PGY-2

**Critical Review Form**

 **Therapy**

[Tanaka H, Takyu H, Sagisaka R, et al. Favorable neurological outcomes by early epinephrine administration within 19 minutes after EMS call for out-of hospital cardiac arrest patients. Am J Emerg Med. 2016;34(12):2284‐2290.](http://pmid.us/27613359)

**Objectives: "to evaluate the time-dependent effect of the early administration of EPI [epinephrine] within 19 minutes after EMS call on neurological outcomes at 1 month in patients with OHCA [out-of-hospital cardiac arrest]." (p. 2285)**

**Methods: This retrospective, observational study included all cases of OHCA for which resuscitation was provided by EMS services in Japan between January 2006 and December 2012. All patients in Japan with OHCA have been enrolled prospectively in a database controlled by the Fire and Disaster Management Agency (FDMA) since 2005 as part of an ongoing observational study, and subjects were enrolled from this database. Exclusion criteria were missing initial rhythm, unknown bystander-initiated CPR, unknown** [**Cerebral Performance Category (CPC) score**](https://www.azdhs.gov/documents/preparedness/emergency-medical-services-trauma-system/save-hearts-az-registry-education/cerebral-performance-categories-scale.pdf)**, unknown airway management device, EMS response time beyond 99th percentile, ROSC before EMS arrival, unknown drug administration, and drug administration post-ROSC. Patients who achieved ROSC within 2 minutes of defibrillation (bystander or EMS) were also excluded.**

**The primary outcome was a favorable neurologic outcome at one month, defined as a CPC of 1 or 2. The secondary outcome was ROSC in the field by EMS.**

**Out of 925288 patients identified in the database over the study period, 119639 were eligible for inclusion. Of these, 99219 did not receive EPI and 20420 did receive EPI. The age range was 15 to 89. Patients who received EPI were further divided into quartiles based on time to EPI administration: early EPI (5-18 minutes, n = 4671), intermediate EPI (19-23 minutes, n = 6015), late EPI (24-29 minutes, n = 4657), and very late EPI (30-62 minutes, n = 5077).**

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| **Critical Review Form: Therapy** |
| Guide | Comments |
| **Are the results valid?** |
| **Did experimental and control groups being the study with a similar prognosis?** |
| Were patients randomized? | No. This was an observational study in which patients were assigned to their group based on time from EMS call to administration of epinephrine, resulting in a high risk of [selection bias](http://pmid.us/21491415). Time cutoffs were not decided *a priori*, but rather were purportedly devised in such a way that the cohort of patients was divided into four equal groups (though the four groups did not end up being equal in size). |
| Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be “randomized” to a particular group? | N/A |
| Were patients analyzed in the groups to which they were randomized? | Yes. Patients who met eligibility criteria were analyzed based on the time to epinephrine administration with no reason for there to be any crossover. |
| Were patients in the treatment and control groups similar with respect to known prognostic factors? | No.Between the EPI and non-EPI groups, patients were similar with respect to age, gender, bystander CPR, use of AED, defibrillation by EMS, and presence of an underlying shockable rhythm. Patients in the EPI group were more likely to be seen between 2010-2012 (63.8% vs. 41.6%), were more likely to receive defibrillation (42.4% vs. 36.2%), were less likely to receive bag-valve-mask ventilation (30.7% vs. 53.9%), and were more likely to receive advanced airway techniques.For the four time-dependent groups, patients were similar with respect to age, gender, and bystander CPR. VF/VT was more common in the early EPI group and much less common in the late EPI group; patients in the early EPI group were more likely to receive defibrillation. Increasing time to EPI administration also appeared to be associated (and likely partly a results of) increasing EMS response time. |
| **Did experimental and control groups retain a similar prognosis after the study started?** |
| Were patients aware of group allocation? | No. They were in cardiac arrest. |
| Were clinicians aware of group allocation? | Yes. This was an observational study with no blinding. It seems unlikely that [performance bias](http://bmg.cochrane.org/assessing-risk-bias-included-studies) on the part of EMS would the affect outcomes. |
| Were outcome assessors aware of group allocation? | Yes. Outcomes were obtained from the same database as all other study information, including epinephrine administration and timing. Given the fairly objective nature of the outcomes it seems unlikely that [observer bias](http://pmid.us/23359047) would have affected the results. |
| Was follow-up complete? | Yes and no. Follow-up was purportedly complete, again using the nationwide database previously mentioned. One-month follow-up is likely reasonable, although [90-day neurologic outcomes have been suggested as a more appropriate measure for studies of cardiac arrest](https://pubmed.ncbi.nlm.nih.gov/21969010/). |
| **What are the results?** |
| How large was the treatment effect? | EPI vs. non-EPI* ROSC was obtained more frequently in the EPI group compared to the non-EPI group (18% vs 9.4%; RR 1.92, 95% CI 1.85 to 1.99).
* A favorable neurologic outcome at one month was seen less frequently in the EPI group compared to the non-EPI group (2.9% vs. 5.2%; RR 0.56, 95% CI 0.52 to 0.61).

