital cardiac arrest (OHCA).[1-3] However, its effectiveness in CPR has not been established. Epinephrine is associated with increased myocardial oxygen consumption and ventricular arrhythmias during the period after resuscitation.[4] Concern has been raised regarding increased myocardial dysfunction[5,6] and disturbed cerebral microcirculation after cardiac arrest.[7] Findings in support of epinephrine use include animal studies that show a beneficial short-term effect of epinephrine,[8,9] and evidence of increased cerebral and coronary perfusion by redirected peripheral blood flow has been reported.[10,11]

To verify the effectiveness of epinephrine in CPR, the influences of other factors, such as patients, bystanders, CPR by bystanders, life support by emergency medical service (EMS) personnel, and time from call to the scene or hospital arrival, need to be controlled. To control for the effects of covariates, a randomized controlled trial needs to be performed. However, such a study is not easily performed because of ethical reasons.

For editorial comment see p 1198.

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As for the effectiveness of epinephrine use in CPR, a large, retrospective registry study in Sweden reported that epinephrine is an independent predictor of mortality.[12] A large, observational before-after study in Singapore showed that epinephrine is not beneficial for immediate or 1-month survival.[13] Recently, 2 randomized controlled trials showed that patients receiving adrenaline during cardiac arrest had no statistically significant improvement in survival to hospital discharge, although there was a significantly improved likelihood of achieving return of spontaneous circulation (ROSC).[14,15] These studies were limited by several methodological problems, such as the use of samples from a single center, type II errors, and imperfect randomization.[14] In view of these previous studies, the findings are not consistent and the effectiveness of epinephrine in CPR has not been established. We thus performed a propensity analysis that sought to determine how epinephrine use in CPR before hospital arrival was associated with immediate and 1-month survival using national data from a whole sample of OHCAs between 2005 and 2008 in Japan.

METHODS

EMS System and Data Collection

The EMS system in Japan has been described previously.[16-18] Briefly, in Japan, municipal governments provide EMS through about 800 fire stations with dispatch centers. Because the Japanese guidelines do not allow EMS providers to terminate resuscitation in the field, all patients with OHCA who are treated by EMS personnel are transported to hospitals.[19] Based on the standardized Utstein style template, registry of all OHCA cases in Japan is performed in a prospective, nationwide, and population-based manner by the Fire and Disaster Management Agency (FDMA). In particular, time from call to the scene or hospital arrival is measured using dispatch records at the fire station and an emergency lifesaving technician watch. Data concerning bystander CPR administration, automated external defibrillator use, and the characteristics of CPR by EMS personnel (eg, initial rhythm, defibrillation, intubation, epinephrine use) are collected using EMS records. To collect 1-month follow-up data, the EMS person in charge of each patient with OHCA has a face-to-face meeting with the physician who treated that patient at the hospital. If the patient is not at the hospital, the EMS personnel conducts a follow-up search. These data are initially handwritten. Then, in cooperation with the physicians in charge of patients with OHCA, the EMS personnel summarize the data of each OHCA case in standardized Utstein style.[20,21] The data at the 807 fire stations with dispatch centers in the 47 prefectures are then electronically integrated into the national registry system on the FDMA database server.

In most cases, an ambulance crew consists of 3 emergency personnel, including at least 1 emergency lifesaving technician. Emergency lifesaving technicians have undergone extensive training in the provision of emergency care until arrival at the hospital. These technicians are permitted to insert an intravenous line and an adjunct airway and to use semiautomated external defibrillators.[16] Specially trained emergency lifesaving technicians have been permitted to insert an intravenous line since July 2004, and certified emergency lifesaving technicians have been permitted to administer intravenous epinephrine since April 2006.[16]

Epinephrine use is implemented according to the FDMA resuscitation guidelines for emergency lifesaving technicians.[22] Specifically, during the resuscitation of patients with OHCA, after checking the initial rhythm and using defibrillation when appropriate, along with CPR, emergency lifesaving technicians perform tracheal intubation and/or insert an intravenous line with approval from an online emergency physician. Then, after verifying the absence of impulse in the carotid artery, the emergency lifesaving technicians administer epinephrine with the approval of the emergency physician.[22]

Study Design and Patients

This was a prospective observational study using national registry data. The study was approved by the ethics committee at Kyushu University Graduate School of Medicine. The requirement for written informed consent was waived.

Patients were aged 18 years or older, had an OHCA before arrival of EMS personnel, were treated by EMS personnel, and were then transported to medical institutions between January 1, 2005, and December 31, 2008, in Japan.

