Importance
Neurologically intact survival after out-of-hospital cardiac arrest (OHCA) has been increasing in Japan. However, associations between increased prehospital care, including bystander interventions and increases in survival, have not been well estimated.

Objective
To estimate the associations between bystander interventions and changes in neurologically intact survival among patients with OHCA in Japan.

Design, Setting, and Participants
Retrospective descriptive study using data from Japan’s nationwide OHCA registry, which started in January 2005. The registry includes all patients with OHCA transported to the hospital by emergency medical services (EMS) and recorded patients’ characteristics, prehospital interventions, and outcomes. Participants were 167,912 patients with bystander-witnessed OHCA of presumed cardiac origin in the registry between January 2005 and December 2012.

Exposures
Prehospital interventions by bystander, including defibrillation using public-access automated external defibrillators and chest compression.

Main Outcomes and Measures
Neurologically intact survival was defined as Glasgow-Pittsburgh cerebral performance category score 1 or 2 and overall performance category scores 1 or 2 at 1 month or at discharge. The association between the interventions and neurologically intact survival was evaluated.

Results
From 2005 to 2012, the number of bystander-witnessed OHCA of presumed cardiac origin increased from 17,882 (14.0 per 100,000 persons [95% CI, 13.8-14.2]) to 23,797 (18.7 per 100,000 persons [95% CI, 18.4-18.9]), and neurologically intact survival increased from 587 cases (age-adjusted proportion, 3.3% [95% CI, 3.0%-3.5%]) to 1710 cases (8.2% [95% CI, 7.8%-8.6%]). The rates of bystander chest compression increased from 38.6% to 50.9%, bystander-only defibrillation increased from 0.1% to 2.3%, bystander defibrillation combined with EMS defibrillation increased from 0.1% to 1.4%, and EMS-only defibrillation decreased from 26.6% to 23.5%. Performance of bystander chest compression, compared with no bystander chest compression, was associated with increased neurologically intact survival (8.4% [6594 survivors/78,592 cases] vs 4.1% [3595 survivors/88,720 cases]; odds ratio [OR], 1.52 [95% CI, 1.45-1.60]). Compared with EMS-only defibrillation (15.0% [6445 survivors/42,916 cases]), bystander-only defibrillation (40.7% [931 survivors/2287 cases]) was associated with increased neurologically intact survival (OR, 2.24 [95% CI, 1.93-2.61]), as was combined bystander and EMS defibrillation (30.5% [444 survivors/1456 cases]; OR, 1.50 [95% CI, 1.31-1.71]), whereas no defibrillation (2.0% [2369 survivors/120,653 cases]) was associated with reduced survival (OR, 0.43 [95% CI, 0.39-0.48]).

Conclusions and Relevance
In Japan, between 2005 and 2012, the rates of bystander chest compression and bystander defibrillation increased and were associated with increased odds of neurologically intact survival.


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Out-of-hospital cardiac arrest (OHCA) is an increasing health concern worldwide, with poor prognoses, particularly in resource-constrained settings.1,2 Efforts have been made to streamline and increase the use of 4 prehospital factors and 1 hospital factor that improve survival.3-4 Improvements in survival rates have been demonstrated for early call to emergency medical services (EMS), increased use of bystander chest compression, use of early defibrillation, and improved postresuscitation care.5-9

Although efforts to improve prehospital care by EMS have plateaued, improving bystander interventions (chest compression and defibrillation) remains an opportunity for improving outcomes. Some countries have started deploying public-access automated external defibrillators (AEDs) and training laypeople in AED use and chest compression.7,10 Although public-access AEDs can improve outcomes by reducing the time to defibrillation for patients with OHCA with shockable rhythms,11,12,17 the potential benefits of public-access AEDs to the population are not clear.13,14

In Japan, expanded use of AEDs by both EMS personnel and laypeople was deployed in 2004. One immediate outcome was the accelerated use of defibrillation by EMS personnel, achieved by eliminating the need for medical instruction previously delivered by radio or telephone.8 Slow but steady changes have occurred with the increase of public-access AED use and chest compression by bystanders.15 Studies in the early AED era in Japan described increased survival with increased bystander defibrillation and accelerated EMS defibrillation but did not examine the association between the increased survival and the improvements in prehospital care.7 A recent study8 showed that the increase in accelerated EMS defibrillation was associated with improved survival but could not appropriately estimate how bystander interventions (particularly slowly increasing but highly effective ones, such as chest compression) were associated with current survival. The purpose of this study was to estimate the association between bystander interventions and neurologically intact survival and to estimate the association between the increase in bystander interventions and the survival increments using nationwide registry data in Japan.

