Duration of Prehospital Resuscitation Efforts After Out-of-Hospital Cardiac Arrest

Running title: Nagao et al.; JCS-ReSS, prehospital resuscitation duration

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Abstract

Background—During out-of-hospital cardiac arrest (OHCA), it is unclear how long prehospital resuscitation efforts should be continued to maximize lives saved.

Methods and Results—Between 2005 and 2012, we enrolled 282,183 adult patients with bystander-witnessed OHCA from the All-Japan Utstein Registry. Prehospital resuscitation duration was calculated as the time interval from call receipt to return of spontaneous circulation (ROSC) in cases achieving prehospital ROSC or from call receipt to hospital arrival in cases not achieving prehospital ROSC. In each of four groups stratified by initial cardiac arrest rhythm (shockable versus non-shockable) and bystander resuscitation (presence versus absence), we calculated minimum prehospital resuscitation duration, defined as the length of resuscitation efforts in minutes required to achieve ≥99% sensitivity for the primary endpoint, favorable 30-day neurological outcome after OHCA. Prehospital resuscitation duration to achieve prehospital ROSC ranged from 1 to 60 minutes. Longer prehospital resuscitation duration reduced the likelihood of favorable neurological outcome (adjusted odds ratio, 0.84; 95% confidence interval, 0.838-0.844). Although the frequency of favorable neurological outcome was significantly different between the four groups, ranging from 20.0% (shockable/bystander resuscitation group) to 0.9% (non-shockable/bystander resuscitation group) \(P<0.001\), minimum prehospital resuscitation duration did not differ widely between the four groups (40 minutes in the shockable/bystander resuscitation group and the shockable/no bystander resuscitation group, 44 minutes in the non-shockable/bystander resuscitation group and 45 minutes in the non-shockable/no bystander resuscitation group).

Conclusions—Based on time intervals from the shockable arrest groups, prehospital resuscitation efforts should be continued for at least 40 minutes in all adults with bystander-witnessed OHCA.

Clinical Trial Registration Information —www.umin.ac.jp/ctr/. Identifier: 000009918.

Key words: cardiopulmonary resuscitation; cardiac arrest; resuscitation; survival; heart arrest
Out-of-hospital cardiac arrest (OHCA) is a major public health problem, affecting approximately 420,000 individuals in the United States\textsuperscript{1} and 110,000 individuals in Japan annually.\textsuperscript{2} Despite decades of efforts to promote resuscitation, neurologically intact survival rates for OHCA remains low worldwide.\textsuperscript{3-9} Frequently, resuscitation efforts are unsuccessful and death occurs.\textsuperscript{4}

Achievement of return of spontaneous circulation (ROSC) is a prerequisite for neurologically intact survival and it may be appropriate to extend resuscitation efforts if ROSC might occur. Recent resuscitation guidelines state that end-of-life decision-making is an important component of resuscitation,\textsuperscript{3-9} and recommend the following termination of resuscitation (TOR) rules for basic life support (BLS) in adult OHCA patients: arrest not witnessed by emergency medical service (EMS) responders; no ROSC after 3 full rounds of BLS and automated external defibrillator (AED) analysis; and no AED shocks were delivered. The TOR rules for advanced life support (ALS) include the BLS criteria, and add three additional criteria: arrest not witnessed by bystander, no bystander resuscitation, and no ROSC after full ALS in the field. When all criteria are met prior to transport, resuscitation efforts can be terminated,\textsuperscript{4} reducing BLS transport by 54\% to 63\%\textsuperscript{10,11} and ALS transport by 31\%.\textsuperscript{11} However, these guidelines only state the mandatory elements of “adequate” resuscitation efforts and do not specify the minimum duration for resuscitation efforts.\textsuperscript{3-9} Recent studies of in-hospital cardiac arrest demonstrate that increasing the duration of resuscitation efforts improves the likelihood of survival.\textsuperscript{12,13} These findings suggest that clearly defining the length of prehospital resuscitation efforts is essential to optimal implementation of TOR rules.

The EMS system in Japan is ideal for evaluating this question: EMS responders must start resuscitation efforts immediately for all OHCA patients except when the victim is obviously moribund; EMS responders must continue resuscitation efforts until achievement of ROSC or
until hospital arrival, whichever comes first; and EMS responders cannot make the decision to terminate resuscitation efforts.2,5,14,15 We therefore assessed prehospital resuscitation duration for neurologically intact survival in all adult patients with bystander-witnessed OHCA. We expected that prehospital resuscitation duration for neurologically intact survival would differ in four groups stratified by initial cardiac arrest rhythm (shockable vs. non-shockable) and bystander resuscitation status (presence vs. absence), with longer prehospital resuscitation duration producing more survivors in the two groups with presence of bystander resuscitation.