Variables

The collected data included information on OHCA patients, CPR initiated by bystander, life support by EMS personnel, and patient outcome. When patients survived cardiac arrest, they were followed up for as long as 1 month after the event, and information on survival and neurological and physical status 1 month after the event was collected. Neurological outcomes 1 month after successful resuscitation were evaluated using the Glasgow-Pittsburgh Cerebral Performance Category (CPC) scale, which has 5 categories: (1) good cerebral performance; (2) moderate cerebral disability; (3) severe cerebral disability; (4) coma or vegetative state; and (5) death; and using the Overall Performance Category (OPC) scale, also with 5 categories: (1): no or mild neurological disability; (2) moderate neurological disability; (3) severe neurological disability; (4) coma or vegetative state; and (5) death.[20,21,23] At 1 month after the event, the EMS person in charge of the patient with OHCA contacted the physician in charge of that patient at the medical facility and collected CPC and OPC data by chart review and an in-person interview. These data were entered into the national database.

The etiology of cardiac arrest (ie, cardiac or noncardiac) was determined clinically by the physician in charge with the aid of the EMS personnel. Regarding first documented rhythm, because an automated external defibrillator analyzes a patient's rhythm automatically and delivers a shock only when it detects ventricular fibrillation

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(VF), the patient's first recorded rhythm was regarded as VF when laypersons delivered shocks with the use of a public-access automated external defibrillator. Additionally, the category of VF included ventricular tachycardia. Only epinephrine was used during prehospital CPR for patients with OHCA, following the FDMA resuscitation guideline for emergency lifesaving technicians.[22]

End Points

The 4 end points were ROSC before hospital arrival, survival at 1 month after cardiac arrest, 1-month survival with CPC category 1 or 2, and 1-month survival with OPC category 1 or 2.[20,21,23]

Statistical Analysis

Data that met the criteria concerning patient age, time course, and epinephrine use were analyzed. Using data for all cases, 3 unconditional logistic regression models were fit using one of the end points as a dependent variable. With an actual 1-month survival rate of 5.4% in the intravenous epinephrine group and 4.7% in the no-epinephrine group, 15 030 samples for each group provided a power level of 92.0% with a type I error of .05.[24]

Epinephrine use before hospital arrival was not randomly assigned in the patient population; therefore, we developed a propensity score for epinephrine use before hospital arrival and controlled for potential confounding and selection bias.[25] By multivariable logistic regression analysis not taking patient outcome into account, the propensity score for prehospital epinephrine use was determined. Specifically, a full nonparsimonious logistic regression model was fit with prehospital epinephrine use as a dependent variable, which included every variable in TABLE 1 (ie, 20 variables, including 3 dummy variables for cases per year) plus dummy variables for the 47 prefectures in Japan (ie, 46 variables) as independent variables. A propensity score for epinephrine use before hospital arrival was calculated from the logistic regression equation for each patient. This propensity score represented the probability that a patient with OHCA would be given epinephrine before hospital arrival. Using the SAS macro program by Parsons et al,[26] based on propensity score, patients with OHCA who were given epinephrine were matched with unique control patients who were not given epinephrine before hospital arrival. Using data for the propensity-matched patients, 4 types of conditional logistic regression models were fit with one of the end point variables as a dependent variable. With an actual 1-month survival rate of 5.1% in the intravenous epinephrine group and 7.0% in the no-epinephrine group, 13 401 samples for each group provided a power level of 94.1% with a type I error of .01.[24]

The 2-sided significance level for all tests was $P < .05$. All analyses were performed using SAS software, version 8.2 (SAS Institute Inc).

RESULTS

Patient Characteristics

Between January 1, 2005, and December 31, 2008, 431 968 OHCAs occurred. Of these cases, 417 188 met the inclusion criteria (FIGURE 1 and Table 1). The mean age of all patients was 72 (SD, 16) years, and no significant difference existed between the mean ages of the 2 groups ($P = .86$). There was a significant difference between those who were given epinephrine and those who were not before hospital arrival. The number of OHCA cases who received epinephrine increased over the study period from 190 in 2005 to 8124 in

Table 1. Baseline Characteristics of Patients With Out-of-Hospital Cardiac Arrest According to Epinephrine Administration, 2005-2008, Japan (N = 417 188)[a]