Methods

Study Settings

In Japan, municipal fire departments dispatch ambulances responding to calls to the nationally uniform EMS number (119). Most ambulance teams include emergency life support technicians certified to provide advanced life support procedures (advanced airway management, intravenous line placement, adrenaline administration, and defibrillation). Ambulances with physicians are not routinely used. EMS personnel follow Japanese guidelines for cardiopulmonary resuscitation, based on the most current American Heart Association guidelines. Endotracheal intubation and administration of adrenaline by specially trained and certified emergency life support technicians started in July 2004 and April 2006, respectively. Use of AEDs by any person for patients with OHCA has been permitted since July 2004: EMS personnel can perform defibrillation without online guidance by a physician. Marukawa et al16 estimated the cumulative number of public-access AEDs in the entire country to be 364,959 in 2012 (Table 1). EMS personnel are not allowed to stop resuscitation at the scene, and all patients with OHCA are transported to a hospital.

The Fire and Disaster Management Agency has managed the All-Japan Utstein Registry since January 2005, which registers all patients with OHCA transported to the hospital by EMS. The EMS personnel collect data using a standardized format.17 The collected data include patient characteristics (age, sex), initial rhythms (ventricular fibrillation or pulseless ventricular tachycardia, pulseless electrical activity, asystole, and other), presumed cause of arrest (clinically determined by physicians after hospital arrival), witnessed status, bystander type (family member, colleague, and other), bystander interventions (chest compression and defibrillation), and activities by EMS, with their time courses. The timing of EMS defibrillation is recorded, but that of bystander defibrillation is not. Other recorded data include return of spontaneous circulation before hospital arrival and survival at 1 month or at discharge, whichever was earlier. Survivors’ neurologic function is assessed at 1 month or discharge by the attending physicians using the Glasgow-Pittsburgh Cerebral Performance Category (CPC) score and Overall Performance Category (OPC) score. The CPC and OPC scores are classified into 5 categories: 1 (good), 2 (moderately disabled), 3 (severely disabled), 4 (vegetative), or 5 (dead).17 The Fire and Disaster Management Agency compiles and checks the quality of the data. Details have been described.18,19

Study Design

This was a descriptive study using prospectively collected nationwide data for patients with OHCA in Japan, obtained from the Utstein Registry database. We described the trends in prehospital care and outcomes during the study period. We then estimated associations of chest compression and defibrillation with neurologically intact survival.

Ethical clearance for the study protocol was granted by the ethics committee of Kanagawa University of Human Services because the study used anonymized public domain data. The research ethics committee at the Graduate School of Medicine, University of Tokyo, approved the study.

We also present values for population-attributable fraction (AFp) (eAppendix 1 in the Supplement),20 the percentage of the current survival that would not occur if an intervention were entirely nonexistent (counterfactual situation). We also estimated how the increase of interventions in a certain period was associated with survival increments using population impact fraction (IFp).21 The IFp is a subtype of the AFp, in which comparison is made between current and past observations (actual situation). Thus, the IFp can be used to evaluate the change during a certain period.

Participants

The present study included patients with bystander-witnessed OHCA of presumed cardiac origin, transported to the hospital by EMS between January 2005 and December 2012,
### Table 1. Patient Characteristics, Out-of-Hospital Care, Outcomes, and Accumulated Sales of Public-Access AEDs in Japan Between 2005 and 2012