Methods

Data Source and EMS System

The All-Japan Utstein Registry, a prospective, nationwide, population-based registry of OHCA, was established January 1, 2005 by the Fire and Disaster Management Agency (FDMA)14-16 following the ethical guidelines in Japan17, and has been described in detail previously.14-16,18 All fire stations with dispatch centers and all collaborating medical institutions participate in the registry. A subcommittee of resuscitation science in the Japanese Circulation Society was provided with registry data following the prescribed governmental legal procedures, and conducted the study with approval from the ethics committee at Surugadai Nihon University Hospital.18 Japan had a population of 127 million in 2011. There are 802 municipally-governed fire stations with dispatch centers operating around-the-clock, following uniform guideline-based resuscitation protocols.14 Each ambulance has three EMS responders including at least one emergency life-saving technician certified to insert intravenous lines and adjunct airways. Specially-trained emergency life-saving technicians are permitted to insert tracheal tubes and administer intravenous epinephrine.14 All OHCA patients receiving prehospital resuscitation
efforts are transported to the nearest emergency hospital.\textsuperscript{2,14-16,18}

**Study Population**

Between January 1, 2005, and December 31, 2012, adult patients with bystander-witnessed OHCA in whom EMS responders performed prehospital resuscitation care and who were transported to the hospital were included. Exclusion criteria were patients younger than 18 years of age, cardiac arrest after EMS responder arrival, unwitnessed OHCA, unidentified witness status, unidentified initial cardiac arrest rhythm, unidentified bystander resuscitation status and do not resuscitate order.

**Data Collection**

Data elements were collected prospectively based on the Utstein guidelines.\textsuperscript{19} Estimated times of collapse and initiation of bystander resuscitation were obtained from bystanders. All event times were synchronized by the dispatch center clock.\textsuperscript{2,14-16,18} EMS responders documented the presence or absence of bystander resuscitation efforts and noted bystander resuscitation technique, classified as documented chest compressions with or without rescue breathings or unidentified resuscitation technique (change of technique, resuscitation without documented chest compressions, etc).\textsuperscript{2,14-16,18,20} The initial cardiac arrest rhythm was classified as shockable (ventricular fibrillation or pulseless ventricular tachycardia) or non-shockable (pulseless electrical activity or asystole) based on AED analysis.\textsuperscript{2,14-16,18} Patients receiving bystander delivered shocks using a public-access AED (PAD) were classified as a shockable arrest.\textsuperscript{14-16} Prehospital ROSC was defined as any spontaneous palpable pulse confirmed by cardiac rhythm monitoring occurring prior to hospital arrival.\textsuperscript{2,14-16,18,20} Causes of arrest were determined clinically by the physicians in charge after hospital arrival and defined as presumed cardiac etiology unless an obvious non-cardiac etiology was elicited.\textsuperscript{2,14-16,18-20} Resuscitation outcomes were collected by the
receiving hospital physicians in collaboration with EMS responders.\textsuperscript{2,14-16,18} For patients discharged from the hospital alive, neurological outcomes were determined during 30-day follow-up interviews,\textsuperscript{2,14-16,18} using the Cerebral Performance Category (CPC) scale.\textsuperscript{19} The data form was filled out by the EMS personnel in cooperation with the physicians in charge of the patients, and the data were integrated into the registry system on the FDMA database server, then logically checked by the computer system. If the data form was incomplete, the FDMA returned it to the respective fire station for data completion.\textsuperscript{2,14-16,18}

**End Points**

The primary endpoint was favorable 30-day neurological outcome, defined as a CPC 1 (good performance) or 2 (moderate disability) on a five-category scale.\textsuperscript{19} CPC 3 (severe disability), 4 (vegetative state), and 5 (death) were regarded as unfavorable neurological outcome. The secondary endpoints were prehospital ROSC and 30-day survival (CPC 1-4).

**Statistical Methods**

The prehospital resuscitation duration, inclusive of EMS responder resuscitation efforts with or without bystander resuscitation efforts, was calculated as the call-receipt-to-ROSC interval in cases achieving prehospital ROSC or the call-receipt-to-hospital-arrival interval in cases not achieving prehospital ROSC. The resuscitation duration provided exclusively by EMS responders was calculated as the scene-arrival-to-ROSC interval in cases achieving prehospital ROSC or the scene-arrival-to-hospital-arrival interval in cases not achieving prehospital ROSC.