Characteristics	Epinephrine (n = 15 030)	No Epinephrine (n = 402 158)
Cases per year		
2005	190 (1.3)	100 514 (25.0)
2006	1764 (11.8)	102 250 (25.4)
2007	4947 (32.9)	96 310 (24.0)
2008	8124 (54.1)	103 017 (25.6)
Age, mean (SD), y	72.38 (15.5)	72.41 (16.4)
Male	9546 (63.5)	236 366 (58.8)
Bystander eyewitness	8938 (59.5)	159 304 (39.6)
Family member bystander eyewitness	5250 (34.9)	82 812 (20.6)
Origin of cardiac arrest		
Cardiac	9088 (60.5)	220 597 (54.9)
Noncardiac	5942 (39.5)	181 561 (45.2)
Cardiopulmonary resuscitation initiated by bystander		
Chest compression	6627 (45.1)	143 975 (36.0)
Rescue breathing	2458 (16.9)	60 691 (15.2)
Use of public-access automated external defibrillator	113 (0.8)	1449 (0.4)
Life support by emergency medical service personnel		
Emergency lifesaving technician present in ambulance	14 929 (99.4)	374 818 (93.2)
Physician present in ambulance	1079 (7.2)	9176 (2.3)
Advanced life support performed by physician	2558 (17.0)	61 302 (15.3)
Time from call to arrival at scene, mean (SD), min	7.54 (4.0)	7.18 (3.8)
Time from call to arrival at hospital, mean (SD), min	38.15 (13.5)	31.68 (13.3)
First documented rhythm		
Ventricular fibrillation/pulseless ventricular tachycardia	2054 (13.7)	29 103 (7.2)
Pulseless electrical activity/asystole	12 975 (86.3)	373 049 (92.8)
Defibrillation by emergency medical service personnel	3117 (20.9)	42 348 (10.5)
Use of advanced life support devices (eg, laryngeal mask/adjunct airway/tracheal tubes)	11 496 (76.5)	172 673 (42.9)
Insertion of intravenous line	14 420 (96.0)	64 246 (16.0)

[a] Data are expressed as No. (%) unless otherwise indicated. All baseline characteristic comparisons between the 2 groups were statistically significant at $P < .001$ except age ($P = .86$). Values were missing for 5 to 10 998 individuals across all variables.

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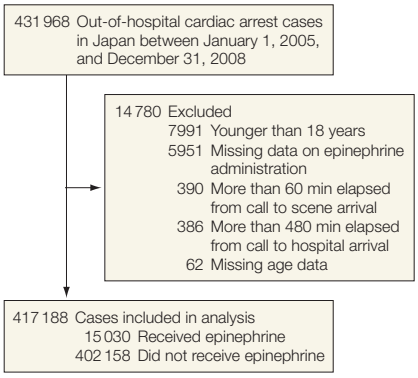
2008, whereas the number of OHCA cases who did not receive epinephrine remained at the same level ($P<.001$) (Table 1). Additionally, we checked the effects of prehospital epinephrine use by VF/non-VF status. Among patients with VF, 432 patients (21.1%) in the epinephrine group and 6478 (22.3%) in the no-epinephrine group had ROSC before hospital arrival ($\chi^2=1.59$; $P=.21$). The numbers of patients with 1-month survival, CPC category 1 or 2, and OPC category 1 or 2, respectively, were 316 (15.4%), 126 (6.1%), and 127 (6.2%) in the epinephrine group and 6209 (21.3%), 3927 (13.5%), and 3920 (13.5%) in the no-epinephrine group ($\chi^2=41.02$, 91.82, and 90.13, respectively; all $P<.001$). Among patients without VF, 2354 (18.2%) in the epinephrine group and 16 564 (4.4%) in the no-epinephrine group had ROSC before hospital arrival ($\chi^2=5052.66$; $P<.001$). The numbers of patients without VF with 1-month survival, CPC category 1 or 2, and OPC category 1 or 2, respectively, were 489 (3.8%), 79 (0.6%), and 84 (0.7%) in the epinephrine group and 12 696 (3.4%), 4975 (1.3%), and 4910 (1.3%), in the no-epinephrine group ($\chi^2=5.08$; $P=.02$; $\chi^2=50.96$; $P<.001$; and $\chi^2=43.91$; $P<.001$, respectively) (eAppendix and eTable 1; available at http://www.jama.com).

