Intravenous Drug Administration During Out-of-Hospital Cardiac Arrest

A Randomized Trial

Theresa M. Olasveengen, MD
Kjetil Sunde, MD, PhD
Cathrine Brunborg, MSc
Jon Thowsen
Petter A. Steen, MD, PhD
Lars Wik, MD, PhD

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-

Author Affiliations: Institute for Experimental Medical Research (Drs Olasveengen and Wik), Centre for Clinical Research (Ms Brunborg), and National Competence Centre for Emergency Medicine (Dr Wik), Departments of Anesthesiology (Dr Olasveengen) and Ambulance (Mr Thowsen and Dr Steen), Surgical Intensive Care Unit (Dr Sunde), and Faculty Division UUH (Dr Steen), Oslo University Hospital, Oslo, Norway.
Corresponding Author: Theresa M. Olasveengen, MD, Institute for Experimental Medical Research, Oslo University Hospital, Ullevaal, N-0407 Oslo, Norway (t.m.olasveengen@medisin.uio.no).

 ©2009 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/ on 06/19/2013

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-

©2009 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/ on 06/19/2013

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

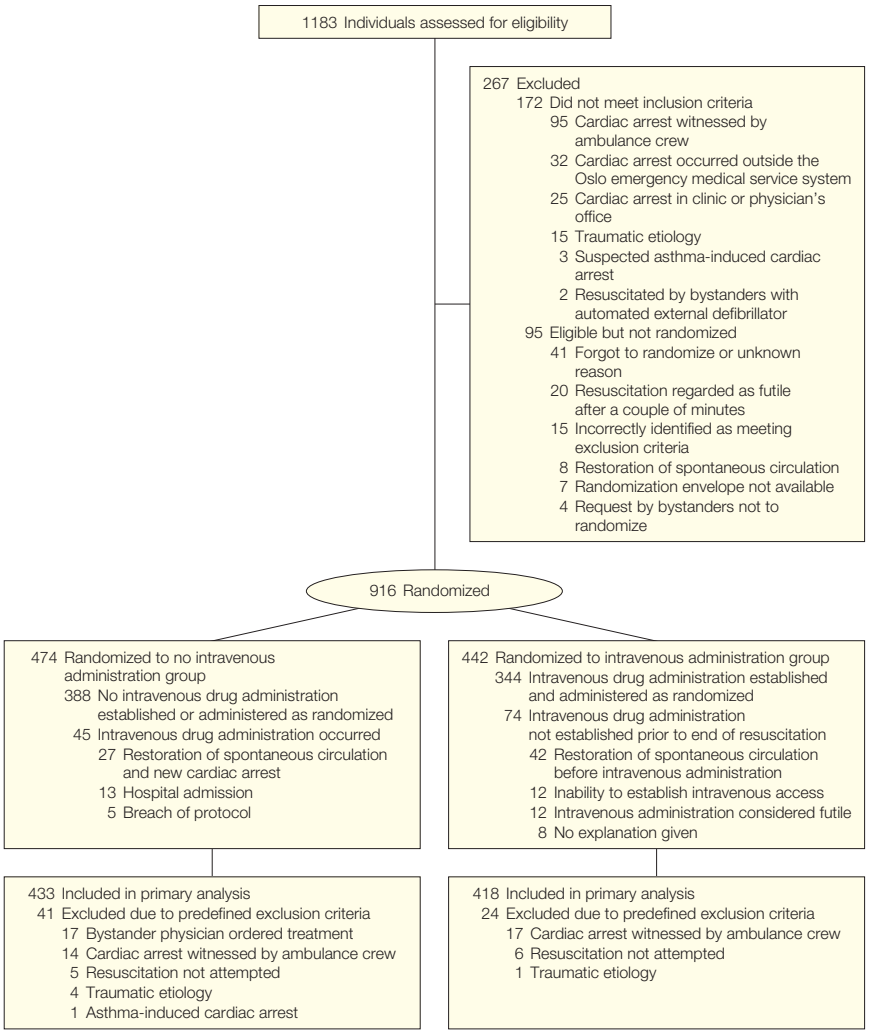
Initial power analysis was based on survival statistics for the Oslo emergency medical service system and assumed that the survival rate would be doubled among patients not receiving epinephrine, as described previously in an observational study.[9] With a projected survival rate of 7% in the intravenous 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

 ©2009 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/ on 06/19/2013

(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.