The study cohort was divided into four groups according to initial cardiac arrest rhythm (shockable vs. non-shockable) and bystander resuscitation status (documented chest compressions with or without rescue breathings vs. no bystander resuscitation). Baseline characteristics and study outcomes were compared using the $\chi^2$ test for categorical variables and the Mann-Whitney
U test or the Kruskal-Wallis rank test for continuous variables. We graphed the distributions of prehospital resuscitation duration using stacked bars in the entire study cohort stratified by prehospital ROSC status. On the basis of the distribution of prehospital resuscitation duration to achieve prehospital ROSC, the following analyses were done in the subset of patients with ≤60 min of prehospital resuscitation duration. We graphed the cumulative rates of 30-day neurological outcomes and favorable 30-day neurological outcome. A multiple logistic-regression analysis was performed for independent predictors of favorable 30-day neurological outcome, including prehospital resuscitation duration, age, study period (year the arrest occurred), gender, bystander resuscitation status, initial cardiac arrest rhythm, ALS and cause of cardiac arrest. In each group stratified by initial cardiac arrest rhythm and bystander resuscitation status, curve estimation in quadratic model was used to illustrate the relationship between the prehospital resuscitation duration and favorable 30-day neurological outcome. We calculated the sensitivity and negative predictive values of the prehospital and EMS responder resuscitation durations for having favorable 30-day neurological outcome in each group. Consistent with previous studies for the TOR rules, \(^{10,11,21,22}\) a sensitivity of ≥99% for favorable 30-day neurological outcome was used to determine the minimum prehospital and EMS responder resuscitation durations; we also calculated the maximum prehospital and EMS responder resuscitation durations associated with a sensitivity of 100% and a negative predictive value of 100%. Compared with previous sample sizes (1,240-13,684 patients\(^{10,11,21,22}\)), our larger sample size (283,183 patients) provided >80% power (1-side \(\alpha=0.05\)) with a misclassification rate <1%. All statistical analyses were performed with SPSS software (version 16.0J).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
Results

Patient Characteristics

Of the 925,288 OHCA victims between 2005 and 2012, 910,581 (98.4%) had prehospital resuscitation attempts and were transported to the hospital (Figure 1). Of these, 628,398 were excluded. This study included 282,183 adult patients with bystander-witnessed OHCA: 23,028 (8.2%) shockable/bystander resuscitation cases, 19,383 (6.9%) shockable/no bystander resuscitation cases, 104,212 (36.9%) non-shockable/bystander resuscitation cases, and 135,560 (48.0%) non-shockable/no bystander resuscitation cases. Baseline characteristics and arrest factors exhibited significant differences between groups, including age, sex, intravenous fluid administration, and cardiac etiology of arrest (Table 1).

Outcomes

Frequencies of prehospital ROSC, 30-day survival and favorable 30-day neurological outcome (Figure 1) were: 31.0% (7,140/23,028), 28.6% (6,597/23,028) and 20.0% (4,601/23,026) in the shockable/bystander resuscitation group; 24.9% (4,827/19,383) and 23.0% (4,452/19,383) and 13.2% (2,556/19,381) in the shockable/no bystander resuscitation group; 8.7% (9,038/104,212), 4.4% (4,538/10,4211) and 0.9% (979/104,206) in the non-shockable/bystander resuscitation group; and 8.2% (11,180/135,560), 4.5% (6,071/135,560) and 1.1% (1,533/135,552) in the non-shockable/no bystander resuscitation group (P< 0.001, respectively).

Prehospital and EMS Responder Resuscitation Durations

The prehospital resuscitation duration ranged from 1 min to 60 min in cases achieving prehospital ROSC and from 1 min to 120 min in cases not achieving prehospital ROSC (Figure 2). In the subset of patients with ≤60 min of prehospital resuscitation duration (Figure 3), 3.5%
(9,530/273,463) had favorable 30-day neurological outcome. Of the patients achieving favorable neurological outcome, 83.1% (7,924/9,530) was in cases achieving prehospital ROSC and 16.9% (1,606/9,530) in cases not achieving prehospital ROSC. Only 0.7% (1,606/241,943) of the cases not achieving prehospital ROSC went on to have favorable neurological outcome. Figure 4 shows a multiple logistic-regression analysis for favorable 30-day neurological outcome in the 273,463 patients with ≤60 min of prehospital duration. Longer prehospital resuscitation duration reduced the likelihood of favorable neurological outcome (adjusted odds ratio, 0.84; 95% confidence interval, 0.838-0.844; P<0.001). In curve estimation in quadratic model of each group stratified by initial cardiac arrest rhythm and bystander resuscitation status (Figure 5), the likelihood of favorable 30-day neurological outcome decreased for every minute that prehospital resuscitation efforts continued (R-squared=0.295-0.037; P<0.001, respectively). Table 2 shows the sensitivity and negative predictive value of the prehospital resuscitation duration and the EMS responder resuscitation duration for favorable 30-day neurological outcome in each group stratified by initial cardiac arrest rhythm and bystander resuscitation status. Similar prehospital resuscitation durations were necessary to achieve a sensitivity of ≥99% for favorable 30-day neurological outcome (minimum) in each of the four groups (40 min in the shockable/bystander resuscitation and the shockable/no bystander resuscitation group, 44 min in the non-shockable/bystander resuscitation group and 45 min in the non-shockable/no bystander resuscitation group). To achieve a sensitivity and negative predictive value of 100% (maximum), concordant prehospital resuscitation durations were needed in the four groups, ranging from 56 min to 59 min. Moreover, similar results were found for the EMS responder resuscitation durations, with the minimum ranging from 33 min to 39 min and the maximum ranging from 51 min to 55 min.
Discussion