Figure 1. Study Participant Selection



Epinephrine Use Before Hospital Arrival and Patient Survival

TABLE 2 and FIGURE 2 summarize survival outcomes based on epinephrine use among all patients. With respect to the 4 end-point variables, in the initial unadjusted model, there was a significant difference between those who were administered epinephrine and those who were not before hospital arrival (all $P<.001$) (Figure 2). A positive association was detected between prehospital epinephrine use and the outcome measure in patients with ROSC before hospital arrival in the 3 models. A significant positive association in the crude model (OR, 1.15; 95% CI, 1.07-1.23; $P<.001$) and a significant negative association in the adjusted model using selected variables (OR, 0.43; 95% CI, 0.39-0.46; $P<.001$) or all variables (OR, 0.46; 95% CI, 0.42-0.51; $P<.001$) were observed for 1-month survival with respect to an association between prehospital epinephrine use and the outcome measures. A significant negative association was detected between prehospital epinephrine use and CPC and OPC in the 3 models.

Table 2. Unconditional Logistic Regression Analyses of Outcomes in Epinephrine Group (vs No-Epinephrine Group) Among All Patients With Out-of-Hospital Cardiac Arrest

	Odds Ratio (95% CI)[a]			
Analysis	ROSC	1-Month Survival	CPC 1 or 2	OPC 1 or 2
Unadjusted (n = 417 155)	3.75 (3.59-3.91)	1.15 (1.07-1.23)	0.61 (0.53-0.70)	0.63 (0.55-0.73)
Adjusted for selected variables (n = 412 078)[b]	3.06 (2.93-3.21)	0.43 (0.39-0.46)	0.21 (0.18-0.24)	0.22 (0.19-0.25)
Adjusted for all covariates (n = 391 046)[c]	2.36 (2.22-2.50)	0.46 (0.42-0.51)	0.31 (0.26-0.36)	0.32 (0.27-0.38)

Abbreviations: CPC, Cerebral Performance Category; OPC, Overall Performance Category; ROSC, return of spontaneous circulation.
[a] For all odds ratios, $P<.001$.
[b] Selected variables included age, sex, bystander eyewitness, relationship of bystander to patient, bystander chest compression, bystander rescue breathing, use of public-access automated external defibrillator by bystander, first documented rhythm, and time from call to arrival at the scene for the model with ROSC as a dependent variable. For other models, ROSC and the above selected variables were adjusted.
[c] All covariates included all variables in Table 1 plus 46 dummy variables for the 47 prefectures in Japan for the model with ROSC as a dependent variable. For other models, ROSC, all variables in Table 1, and 46 dummy variables for the 47 prefectures in Japan were adjusted.

Prehospital Epinephrine Use and Survival in Propensity-Matched Patients

To calculate the propensity score, a full nonparsimonious logistic regression model was fit. This model yielded a C statistic of 0.96, which indicated a very strong ability to differentiate between those who used epinephrine before hospital arrival and those who did not. The propensity score ranged from 0.007 to 1.000, which indicated that the probability of epinephrine use before hospital arrival by a patient with OHCA would be between 0 and 1. In the study, 13 401 patients who were given epinephrine were matched with 13 401 patients who were not given epinephrine (TABLE 3). With respect to every predictor variable, no significant difference was detected between patients who were given epinephrine and patients who were not given epinephrine, which showed that these propensity-matched patients were well matched.

TABLE 4 and FIGURE 3 summarize survival outcomes based on epinephrine use among propensity-matched patients. With respect to the 4 end-point variables, in the initial unadjusted model, there was a significant difference between those who were administered epinephrine and those who were not before hospital arrival (all $P<.001$) (Figure 3). For ROSC, a positive association was detected between prehospital epinephrine use and the outcome measures in the 4 models. The positive association became increasingly more evident after adjustment for selected variables and after adjustment for all variables. Inversely, for 1-month survival and survival with minimal neurological impairment (ie, CPC category 1 or 2, OPC category 1

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or 2), a significant negative association was observed between epinephrine use before hospital arrival and the outcome measures. These negative associations became increasingly more evident after adjustment for selected variables and after adjustment for all variables (eAppendix and eTable 2).