©2009 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/ on 06/19/2013

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.

 ©2009 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/ on 06/19/2013

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.

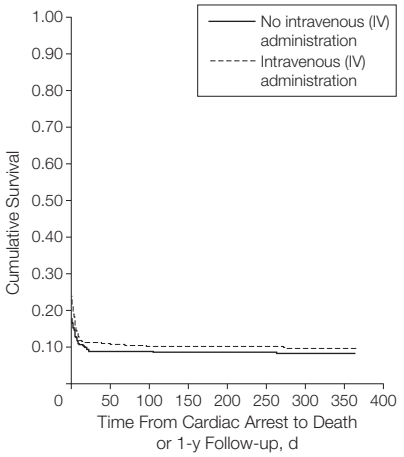
However, long-term survival cannot be achieved without first restoring circulation. Improved brain-directed postresuscitation treatment might at some point prevent irreversible cerebral damage and increase survival. At present, the only established brain-directed treatment is therapeutic hypothermia,[26,27] 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



No. at risk

No IV	433	39	39	38	38	37	37	37	37
IV	418	46	44	44	44	44	42	42	41

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-

©2009 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/ on 06/19/2013

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.
Funding/Support: The study was supported by grants from the Eastern Norway Regional Health Authority, Oslo University Hospital, Norwegian Air Ambulance Foundation, Laerdal Foundation for Acute Medicine, and the Anders Jahres Fund.
Role of the Sponsors: The funding organizations had no involvement with the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript
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.

REFERENCES

1. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 7.2: management of cardiac arrest. *Circulation*. 2005;112(24)(suppl):IV-58-IV-66. doi: 10.1161/CIRCULATIONAHA.105.16657.
2. Gazmuri RJ, Nolan JP, Nadkarni VM, et al. Scientific knowledge gaps and clinical research priorities for cardiopulmonary resuscitation and emergency cardiovascular care identified during the 2005 International Consensus Conference on ECC and CPR Science with Treatment Recommendations. *Resuscitation*. 2007;75(3):400-411.
3. Pearson JW, Redding JS. Epinephrine in cardiac resuscitation. *Am Heart J*. 1963;66:210-214.
4. Michael JR, Guerci AD, Koehler RC, et al. Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs. *Circulation*. 1984;69(4):822-835.
5. Otto CW, Yakaitis RW. The role of epinephrine in CPR: a reappraisal. *Ann Emerg Med*. 1984;13(9 Pt 2): 840-843.
6. Tang W, Weil MH, Sun S, et al. Epinephrine increases the severity of postresuscitation myocardial dysfunction. *Circulation*. 1995;92(10):3089-3093.
7. Angelos MG, Butke RL, Panchal AR, et al. Cardiovascular response to epinephrine varies with increasing duration of cardiac arrest. *Resuscitation*. 2008; 77(1):101-110.
8. Ristagno G, Sun S, Tang W, et al. Effects of epinephrine and vasopressin on cerebral microcirculatory flows during and after cardiopulmonary resuscitation. *Crit Care Med*. 2007;35(9):2145-2149.
9. Holmberg M, Holmberg S, Herlitz J. Low chance of survival among patients requiring adrenaline epinephrine or intubation after out-of-hospital cardiac arrest in Sweden. *Resuscitation*. 2002;54(1):37-45.
10. Wik L, Kramer-Johansen J, Myklebust H, et al. Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. *JAMA*. 2005;293(3): 299-304.
11. Abella BS, Alvarado JP, Myklebust H, et al. Quality of cardiopulmonary resuscitation during in-hospital cardiac arrest. *JAMA*. 2005;293(3):305-310.
12. Ødegaard S, Kramer-Johansen J, Bromley A, et al. Chest compressions by ambulance personnel on chests with variable stiffness. *Resuscitation*. 2007;74(1): 127-134.
13. Pytte M, Kramer-Johansen J, Eilevstjonn J, et al. Haemodynamic effects of adrenaline (epinephrine) depend on chest compression quality during cardiopulmonary resuscitation in pigs. *Resuscitation*. 2006; 71(3):369-378.
14. Part 1: introduction to the International Guidelines 2000 for CPR and ECC. *Circulation*. 2000; 102(8 suppl):I1-I11.