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>17 882</td>
</tr>
<tr>
<td>2006</td>
<td>18 897</td>
</tr>
<tr>
<td>2007</td>
<td>19 696</td>
</tr>
<tr>
<td>2008</td>
<td>20 769</td>
</tr>
<tr>
<td>2009</td>
<td>21 112</td>
</tr>
<tr>
<td>2010</td>
<td>22 463</td>
</tr>
<tr>
<td>2011</td>
<td>23 296</td>
</tr>
<tr>
<td>2012</td>
<td>23 797</td>
</tr>
<tr>
<td><strong>Incidence per 100 000 population</strong> (95% CI)</td>
<td>14.0 (13.8-14.2)</td>
</tr>
<tr>
<td><strong>Cumulative sales of public-access AEDs</strong></td>
<td>10 961</td>
</tr>
<tr>
<td>Male sex</td>
<td>11 306 (63.2)</td>
</tr>
<tr>
<td>Age, y</td>
<td>11 972 (63.4)</td>
</tr>
<tr>
<td>&lt;15</td>
<td>115 (0.6)</td>
</tr>
<tr>
<td>15–44</td>
<td>901 (5.0)</td>
</tr>
<tr>
<td>45–64</td>
<td>3722 (20.8)</td>
</tr>
<tr>
<td>65–74</td>
<td>3996 (22.3)</td>
</tr>
<tr>
<td>75–84</td>
<td>5069 (28.3)</td>
</tr>
<tr>
<td>≥85</td>
<td>4079 (22.8)</td>
</tr>
<tr>
<td><strong>Initial rhythm</strong></td>
<td>3859 (21.6)</td>
</tr>
<tr>
<td>VF/VF</td>
<td>4329 (22.9)</td>
</tr>
<tr>
<td>Asystole</td>
<td>8430 (47.1)</td>
</tr>
<tr>
<td>Other</td>
<td>437 (2.4)</td>
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<tr>
<td><strong>Bystander chest compression</strong></td>
<td>6898 (38.6)</td>
</tr>
<tr>
<td>Bystander only</td>
<td>25 (0.1)</td>
</tr>
<tr>
<td>EMS only</td>
<td>4749 (26.6)</td>
</tr>
<tr>
<td>Combined</td>
<td>21 (0.1)</td>
</tr>
<tr>
<td>Advanced airway use</td>
<td>9043 (50.6)</td>
</tr>
<tr>
<td><strong>Adrenaline use</strong></td>
<td>39 (0.2)</td>
</tr>
<tr>
<td>Call-to-contact interval, median (IQR, min)</td>
<td>8 (6-10)</td>
</tr>
<tr>
<td>Call-to-defibrillation interval, median (IQR, min)</td>
<td>10 (8-14)</td>
</tr>
<tr>
<td>Contact-to-hospital arrival interval, median (IQR, min)</td>
<td>21 (16-27)</td>
</tr>
<tr>
<td>Neurologically intact survival</td>
<td>587 (3.3)</td>
</tr>
<tr>
<td>Age-adjusted proportion (95% CI)</td>
<td>3.3 (3.0-3.5)</td>
</tr>
<tr>
<td>1-mo survival</td>
<td>1282 (7.2)</td>
</tr>
<tr>
<td>Age-adjusted proportion (95% CI)</td>
<td>7.2 (6.8-7.5)</td>
</tr>
<tr>
<td>ROSC before hospital arrival</td>
<td>1533 (8.6)</td>
</tr>
</tbody>
</table>

Abbreviations: AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; IQR, interquartile range; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VF/VF, ventricular fibrillation or pulseless ventricular tachycardia.

*Data derived from Marukawa et al (cumulative numbers estimated from annual sales data from AED manufacturers).

* Patients received both bystander defibrillation and EMS defibrillation.

* Those with outlying (>120 min) or impossible (≤0 min) time data were excluded.

* Only EMS defibrillations were included because the timing of bystander defibrillations was not recorded.

* Defined as survival with Glasgow-Pittsburgh Cerebral Performance Category scores 1 or 2 and Overall Performance Category scores 1 or 2.

* With direct standardization using age-specific population in 2005.
excluding cases with unknown witness status or witnessed by EMS. The causes of arrest were presumed to be of cardiac origin unless diagnosed otherwise by physicians after hospital arrival. We also excluded those with unknown or unrealistic (ie, >150 years) age (n = 67 [0.04%]).

**Primary Outcome**

The primary outcome was neurologically intact survival, defined as CPC score of 1 or 2 and OPC score of 1 or 2 at 1 month or at discharge, whichever was earlier.