Time to EPI administration (unadjusted):* There was a notable decline in rates of ROSC with increasing time to EPI administration without adjustment for confounders: 24.8% of early EPI cases, 18.9% of intermediate EPI cases, 14.7% of late EPI cases, and 11.5% of very late EPI cases.
* A similar trend in decreasing rates of favorable neurologic outcome was seen with increasing time to EPI administrations: 5.7% of early EPI cases, 2.9% of intermediate EPI cases, 1.5% of late EPI cases, and 1.6% of very late EPI cases.

Time to EPI administration (after logistic regression):* Using the late EPI group as a reference, rates of ROSC were again associated with time to EPI administration, being greatest in the early EPI group (AOR, 1.66; 95% CI, 1.49-1.85) and gradually decreasing with increased time: (intermediate EPI, AOR, 1.25; 95% CI, 1.12-1.40), very late EPI, AOR, 0.75; 95% CI, 0.67-0.87).
* A similar trend in decreasing rates of favorable neurologic outcome was seen with increasing time to EPI administration, again using the late EPI group as a reference:
	+ Early EPI: AOR, 2.49; 95% CI, 1.90-3.27.
	+ Intermediate EPI: AOR, 1.53; 95% CI, 1.14-2.05.
	+ Very late EPI: AOR, 0.71; 95% CI, 0.47-1.08).
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| How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?) | See above. This was a large study with fairly narrow 95% confidence intervals. |
| **How can I apply the results to patient care?** |
| Were the study patients similar to my patient? | No. This study was conducted entirely in Japan, [where life expectancy is several years longer than in the US](https://www.worldlifeexpectancy.com/world-rankings-total-deaths) and where leading [causes of death](https://www.worldlifeexpectancy.com/usa-vs-japan-top-10-causes-of-death) are quite different. The prevalence of several key risk factors for cardiovascular disease are much higher in the US (including [diabetes mellitus](https://www.webmd.com/diabetes/news/20040426/diabetes-rates-worldwide#1) and [obesity](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2676846/)), and [death due to cardiovascular disease is more common among young people in the US when compared with a similar age group in Japan](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2676846/). The median age for OHCA [in the US was found to be 66](https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000152), which is lower than the previously reported [median age of 74 in Japan](http://pmid.us/26994129). It is likely that these factors would affect outcomes following cardiac arrest. |
| Were all clinically important outcomes considered? | Mostly. The authors do report neurologically favorable outcomes, which are more [patient-centered](http://omerad.msu.edu/ebm/Intro/Intro6.html) than survival alone, but [some experts](http://pmid.us/21969010) recommend looking at longer-term outcomes as far out as 90 days. |
| Are the likely treatment benefits worth the potential harm and costs? | Uncertain, despite the use of logistic regression to attempt to control for several known confounders, this is still an observational study. The association found between increasing time to EPI administration and worsening outcomes [does not necessarily prove causation](http://www.jstor.org/stable/2288332), and it is quite possible that other factors affecting time to EPI administration impacted the outcomes observed. Regardless, if EPI is to be given in OHCA, it seems reasonable to ensure prompt administration (without incurring significant interruptions in high-quality CPR). |

**Limitations:**

1. **The authors report conflicting numbers, including reporting 90094 subjects eligible in the body of the paper, but 119639 in the figure and later reporting. The authors also report they chose time cutoffs to make "4 groups equally partitioned," but ended up with 4 unequal groups.**
2. **This was an observational study in which patients were assigned to their group based on time from EMS call to administration of epinephrine, resulting in a high risk of** [**selection bias**](http://pmid.us/21491415)**.**
3. **One-month follow-up as used in this study is likely reasonable, although** [**90-day neurologic outcomes have been suggested as a more appropriate measure for studies of cardiac arrest**](https://pubmed.ncbi.nlm.nih.gov/21969010/)**.**
4. **Despite the use of logistic regression, this observational study is capable of demonstrating an association between increasing time to EPI administration and worsening outcomes,** [**but cannot prove causation**](http://www.jstor.org/stable/2288332)**.**

**Bottom Line:**

**This large, retrospective, observational study using prospectively collected nationwide data found a significant association between increasing time to epinephrine administration for OHCA and decreased survival and neurologically intact survival at one month. This should not be interpreted as proof of causation given the nature of the study, and additional confounders likely impacted the observed outcomes.**