COMMENT

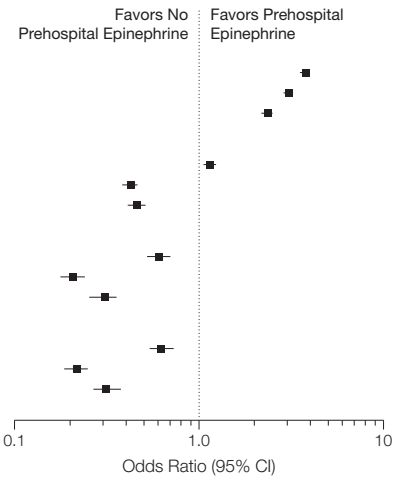
Our findings, based on propensity-matched analyses using 4 different models, clearly show that intravenous epinephrine administration before hospital arrival is independently associated with reduced 1-month survival (Table 4). As for the effectiveness of prehospital epinephrine use in cardiopulmonary resuscitation, 1 large observational study supported effectiveness[12] while others did not.[13,27] Although recent randomized controlled trials showed that epinephrine use before hospital arrival was not associated with long-term survival, there were several methodological problems with these trials.[15,25] Previous findings are inconsistent, so the effectiveness of epinephrine in CPR has not been established. Our findings are derived from national registry data, and sample size for propensity analysis posed no problem. Based on a valid propensity analysis controlling for the effects of selection bias and confounding factors, we observed that intravenous epinephrine use before hospital arrival was a significant predictor of poor long-term outcome. We believe that the present findings are important both theoretically and practically. As noted previously, epinephrine is reportedly associated with increased myocardial dysfunction, disturbed cerebral microcirculation after cardiac arrest, and ventricular arrhythmias during the period after resuscitation.[4-7] The adverse long-term effect might be due to these pharmacological effects of epinephrine.

Epinephrine use before hospital arrival was consistently a significant and positive predictor of ROSC before hospital arrival in the 4 different models, and the ORs ranged from 1.91 to 2.51 (all $P < .001$) (Table 4). Our results are based on propensity-matched data and are consistent with previous findings.[14,15,27] Several results have been reported that can explain the biological or pharmacological aspects of intravenous epinephrine administration leading to improved short-term outcomes, including animal studies showing short-term effects of epinephrine[8,9] and evidence to indicate increased cerebral and coronary perfusion by redirected peripheral blood flow.[10,11] Thus, the short-term effect might be attributable to these pharmacological effects of epinephrine.

A major confounder in this analysis is that patients who did not receive epinephrine in the prehospital setting may have received epinephrine after hospital arrival. Therefore, the differences may reflect changes in the type of care after hospital arrival and may not be attributable to the drug itself. Thus, we conducted a sensitivity analysis. In matched subsets of patients who had ROSC prior to hospital arrival, there would be no indication to receive epinephrine in the hospital, so the pure effect of the drug could be determined. Thus, we compared long-term survival between these patients. The numbers of 1-month survivors in the epinephrine and no-

Figure 2. Results of Unconditional Logistic Regression Analyses Comparing Prehospital Epinephrine Use vs No Prehospital Epinephrine Use in Patients With Out-of-Hospital Cardiac Arrest

Model	Total No. of Cases	No. (%) With Outcome: Epinephrine	No. (%) With Outcome: No Epinephrine	Odds Ratio (95% CI)
ROSC				
Unadjusted	417 155	2786 (18.5)	23 042 (5.7)	3.75 (3.59-3.91)
Adjusted for selected variables[a]	412 078	2692 (18.6)	22 804 (5.7)	3.06 (2.93-3.21)
Adjusted for all covariates[b]	391 046	2556 (18.6)	21 629 (5.7)	2.36 (2.22-2.50)
1-Month survival				
Unadjusted	417 186	805 (5.4)	18 906 (4.7)	1.15 (1.07-1.23)
Adjusted for selected variables[a]	412 078	772 (5.3)	18 637 (4.7)	0.43 (0.39-0.46)
Adjusted for all covariates[b]	391 046	733 (5.3)	17 677 (4.7)	0.46 (0.42-0.51)
CPC 1 or 2				
Unadjusted	417 187	205 (1.4)	8903 (2.2)	0.61 (0.53-0.70)
Adjusted for selected variables[a]	412 078	197 (1.4)	8781 (2.2)	0.21 (0.18-0.24)
Adjusted for all covariates[b]	391 046	187 (1.4)	8329 (2.2)	0.31 (0.26-0.36)
OPC 1 or 2				
Unadjusted	417 187	211 (1.4)	8831 (2.2)	0.63 (0.55-0.73)
Adjusted for selected variables[a]	412 078	202 (1.4)	8710 (2.2)	0.22 (0.19-0.25)
Adjusted for all covariates[b]	391 046	192 (1.4)	37 732 (2.2)	0.32 (0.27-0.38)



CPC indicates Cerebral Performance Category; OPC, Overall Performance Category; ROSC, return of spontaneous circulation. Different sample sizes in the 3 models result from increasing numbers of cases with missing data as the number of independent variables increased.

[a] Selected variables included age, sex, bystander eyewitness, relationship of bystander to patient, bystander chest compression, bystander rescue breathing, use of public-access automated external defibrillator by bystander, first documented rhythm, and time from call to arrival at the scene for the model with ROSC as a dependent variable. For other models, ROSC and the above selected variables were adjusted.