**Analysis**

**Trend of Neurologically Intact Survival**

We described the patient characteristics, procedures received, and the survival in numbers and proportions (crude and age-adjusted). The age-adjusted proportions were shown with 95% CIs. Direct age adjustment was used, with the age-specific population in 2005 as the standard. The expected number of neurologically intact survivors was calculated by applying the age-specific survival rates in 2005 to the population in each year. Excess survival (total survival increment) was the difference between the expected and actual numbers of survivors.

**Logistic Regression Analysis**

The logistic model estimated the ORs with 95% CIs for defibrillation (4 categories) and bystander chest compression, adjusting for calendar year, prefecture, age, sex, initial rhythms, EMS call-to-contact interval, contact-to-hospital arrival interval, adrenaline administration, and advanced airway management. We excluded patients with impossible (≥0 minute) or outlying (>120 minutes) data in the above-mentioned intervals (n = 600 [0.4%]). Accurate estimation of the relative risks for adrenaline administration and advanced airway management cannot be made in our model. This requires adjustment of time-dependent selection biases (severely affected patients with poor outcomes tend to require longer resuscitation and to receive advanced procedures). Thus, these factors were used in our model as indicators of severity of the patients. The calibration of the model was tested using a calibration graph as well as Hosmer-Lemeshow test, respectively.

**IFp**

The IFp indicates theoretical proportional change of the targeted outcome by comparing with the counterfactual baselines for which only the targeted exposure (intervention) was lacking, assuming the other factors were constant. This assumption is in some cases unrealistic. For example, without public-access AEDs, EMS personnel would give defibrillation as needed. Bystander defibrillations substitute for or supplement the EMS defibrillations. The AFp indicates share of current association rather than how the increased interventions were associated with survival increment.

The evaluation of defibrillation also included EMS defibrillation to compare with its associations and to consider the interaction between bystander and EMS defibrillation: patients requiring both defibrillations would show worse outcomes than those receiving only bystander defibrillation, reflecting the severity. Thus, 4 defibrillation categories were created: those receiving bystander defibrillation only, EMS defibrillation only, bystander defibrillation combined with EMS defibrillation, and no defibrillation. The AFp for each category was calculated by comparing with the situation in which only that category was lacking.

To estimate the associations between the increase in each intervention and the survival increment, we used IFp values based on comparisons with more realistic baselines (actual situations in the past) (eAppendix 3 in the Supplement). For the bystander defibrillation, the situation in each year was compared with a situation in which there are no public-access AEDs but EMS personnel provide defibrillation (actual situations before June 2004). We compared the situation for chest compression in each year with that in 2005 (information before 2004 was unavailable). A partial survival increment attributable to increased exposure to an intervention and proportions of the partial increments in the total increments were estimated (eAppendix 4 in the Supplement).

**Results**

Of the 925,288 patients with OHCA registered in the database between 2005 and 2012, 167,912 patients met the above-mentioned criteria (Figure). Of these, 46,882 received defibrillation by EMS personnel, a bystander, or both, and 78,863 received bystander chest compression.

From 2005 to 2012, the number of bystander-witnessed OHCA of presumed cardiac origin increased from 17,882 cardiac arrests (14.0 per 100,000 persons [95% CI, 13.8-14.2]) to 23,792 cardiac arrests (18.7 per 100,000 persons [95% CI, 18.4-18.9]) (Table 1). The proportion of patients 75 years or older increased. Neither the interval from the call to EMS patient contact nor the interval from the call to first defibrillation decreased. The rates of bystander chest compression increased from 38.6% to 50.9%; rates of bystander-only defibrillation increased from 0.1% to 2.3%; rates of bystander defibrillation combined with EMS defibrillation increased from 0.1% to 1.4%; and rates of EMS-only defibrillation decreased from 26.6% to 23.5%. Nonfamily bystanders were more likely than family bystanders to perform both chest compression and defibrillation using a public-access AED (eTable 1 in the Supplement).
Neurologically intact survival increased from 587 cases (age-adjusted proportion, 3.3% [95% CI, 3.0%-3.5%]) to 1710 cases (8.2% [95% CI, 7.8%-8.6%]) (Table 2). Among patients who achieved neurologically intact survival, rates of bystander-only defibrillation increased from 1.0% to 12.7%; rates of bystander defibrillation combined with EMS defibrillation increased from 0.9% to 5.8%; rates of EMS-only defibrillation decreased from 73.4% to 56.1%; and rates of chest compression increased from 53.7% to 68.9%.