 ©2009 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/ on 06/19/2013

15. Wik L, Hansen TB, Fylling F, et al. Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation. *JAMA*. 2003;289(11):1389-1395.
16. Nolan JP, Deakin CD, Soar J, et al; European Resuscitation Council. European Resuscitation Council Guidelines for Resuscitation 2005. *Resuscitation*. 2005; 67(suppl 1):S39-S86.
17. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation*. 2007;73(1):29-39.
18. Jacobs I, Nadkarni V, Bahr J, et al; International Liaison Committee on Resuscitation; American Heart Association; European Resuscitation Council; Australian Resuscitation Council; New Zealand Resuscitation Council; Heart and Stroke Foundation of Canada; InterAmerican Heart Foundation; Resuscitation Councils of Southern Africa; ILCOR Task Force on Cardiac Arrest and Cardiopulmonary Resuscitation Outcomes. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. *Circulation*. 2004;110(21):3385-3397.
19. Pocock SJ. Chapter 9: the size of a clinical trial. In: *Clinical Trials: A Practical Approach.* Chichester, England: Wiley; 1983:123-142.
20. Breslow NE, Day DN. Statistical methods in cancer research. In: *Vol 1: The Analysis of Case-Control Studies.* Lyon, France: International Agency for Research on Cancer; 1980. IARC scientific publications No. 32.
21. Kleinbaum DG, Kupper LL, Morgenstern H. Chapter 19: interaction, effect modification, and synergism. *Epidemiologic Research: Principles and Quantitative Methods.* New York, NY: Van Nostrand Reignold Co Inc; 1982:403-447.
22. Stiell IG, Wells GA, Field B, et al; Ontario Prehospital Advanced Life Support Study Group. Advanced cardiac life support in out-of-hospital cardiac arrest. *N Engl J Med*. 2004;351(7):647-656.
23. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med*. 1999; 341(12):871-878.
24. Stueven HA, Tonsfeldt DJ, Thompson BM, et al. Atropine in asystole: human studies. *Ann Emerg Med*. 1984;13(9 pt 2):815-817.
25. Vandycke C, Martens P. High dose versus standard dose epinephrine in cardiac arrest. *Resuscitation*. 2000;45(3):161-166.
26. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346(8):557-563.
27. Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. 2002; 346(8):549-556.
28. Grogaard HK, Wik L, Eriksen M, et al. Continuous mechanical chest compressions during cardiac arrest to facilitate restoration of coronary circulation with percutaneous coronary intervention. *J Am Coll Cardiol*. 2007;50(11):1093-1094.
29. Chen YS, Lin JW, Yu HY, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest. *Lancet*. 2008;372(9638):554-561.
30. Birks EJ, Tansley PD, Hardy J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. *N Engl J Med*. 2006;355(18):1873-1884.
31. Silfvast T. Cause of death in unsuccessful prehospital resuscitation. *J Intern Med*. 1991;229(4): 331-335.
32. Virkkunen I, Paasio L, Ryynanen S, et al. Pulseless electrical activity and unsuccessful out-of-hospital resuscitation. *Resuscitation*. 2008;77(2): 207-210.
33. Spaulding CM, Joly LM, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *N Engl J Med*. 1997;336 (23):1629-1633.
34. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH; European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med*. 2004;350(2):105-113.
35. Ewy GA, Kern KB. Recent advances in cardiopulmonary resuscitation: cardiocerebral resuscitation. *J Am Coll Cardiol*. 2009;53(2):149-157.
36. Morris DC. Vasopressors in cardiopulmonary resuscitation. *N Engl J Med*. 2008;359(15):1624.

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)

©2009 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/ on 06/19/2013