[b] All covariates included all variables in Table 1 plus 46 dummy variables for the 47 prefectures in Japan for the model with ROSC as a dependent variable. For other models, ROSC, all variables in Table 1, and 46 dummy variables for the 47 prefectures in Japan were adjusted.

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epinephrine groups were 438 (18.0%) and 661 (46.8%), respectively ($P<.001$). The numbers of patients with CPC category 1 or 2 in the epinephrine and no-epinephrine groups were 113 (4.7%) and 354 (25.0%), respectively ($P<.001$). The numbers of patients with OPC category 1 or 2 in the epinephrine and no-epinephrine groups were 115 (4.7%) and 351 (24.8%), respectively ($P<.001$). Additionally, we compared time from call to scene arrival or hospital arrival between the epinephrine and no-epinephrine groups. The mean times from call to scene arrival in the epinephrine and no-epinephrine groups were 7.37 (SD, 3.73) minutes and 6.72 (SD, 3.05) minutes, respectively ($P<.001$). The mean times from call to hospital arrival in the epinephrine and no-epinephrine groups were 40.01 (SD, 14.19) minutes and 40.43 (SD, 21.84) minutes, respectively ($P=.53$). Because the no-epinephrine group was not transported more quickly to the emergency department, improved long-term outcomes might not reflect more rapid delivery to definitive care. In summary, the sensitivity analysis showed that the use of epinephrine might be related to decreased 1-month survival.

There are several notable findings of this study. First, the number of patients with OHCA who were given epinephrine increased dramatically from 190 in 2005 to 8123 in 2008. Since April 2006, certified emergency lifesaving technicians have been permitted to administer intravenous epinephrine.[16] The large increase in the number of patients who were administered epinephrine might be due to this change in the Japanese guidelines. In 2005, epinephrine was administered in 190 cases. Physicians were in ambulances in 2.5% of the 417 168 cases occurring during the study period. Thus, physicians likely administered intravenous epinephrine to the 190 patients in 2005. Second, in the total sample, only 1.4% of patients in the epinephrine group had good neurological outcomes, despite a 5.4% survival rate (Table 1). Thus, only about 25% of survivors had good neurological outcomes. The same basic pattern was found among propensity-matched patients (Table 3). This rate is substantially lower than those reported in most OHCA studies, in which the majority of long-term survivors had good outcomes.[12,13,15,25,27] This finding implies that epinephrine administration might save the heart but not the

Table 3. Baseline Characteristics of Patients With Out-of-Hospital Cardiac Arrest According to Epinephrine Administration in Propensity-Matched Patients[a]

Characteristics	Epinephrine (n = 13 401)	No Epinephrine (n = 13 401)
Cases per year		
2005	183 (1.4)	174 (1.3)
2006	1704 (12.7)	1664 (12.4)
2007	4124 (30.8)	4183 (31.2)
2008	7390 (55.2)	7380 (55.1)
Age, mean (SD), y	72.43 (15.5)	72.40 (15.7)
Male	8480 (63.3)	8427 (62.9)
Bystander eyewitness	7729 (57.7)	7866 (58.7)
Family member bystander eyewitness	4519 (33.7)	4533 (33.8)
Origin of cardiac arrest		
Cardiac	8039 (60.0)	7984 (59.6)
Noncardiac	5362 (40.0)	5417 (40.4)
Cardiopulmonary resuscitation initiated by bystander		
Chest compression	5854 (43.7)	5918 (44.2)
Rescue breathing	2205 (16.5)	2243 (16.7)
Use of public-access automated external defibrillator	102 (0.8)	99 (0.7)
Life support by emergency medical service personnel		
Emergency lifesaving technician present in ambulance	13 316 (99.4)	13 308 (99.3)
Physician present in ambulance	811 (6.1)	873 (6.5)
Advanced life support performed by physician	2122 (15.8)	2233 (16.7)
Time from call to arrival at scene, mean (SD), min	7.50 (4.0)	7.47 (4.0)
Time from call to arrival at hospital, mean (SD), min	37.92 (13.2)	37.66 (18.3)
First documented rhythm		
Ventricular fibrillation/pulseless ventricular tachycardia	1758 (13.1)	1781 (13.3)
Pulseless electrical activity/asystole	11 643 (86.9)	11 620 (86.7)
Defibrillation by emergency medical service personnel	2610 (19.5)	2602 (19.4)
Use of advanced life support devices (eg, laryngeal mask/adjunct airway/tracheal tubes)	10 294 (76.8)	10 290 (76.8)
Insertion of intravenous line	12 868 (96.0)	12 865 (96.0)

[a] Data are expressed as No. (%) unless otherwise indicated. All baseline characteristic comparisons between the 2 groups were not statistically significant.