The logistic models yielded odds ratios (ORs) indicating the associations between bystander interventions and neurologically intact survival (Table 3 and eTable 2 in the Supplement). During the overall study period, performance of bystander chest compression, compared with no bystander chest compression, was associated with increased neurologically intact survival (8.4% [6594 survivors/78 592 cases] vs 4.1% [3595 survivors/88 720 cases]; OR, 1.52 [95% CI, 1.45-1.60]). Compared with EMS-only defibrillation (15.0% [6445 survivors/42 916 cases]), bystander-only defibrillation (40.7% [931 survivors/2287 cases]) was associated with increased neurologically intact survival (OR, 2.24 [95% CI, 1.93-2.61]), as was combined bystander and EMS defibrillation (30.5% [444 survivors/1456 cases]; OR, 1.50 [95% CI, 1.31-1.71]), whereas no defibrillation (2.0% [2369 survivors/120 653 cases]) was associated with reduced survival (OR, 0.43 [95% CI, 0.39-0.48]). Hosmer-Lemeshow test was significant (P = .02), but model calibration was good (eFigure in the Supplement). AUC was 0.91 (95% CI, 0.907-0.913). The result from the link test was not significant (P = .18).

Attributable Fraction and Population Impact Fraction

Odds ratios were used in calculating AFp values and IFp values. The AFp values for bystander-only defibrillation increased from 0.8% (95% CI, 0.0%-1.6%) in 2005 to 10.2% (95% CI, 8.6%-11.8%) in 2012 (eTable 3 in the Supplement). Similarly, the AFp values for bystander defibrillation combined with EMS defibrillation increased from 0.6% (95% CI, 0.0%-1.3%) in 2005 to 4.1% (95% CI, 3.0%-5.3%) in 2012. In contrast, AFp values for EMS-only defibrillation decreased from 41.5% (95% CI, 35.0%-47.4%) to 31.7% (95% CI, 27.8%-35.4%). AFp values for bystander chest compression increased from 18.4% (95% CI, 13.7%-22.8%) to 23.6% (95% CI, 20.0%-27.1%).

The IFp for bystander defibrillation, regardless of combination with EMS defibrillation, increased to 9.0% (range, 7.5%-10.3%) in 2012. The IFp for chest compression was smaller than that for bystander defibrillation, despite its larger AFp (5.1% [range, 4.5%-5.7%]), in 2012. Overall, the increase in bystander interventions was associated with 23% of the total survival increments between 2005 and 2012.

Discussion

This study demonstrated that among bystander-witnessed OHCA episodes of presumed cardiac origin in Japan, use of chest compressions and defibrillation increased between 2005 and 2012.
and 2012. In addition, likelihood of neurologically intact survival improved but remained quite low. The increase in neurologically intact survival was associated with bystander defibrillation and chest compressions.

Controversies exist over population benefits and cost-effectiveness of public-access AED deployment in public places,12-14 despite the effectiveness of defibrillation by non-health care professionals in improving the outcomes of patients with OHCA.7,10,11,18 The differing population benefit and cost-effectiveness results reported may depend on whether public-access AEDs are deployed in places at high risk with cardiac arrest occurrence. In this study we found that the proportion of survival rate associated with bystander interventions (IFp) and the increment of survival rate associated with increased bystander interventions (IFp) both increased during the study.