Since 1992, all resuscitation guidelines have stated that early access, early BLS, early defibrillation, and early ALS, are essential components of a series of actions designed to reduce the mortality associated with cardiac arrest.\textsuperscript{3-9,19} We analyzed the prehospital resuscitation duration from call accept, inclusive of EMS responder resuscitation efforts with or without bystander resuscitation efforts, to determine the minimum period of prehospital resuscitation efforts to maximize good neurologic outcomes. This nationwide, population-based study of prehospital resuscitation without implementation of TOR rules demonstrates that the prehospital resuscitation duration for favorable 30-day neurological outcome did not differ widely among four groups stratified by initial cardiac arrest rhythm and bystander resuscitation status, with the minimum, to achieve \(\geq 99\%\) sensitivity, ranging from 40 min to 45 min and the maximum, to achieve 100% sensitivity and 100\% negative predictive value, ranging from 56 min to 58 min. Furthermore, similar results were found for the EMS responder resuscitation duration, with the minimum ranging from 33 min to 39 min and the maximum ranging from 51 min to 55 min. These findings suggest prehospital resuscitation efforts should be continued for at least 40 min or longer from call receipt, including at least 33 min or longer of EMS responder resuscitation efforts from scene arrival, in all adult patients with bystander-witnessed OHCA.

In 2000, the national association of EMS physicians standards and clinical practice committee suggested that EMS responder resuscitation efforts could be terminated in patients who do not respond to 20 to 30 min of ALS.\textsuperscript{23} However, our study suggests that prehospital resuscitation efforts, inclusive of EMS responder resuscitation efforts, can be continued for longer intervals with the possibility of success than previous thought. Several factors might account for longer durations of prehospital resuscitation efforts being associated with successful resuscitation
in our study. Since 2000, the resuscitation protocols have been revised four times.\textsuperscript{3-9} Our previous study revealed a significant increase in neurologically intact survival, from 2.1% in 2005 to 4.3% in 2009 for bystander-witnessed OHCA,\textsuperscript{2} suggesting that the overall quality of resuscitation care, inclusive of the increment of bystander resuscitation with or without PAD\textsuperscript{2,16,17,20} and post cardiac arrest care,\textsuperscript{24} has improved. Similar results were shown in this study. In 2012, Goldberger et al demonstrated that patients with cardiac arrest occurring in hospitals where the median length of resuscitation efforts was longer were more likely to survive to discharge than those in hospitals where the median length of resuscitation efforts was shorter.\textsuperscript{12} In-hospital resuscitation duration ranged from 1 min to 60 min for 31,198 patients achieving ROSC. In our study, the range of prehospital resuscitation duration to achieve prehospital ROSC was similar; however, frequencies of favorable 30-day neurological outcome were lower. Possible explanations for these findings include differences in characteristics between the two study populations, more rapid deployment of high-quality resuscitation during in-hospital arrest, and improved access to high-quality post-cardiac care in the in-hospital setting. Regardless, our findings suggest that high-quality resuscitation care expands the length of prehospital resuscitation efforts that produce favorable neurologic outcomes, similar to the findings for in-hospital arrests.

In the 2010 resuscitation guidelines, the TOR rules included no ROSC after 3 full rounds of BLS or no ROSC after full ALS prior to transport.\textsuperscript{4} In 2013, Reynolds et al reported EMS responder resuscitation duration under the TOR rules.\textsuperscript{25} They showed that 90% of the neurologically intact survivors had achieved prehospital ROSC within 16.1 min of EMS responder resuscitation duration. However, 57.5% (3,168/5,517) of the OHCA patients met BLS TOR rules and did not receive EMS responder resuscitation attempts. In an analysis of data from the All-Japan Utstein Registry where EMS responders do not implement TOR rules, Kajino et al
showed that standard TOR rules had high specificity and positive predictive value for predicting unfavorable neurological outcome, but the specificity did not reach 99%. These findings suggest that TOR rules affect the length of prehospital resuscitation efforts and the number of neurologically intact survivors.