Table 4. Conditional Logistic Regression Analyses of Outcome in Epinephrine Group (vs No-Epinephrine Group) Among Propensity-Matched Patients With Out-of-Hospital Cardiac Arrest (n = 26 802)

	Odds Ratio (95% CI)[a]			
Analysis	ROSC	1-Month Survival	CPC 1 or 2	OPC 1 or 2
Unadjusted	1.91 (1.78-2.05)	0.71 (0.64-0.79)	0.41 (0.34-0.49)	0.43 (0.36-0.51)
Adjusted for propensity	2.01 (1.83-2.21)	0.71 (0.62-0.81)	0.41 (0.33-0.52)	0.43 (0.34-0.54)
Adjusted for propensity and selected variables[b]	2.24 (2.03-2.48)	0.60 (0.49-0.74)	0.40 (0.26-0.63)	0.43 (0.28-0.66)
Adjusted for propensity and all covariates[c]	2.51 (2.24-2.80)	0.54 (0.43-0.68)	0.21 (0.10-0.44)	0.23 (0.11-0.45)

Abbreviations: CPC, Cerebral Performance Category; OPC, Overall Performance Category; ROSC, return of spontaneous circulation.

[a] For all odds ratios, $P<.001$.

[b] Selected variables included age, sex, bystander eyewitness, relationship of bystander to patient, bystander chest compression, bystander rescue breathing, use of public-access automated external defibrillator by bystander, first documented rhythm, and time from call to arrival at the scene for the model with ROSC as a dependent variable. For other models, ROSC and the above selected variables were adjusted.

[c] All covariates included all variables in Table 1 plus 46 dummy variables for the 47 prefectures in Japan for the model with ROSC as a dependent variable. For other models, ROSC, all variables in Table 1, and 46 dummy variables for the 47 prefectures in Japan were adjusted.

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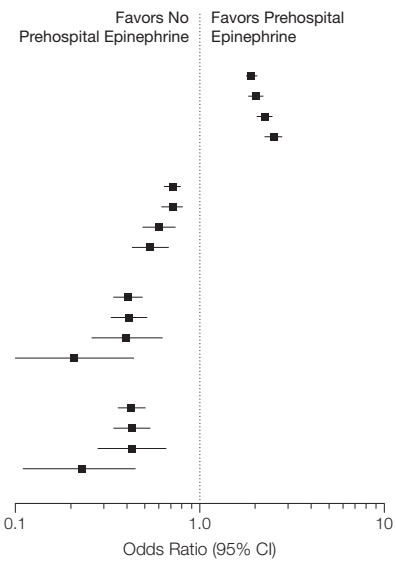
brain, which is worth further study. Third, we also conducted an analysis of the association between prehospital epinephrine use and outcomes in the total sample (Table 2). Analyses of CPC and OPC both yielded ORs less than 1 for the association between prehospital epinephrine use and long-term neurological outcome, which was consistent with the results obtained for propensity-matched patients (Table 4). A crude analysis revealed a significant positive association between prehospital intravenous epinephrine administration and 1-month survival (OR, 1.15; $P < .001$). However, after adjusting for the effects of the selected variables, a significant negative association between prehospital epinephrine use and 1-month survival emerged (OR, 0.43; $P < .001$); this association remained significant after adjusting for all variables in the third model (OR, 0.46; $P < .001$). Generally, an observational study cannot be free from selection bias and confounding factors.[25] Concomitant with this theoretical expectation, inconsistent associations between epinephrine administration before hospital arrival and the 1-month survival rate were observed.

Several limitations and caveats to our study must be acknowledged. First, the major limitation was that epinephrine use before hospital arrival was not assigned by random allocation. We performed propensity analysis and made a rigorous adjustment for selection bias and confounding factors, which would be expected with a standard multivariable analysis.[25] Nevertheless, we must acknowledge that observational studies can only partially control and adjust for factors actually measured, whereas randomized allocation can control both known and unknown confounding factors and avoid the introduction of bias. Second, data on in-hospital CPR after arrival were not included in the analysis. Long-term survival cannot be achieved without first restoring circulation. A positive association was observed between epinephrine use before hospital arrival and short-term survival, whereas a negative association was detected between epinephrine use before hospital arrival and long-term survival. It is possible that these findings might have been due to a difference in in-hospital resuscitation modes, such as induced hypothermia[28] and mechanical chest compression devices,[29] between those who were administered epinephrine and those were not. Specifically, hypothermia is not a routine treatment for in-hospital CPR patients with OHCA in Japan. Additionally, no standard regimen of care after hospital arrival has been established. Thus, the use of induced hypothermia, cardiac catheterization, or epinephrine or other pressors (eg, vasopressin) may differ among hospitals. In summary, although the quality of in-hospital resuscitation might influence 1-month survival, we could not control for the effects of such factors. Third, some variables were problematic. The etiology of OHCA was determined clinically by the physician in charge with the aid of EMS personnel. However, we must recognize that