Bystander defibrillation with public-access AEDs had a relatively large association with survival increments despite its low prevalence, reflecting its rapidly increasing availability. In contrast, chest compression was associated with a relatively large proportion of survival rate in each year, reflecting its high prevalence despite its relatively small association with the survival increments. A recent study in Copenhagen that evaluated an initiative to increase public-access AEDs showed AED deployments in high-risk places were associated with a larger increase in OHCA cases occurring in proximity to an AED (<100m) than was deployment in low-risk places.23

To optimize the utility of AED placement information on the locations where cardiac arrests with ventricular fibrillation or pulseless ventricular tachycardia are likely to occur, information on frequency of use of already deployed public-access AEDs would be useful. Further community-based investigations are needed because high-risk places and optimum AED placements differ by community. High-risk places in North America include recreation facilities (eg, race tracks or casinos), accommodation facilities, and business places.24-26 Those in Copenhagen include busy traffic connecting points (railway stations and bus terminals), high-density public places, and sports centers.27 Those in Scotland include accommodation facilities, bars and restaurants, shops and banks, workplaces, and sports facilities.28 In England, rates of OHCA are highest in airports and railway stations.29

In Japan, both OHCA occurrence and public-access AED use are high in major railway stations and sports facilities.30-32 Railways are a major form of transportation, particularly in urban areas, and stations are extremely densely populated. For example, Shinjuku Station is the world’s busiest station, serving 3.6 million passengers per day. Thus, public-access AEDs in such stations would represent efficient use, regardless of how small the risk is for each individual. Furthermore, training in AED use for the staff of stations and sports facilities is more efficient than that for the general public.

In contrast, the proportion of neurologically intact survival associated with EMS defibrillation did not increase during the study period, for 2 likely reasons. First, bystander defibrillation is increasing replacing EMS defibrillation. For some patients, bystander defibrillation is effective, making EMS defibrillation unnecessary. Second, the interval before EMS defibrillation did not decrease during the study period. The introduction of AEDs shortened the interval by allowing EMS personnel to skip a process of online medical instructions.33 This benefit was realized in 2004 when EMS vehicles in Japan were equipped with AEDs. Traffic congestion and increasing demand for EMS made it harder to reduce the interval between EMS call and defibrillation.

Further increases in use of chest compression by bystanders should be promoted. In Japan it is used in just 50% of patients and is increasing slowly. Simplifying the basic life support procedure by omitting mouth-to-mouth breathing may have reduced hesitancy and increased its use. Facilitating chest compression has an economic advantage over deployment of expensive public-access AEDs. Fire departments provide training to more than 1 400 000 citizens every year to increase the prevalence of skills in basic resuscitation procedures, including chest compression and AED use.35 This effort should be further strengthened.

Use of chest compression by family bystanders should be further emphasized. Patients with OHCA witnessed by fami-
ily members were less likely to receive chest compression. These arrests presumably occurred in the home, although the database does not include place information. Because the majority of arrests were witnessed by family, interventions at home would have greater population impact. Since private residences are low-risk places in terms of density of arrest occurrence, emphasis should be placed on chest compression rather than placement of AEDs in the home.33

Several limitations of this study should be noted. First, our analyses include a small fraction of patients with OHCA—ie, only bystander-witnessed cases with presumed cardiac origin. Some unwitnessed cases might have been transported to hospital by EMS although resuscitation was not indicated, because EMS personnel have no discretion to terminate resuscitation at the scene. Defibrillation might not have been indicated for the majority of patients with OHCAs of noncardiac origin. Misclassification might have been inevitable in the diagnosis made clinically, but we could at least exclude obvious noncardiac origin.

Second, appropriateness of AED use and chest compression by bystanders is not recorded. Although inappropriate and ineffective bystander interventions would have resulted in underestimation of the association between the interventions and outcomes, our analyses still showed that patients who received bystander intervention had better outcomes.

Third, the present study showed that only 23% of the increments of neurologically intact survival were associated with improved bystander interventions. The remaining survival increments may be associated with overall improvement in prehospital care procedures (eg, continuous chest compression by EMS personnel) and hospital care including postresuscitation care (eg, hypothermia). The present study could not evaluate these factors because the database did not include such information. Advanced life support procedures (adrenaline administration and advanced airway management) are unlikely to be associated with the majority of remaining increments, although we did not investigate their contributions. The effectiveness of these procedures is controversial and likely to be minimal, particularly for patients with shockable rhythms, who account for the majority of survival.19

Conclusions

In Japan, the likelihood of neurologically intact survival improved between 2005 and 2012 but remained low. The rates of bystander chest compression and bystander defibrillation increased and were associated with increased odds of neurologically intact survival.

REFERENCES


Neurologically Intact Survival in Bystander-Witnessed Out-of-Hospital Cardiac Arrest