The central question raised by this study is how long EMS responders should continue resuscitation efforts. This is a difficult question to answer because community systems of emergency care vary around the world, and ethical and culture norms must be considered. It is clear that field termination reduces transport to the hospital, but the optimal prehospital resuscitation duration has not previously been established. Our results demonstrate that prehospital resuscitation efforts to achieve favorable neurological outcome should be continued for at least 40 min from call receipt, inclusive of bystander and EMS responder resuscitation efforts, and for at least 33 min from scene arrival for EMS responder resuscitation efforts exclusively. We believe that this study will help optimize treatment for OHCA patients to maximize the number of neurologically intact survivors of cardiac arrest and will inform the development of future TOR rules.

This study has several limitations. First, in all epidemiological studies, data integrity, validity, and ascertainment bias are potential limitations. However, uniform data collection, a large sample size, and a population-based design covering all known OHCA in Japan minimize these potential sources of bias. Second, the time of call receipt was used as the time of first resuscitation care to calculate the prehospital resuscitation duration. Collapse or first bystander resuscitation attempts might be better time indicators, but both are difficult to accurately record. If bystander resuscitation is not performed, the “call-receipt to ROSC interval” includes a period of no flow followed by a period of EMS responder resuscitation efforts; when bystander resuscitation is performed, we have no way of knowing what percentage of the
time from call receipt to EMS arrival: the bystanders actually performed resuscitation. However, we found similar lengths of time in all four groups when we analyzed the length of EMS responder resuscitation efforts exclusive of bystander attempts, suggesting that the presence of absence of bystander efforts does not substantially alter the timeframe needed to maximize neurologically intact survivors. Furthermore, the time interval from call receipt to scene arrival is critical for survival. The time of scene arrival was used as the time of first EMS responder resuscitation care to calculate the EMS responder resuscitation duration. Arrival at patient’s side or first EMS responder resuscitation attempts might be better time indicators, but the time interval rushing to the patient’s side from scene arrival is an important part of EMS responder resuscitation efforts. Third, although the quality of resuscitation affects neurological outcome, resuscitation quality were lacking. Fourth, information on ongoing resuscitation efforts after hospital arrival was lacking. We provided data demonstrating that 16.9% of patients who had favorable neurologic outcomes achieved ROSC after hospital arrival; however, <1% of all patients who did not achieve prehospital ROSC went on to have favorable neurological outcome. Our analysis of this subgroup is limited because we do not have information about whether these patients received epinephrine, further defibrillation, or how long resuscitation effort was continued after hospital arrival. Fifth, details of post-cardiac arrest care and use of extracorporeal CPR were lacking. With broader adoption of these treatments, optimum length of the prehospital recitation efforts may need to be extended. Finally, neurological outcomes were measured at 30 days after OHCA but some patients might recover more gradually. A recent consensus statement acknowledged that optimal times for follow-up after OHCA have yet to be established. A 3-month post-discharge period would balance the opportunity for recovery with the number of patients lost to follow-up.
Conclusions

Based on results from the two shockable arrest groups, prehospital resuscitation efforts should be continued for at least 40 min from call receipt, including at least 33 min of EMS responder resuscitation efforts from scene arrival, in all adult patients with bystander-witnessed OHCA to achieve a $\geq 99\%$ sensitivity of favorable 30-day neurological outcome. The costs and benefits of prolonging prehospital resuscitation efforts must be taken into consideration when translating these results into clinical practice and further studies are needed.

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Promotion Foundation” in Fukuoka, Japan. The other authors did not have any Disclosure of Potential Conflicts of Interest.

References:


Clinical Perspective

Since 1992, all cardiopulmonary resuscitation (CPR) guidelines have stated that the chain of survival (early access, early basic life support, early defibrillation and advanced cardiovascular life support) is an essential series of actions designed to reduce the mortality associated with out-of-hospital cardiac arrest (OHCA). Recent CPR guidelines state that termination of resuscitation (TOR) rules are an important component of CPR, but TOR rules have not specified the minimum duration for prehospital resuscitation efforts. Further, TOR rules are difficult to objectively define because community systems of emergency care vary around the world and ethical and culture norms must be considered. It is clear that field termination reduces transport to the hospital, but the optimal prehospital CPR duration to maximize the number of patients with good neurologic outcome has not previously been established. From the All-Japan Utstein Registry, where emergency medical service (EMS) responders do not implement TOR rules, we demonstrate that prehospital resuscitation efforts to achieve favorable neurological outcome should be continued for at least 40 min from call receipt, inclusive of bystander and EMS responder resuscitation efforts, and for at least 33 min from scene arrival for EMS responder resuscitation efforts exclusively. We believe that this study will help optimize treatment for OHCA patients to maximize the number of neurologically intact survivors of cardiac arrest and will inform the development of future TOR rules. The costs and benefits of prolonging prehospital resuscitation efforts must be taken into consideration when translating these results into clinical practice and further studies are needed.
Table 1. Baseline Characteristics of the Patients Stratified by Initial Cardiac Arrest Rhythm and Bystander Resuscitation Status \(^*\)