Figure 3. Results of Conditional Logistic Regression Analyses Comparing Prehospital Epinephrine Use vs No Prehospital Epinephrine Use in Propensity-Matched Patients With Out-of-Hospital Cardiac Arrest

Model	Total No. of Cases	No. (%) With Outcome: Epinephrine	No. (%) With Outcome: No Epinephrine	Odds Ratio (95% CI)
ROSC	26 802	2446 (18.3)	1400 (10.5)	
Unadjusted				1.91 (1.78-2.05)
Adjusted for propensity				2.01 (1.83-2.21)
Adjusted for propensity and selected variables[a]				2.24 (2.03-2.48)
Adjusted for all covariates[b]				2.51 (2.24-2.80)
1-Month survival	26 802	687 (5.1)	944 (7.0)	
Unadjusted				0.71 (0.64-0.79)
Adjusted for propensity				0.71 (0.62-0.81)
Adjusted for propensity and selected variables[a]				0.60 (0.49-0.74)
Adjusted for all covariates[b]				0.54 (0.43-0.68)
CPC 1 or 2	26 802	173 (1.3)	413 (3.1)	
Unadjusted				0.41 (0.34-0.49)
Adjusted for propensity				0.41 (0.33-0.52)
Adjusted for propensity and selected variables[a]				0.40 (0.26-0.63)
Adjusted for all covariates[b]				0.21 (0.10-0.44)
OPC 1 or 2	26 802	178 (1.3)	410 (3.1)	
Unadjusted				0.43 (0.36-0.51)
Adjusted for propensity				0.43 (0.34-0.54)
Adjusted for propensity and selected variables[a]				0.43 (0.28-0.66)
Adjusted for all covariates[b]				0.23 (0.11-0.45)



CPC indicates Cerebral Performance Category; OPC, Overall Performance Category; ROSC, return of spontaneous circulation.
[a] Selected variables included age, sex, bystander eyewitness, relationship of bystander to patient, bystander chest compression, bystander rescue breathing, use of public-access automated external defibrillator by bystander, first documented rhythm, and time from call to arrival at the scene for the model with ROSC as a dependent variable. For other models, ROSC and the above selected variables were adjusted.
[b] All covariates included all variables in Table 1 plus 46 dummy variables for the 47 prefectures in Japan for the model with ROSC as a dependent variable. For other models, ROSC, all variables in Table 1, and 46 dummy variables for the 47 prefectures in Japan were adjusted.

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the determination of a noncardiac etiology is highly atypical and problematic except among arrests due to trauma, drowning, strangulation, or drug overdose.[30] Epinephrine dosage has been reported to influence the outcome of patients with OHCA.[31] According to our interviews with emergency medicine physicians, a single dose of epinephrine was administered in the majority of cases. However, because of lack of data, we could not consider the number of epinephrine doses used in the cases included this study.

In summary, despite the limitations to the study, the associations between epinephrine use before hospital arrival and short- and long-term outcomes were strong and consistent. Specifically, our data show that intravenous epinephrine use before hospital arrival was associated with decreased 1-month survival on the basis of propensity-matched national data. Epinephrine use before hospital arrival was a positive predictor of short-term survival, which is in line with previous findings. Our findings need to be verified by studies that include in-hospital resuscitation data.

Author Contributions: Dr Hagihara had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hagihara, Hasegawa.
Acquisition of data: Hagihara, Hasegawa.
Analysis and interpretation of data: Hagihara, Hasegawa, Abe, Nagata, Wakata, Miyazaki.
Drafting of the manuscript: Hagihara, Wakata.
Critical revision of the manuscript for important intellectual content: Hagihara, Hasegawa, Abe, Nagata, Wakata, Miyazaki.
Statistical analysis: Hagihara, Abe.
Administrative, technical, or material support: Hagihara, Hasegawa, Abe, Nagata, Wakata, Miyazaki.
Study supervision: Hagihara.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.
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Online-Only Material: eTables 1 and 2 and the eAppendix are available at http://www.jama.com.

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