<table>
<thead>
<tr>
<th></th>
<th>Shockable/bystander resuscitation group (n=23,028)</th>
<th>Shockable/no bystander resuscitation group (n=19,383)</th>
<th>Non-shockable/bystander resuscitation group (n=104,212)</th>
<th>Non-shockable/no bystander resuscitation group (n=135,560)</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66 (56-77)</td>
<td>67 (57-76)</td>
<td>81 (71-88)</td>
<td>77 (66-85)</td>
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<tr>
<td>Male sex, No. (%)</td>
<td>17,792 (77.3)</td>
<td>15,285 (78.9)</td>
<td>55,400 (53.2)</td>
<td>82,725 (61.0)</td>
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<td>Dispatcher resuscitation instruction, No. (%)</td>
<td>13,399 (58.2)</td>
<td>4,422 (22.8)</td>
<td>65,058 (62.4)</td>
<td>34,082 (25.1)</td>
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<td>Bystander resuscitation, No. (%)</td>
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<tr>
<td>Chest compression only</td>
<td>14,963 (65.0)</td>
<td>71,320 (68.4)</td>
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<tr>
<td>Chest compression with rescue breathing</td>
<td>8,065 (35.0)</td>
<td>32,892 (31.6)</td>
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<td>Public access defibrillation, No. (%)</td>
<td>3,437 (14.9)</td>
<td>27 (0.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<td>Initial cardiac arrest rhythm, No. (%)</td>
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<tr>
<td>Pulseless ventricular tachycardia</td>
<td>43 (1.9)</td>
<td>505 (2.6)</td>
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<td>Ventricular Fibrillation</td>
<td>22,594 (98.1)</td>
<td>18,878 (97.4)</td>
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<td>Pulseless electrical activity</td>
<td>39,230 (37.6)</td>
<td>55,305 (40.8)</td>
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<td>Asystole</td>
<td>64,982 (62.4)</td>
<td>80,255 (59.2)</td>
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<td>Defibrillation by EMS responder, No. (%)</td>
<td>20,282 (88.1)</td>
<td>18,481 (95.3)</td>
<td>5,154 (4.9)</td>
<td>7,085 (5.2)</td>
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<td>Advanced airway management, No. (%)</td>
<td>9,945 (43.2)</td>
<td>9,224 (47.6)</td>
<td>50,833 (48.8)</td>
<td>61,911 (45.7)</td>
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<td>Intravenous fluid, No. (%)</td>
<td>7,409 (32.2)</td>
<td>6,434 (33.2)</td>
<td>29,732 (28.5)</td>
<td>37,031 (27.3)</td>
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<td>Prehospital epinephrine, No. (%)</td>
<td>3,795 (16.5)</td>
<td>3,085 (15.9)</td>
<td>15,002 (14.4)</td>
<td>16,455 (12.1)</td>
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<td>Cardiac etiology, No. (%)</td>
<td>20,179 (87.6)</td>
<td>16,992 (87.7)</td>
<td>53,797 (51.6)</td>
<td>67,583 (49.9)</td>
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<td>Achievement of prehospital ROSC, No. (%)</td>
<td>7,140 (31.0)</td>
<td>4,827 (24.9)</td>
<td>9,038 (8.7)</td>
<td>11,180 (8.2)</td>
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<td>Time interval, min</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>From collapse to call receipt†</td>
<td>2 (0-4)</td>
<td>1 (0-4)</td>
<td>2 (0-5)</td>
<td>2 (0-5)</td>
</tr>
<tr>
<td>From call receipt to scene‡</td>
<td>7 (5-9)</td>
<td>6 (5-8)</td>
<td>7 (5-9)</td>
<td>7 (5-9)</td>
</tr>
<tr>
<td>From call receipt to hospital arrival§</td>
<td>30 (24-38)</td>
<td>30 (24-37)</td>
<td>31 (25-38)</td>
<td>31 (25-39)</td>
</tr>
<tr>
<td>Prehospital resuscitation duration , min</td>
<td>27 (18-35)</td>
<td>27 (20-34)</td>
<td>30 (24-37)</td>
<td>30 (24-38)</td>
</tr>
<tr>
<td>EMS responder resuscitation duration§, min</td>
<td>19 (12-27)</td>
<td>20 (14-27)</td>
<td>22 (17-29)</td>
<td>23 (17-30)</td>
</tr>
</tbody>
</table>

ROSC indicates return of spontaneous circulation; EMS, emergency medical service.

†Values are expressed as median (the 25th percentile to the 75th percentile). The time intervals from collapse to call receipt, scene, and hospital arrival were calculated in 97.6% (273,322/282,183), 99.9% (281,864/282,183) and 99.7% (281,436/282,183) of the patients, respectively. The durations of prehospital resuscitation and EMS responder resuscitation were calculated in 99.6% (281,005/282,183) and 99.5% (280,793/282,183) of the patients, respectively. There were significant differences among the groups with respect to any of variables listed (P<0.001).
Table 2. Durations of Prehospital Resuscitation Efforts and EMS Responder Resuscitation Efforts for Favorable 30-Day Neurological Outcome.

<table>
<thead>
<tr>
<th>Minimum duration</th>
<th>Shockable/bystander resuscitation group (n=22,380)</th>
<th>Shockable/no bystander resuscitation group (n=19,004)</th>
<th>Non-shockable/bystander resuscitation group (n=100,934)</th>
<th>Non-shockable/no bystander resuscitation group (n=131,145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prehospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>resuscitation</td>
<td>40 min</td>
<td>40 min</td>
<td>44 min</td>
<td>45 min</td>
</tr>
<tr>
<td>duration</td>
<td>n* /total n (%) 4,490/4,536 (99.0)</td>
<td>2,487/2,513 (99.0)</td>
<td>952/961 (99.1)</td>
<td>1,505/1,520 (99.0)</td>
</tr>
<tr>
<td>Sensitivity %</td>
<td>99.0 (98.7-99.3)</td>
<td>99.0 (98.6-99.4)</td>
<td>99.1 (98.5-99.7)</td>
<td>99.0 (98.5-99.5)</td>
</tr>
<tr>
<td>Negative</td>
<td>2,594/2,640 (99.0)</td>
<td>2,140/2,166 (99.0)</td>
<td>9,650/9,659 (99.0)</td>
<td>11,491/11,506 (99.0)</td>
</tr>
<tr>
<td>predictive value</td>
<td>98.3 (97.8-98.8)</td>
<td>98.8 (98.3-99.3)</td>
<td>99.9 (99.8-100)</td>
<td>99.9 (99.8-99.9)</td>
</tr>
<tr>
<td>Maximum duration</td>
<td>58 min</td>
<td>59 min</td>
<td>56 min</td>
<td>58min</td>
</tr>
<tr>
<td></td>
<td>n* /total n (%) 4,536/4,536 (100)</td>
<td>2,513/2,513 (100)</td>
<td>961/961 (100)</td>
<td>1,520/1,520 (100)</td>
</tr>
<tr>
<td></td>
<td>79/79 (100)</td>
<td>27/27 (100)</td>
<td>1,219/1,219 (100)</td>
<td>690/690 (100)</td>
</tr>
<tr>
<td>EMS responder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>resuscitation</td>
<td>33 min</td>
<td>34 min</td>
<td>37 min</td>
<td>39min</td>
</tr>
<tr>
<td>duration</td>
<td>n* /total n (%) 4,434/4,479 (99.0)</td>
<td>2,491/2,513 (99.0)</td>
<td>943/952 (99.1)</td>
<td>1,506/1,521 (99.0)</td>
</tr>
<tr>
<td>Sensitivity %</td>
<td>99.0 (98.7-99.3)</td>
<td>99.1 (98.8-99.5)</td>
<td>99.1 (98.4-99.7)</td>
<td>99.0 (98.5-99.5)</td>
</tr>
<tr>
<td>Negative</td>
<td>2,313/2,358 (99.0)</td>
<td>1,886/1,908 (99.0)</td>
<td>8,289/8,298 (99.0)</td>
<td>9,490/9,505 (99.0)</td>
</tr>
<tr>
<td>predictive value</td>
<td>98.1 (97.5-98.6)</td>
<td>98.8 (98.4-99.3)</td>
<td>99.9 (99.8-100)</td>
<td>99.8 (99.8-99.9)</td>
</tr>
<tr>
<td>Maximum duration</td>
<td>54 min</td>
<td>54 min</td>
<td>51 min</td>
<td>55min</td>
</tr>
<tr>
<td></td>
<td>n* /total n (%) 4,479/4,479 (100)</td>
<td>2,513/2,513 (100)</td>
<td>952/952 (100)</td>
<td>1,521/1,521 (100)</td>
</tr>
<tr>
<td></td>
<td>10/10 (100)</td>
<td>70/70 (100)</td>
<td>1,104/1,104 (100)</td>
<td>696/696 (100)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; EMS, emergency medical service. * Number of patients with favorable 30-day neurological outcome. † Number of patients with unfavorable 30-day neurological outcome. Sensitivity and negative predictive value for favorable 30-day neurological outcome were calculated in the study cohort with ≤60 min of prehospital resuscitation duration who were stratified by initial cardiac arrest rhythm and bystander resuscitation status.
**Figure Legends:**

**Figure 1.** Study flow diagram and outcomes. EMS indicates emergency medical service; ROSC, return of spontaneous circulation. Each percent represents the number of each study outcome/the total number of patients in each of the four subgroups stratified by initial cardiac arrest rhythm and bystander resuscitation status. *Includes patients with Do Not Resuscitate (DNR) order.

**Figure 2.** Distributions of prehospital resuscitation duration for the entire study patients. Each stacked bar shows the number of cases stratified by prehospital ROSC status. Each box plot (5th, 25th, 50th, 75th and 95th percentile values) represents the prehospital resuscitation duration stratified by prehospital ROSC status.

**Figure 3.** Cumulative rates of 30-day neurological outcomes (A) and favorable 30-day neurological outcome (B).

**Figure 4.** Adjusted odds ratios for favorable 30-day neurological outcome. EMS indicates emergency medical service; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

**Figure 5.** The relationship between prehospital resuscitation duration and favorable 30-day neurological outcome. The curve estimation in quadratic model of the shockable/bystander Resuscitation group (A), the shockable/no bystander resuscitation group (B), the non-shockable/bystander resuscitation group (C) and the non-shockable/no bystander resuscitation Group (D). Each solid curve with dotted lines shows predicted values with 95%
confidence intervals for favorable 30-day neurological. Each light gray color box represents the actual no. of cases achieving favorable 30-day neurological outcome and each deep gray color box represents the actual no. of cases not achieving favorable 30-day neurological outcome.
Confirmed cardiac arrest outside the hospital  n=925,288

Resuscitation attempted  n=910,581

Adults  n=896,344

Arrest witnessed by bystanders, identified initial cardiac arrest rhythm and identified bystander resuscitation status  n=282,183

No resuscitation*  n=14,707

Age<18 years  n=14,173
Unidentified age  n=64

Arrest witnessed by EMS responders  n=72,874
Arrest not witnessed  n=529,092
Unidentified witness status  n=2,330
Unidentified cardiac arrest rhythm  n=6,853
Unidentified bystander resuscitation  n=3,009

Shockable arrest  n=42,411

Bystander resuscitation  n=23,028

Prehospital ROSC  n=7,140 (31.0%)
30-day survival  n=6,597 (28.6%)
30-day favorable neurological outcome  n=4,601 (20.0%)

No bystander resuscitation  n=19,383
Prehospital ROSC  n=4,827 (24.9%)
30-day survival  n=4,452 (23.0%)
30-day favorable neurological outcome  n=2,556 (13.2%)

Non-shockable arrest  n=239,772

Bystander resuscitation  n=104,212
Prehospital ROSC  n=9,038 (8.7%)
30-day survival  n=4,538 (4.4%)
30-day favorable neurological outcome  n=979 (0.9%)

No bystander resuscitation  n=135,560
Prehospital ROSC  n=11,180 (8.2%)
30-day survival  n=6,071 (4.5%)
30-day favorable neurological outcome  n=1,553 (1.1%)

1 lost to follow up
5 lost to follow up
8 lost to follow up

Figure 1
Figure 4

Adjusted Odds Ratio (95% confidence interval)

Patients with ≤60 min of prehospital resuscitation duration (n=273,463)

- Age, y: 0.97 (0.969-0.972) < 0.001
- Prehospital resuscitation duration, min: 0.84 (0.828-0.844) < 0.001
- Year (reference year: 2005): 1.14 (1.13-1.15) < 0.001
- Male: 1.13 (1.07-1.20) < 0.001
- Presence of bystander resuscitation: 1.26 (1.20-1.32) < 0.001
- Initial arrest rhythm (reference: PEA or Asystole)
  - Shockable (VF or pulseless VT): 7.53 (7.10-7.96) < 0.001
- Advanced life support by EMS responders
  - Use of epinephrine: 1.02 (0.93-1.12) 0.646
  - Use of supraglottic airway or endotracheal intubation
- Cardiac etiology: 1.85 (1.73-1.98) < 0.001

Unfavorable 30-day neurological outcome  Favorable 30-day neurological outcome
Figure 5

A. Shockable/bystander resuscitation group (n=22,380)

- R-squared = 0.295
- P < 0.001

B. Shockable/no bystander resuscitation group (n=19,383)

- R-squared = 0.234
- P < 0.001
Figure 5, cont’d