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This supplemental material has been provided by the authors to give readers additional information about their work.
eMethods.

Time-dependent propensity score

We calculated propensity score as the time-varying probability of receiving epinephrine which was estimated from the hazard component at any given minutes after ALS arrival from Fine-Gray regression model with time-dependent covariates, time-independent covariates, competing risk events, and a censoring. The time-dependent covariates were shock delivery (if a patient received shock), AAM (if a patient received AAM), and departure from the scene (if a patient was transported) after ALS arrival. The time-independent covariates were patient age, sex, race, location of arrest, etiology of arrest, witness status, layperson CPR, shock delivery before ALS arrival, and EMS response time. The time-dependent and time-independent covariates are presented in Table 1. We used spline functions (B-spline) for continuous variables (age and EMS response time). We chose these covariates a priori based on their association with survival from prior knowledge, biologic plausibility, and adequate ascertainment. We included prehospital ROSC and TOR before epinephrine administration as competing risks in the model because (1) epinephrine administration never occurs after ROSC and TOR except cases with re-arrest after ROSC, (2) our interest was timing of epinephrine for initial arrest, and (3) ROSC and TOR are informative censorings. We modelled hospital arrival as a censoring because our main interest was the timing of the first prehospital epinephrine administration.

Linear assumption in a model treating the timing of epinephrine as a continuous variable

We assumed a linear relation between each outcome and the timing of epinephrine administration. To investigate the robustness of this linear assumption, we demonstrated the overlapping of RRs with 95% CIs in two models. We also explored a spline regression model assuming a nonlinear relationship between each outcome and the timing of epinephrine administration.
administration. The linear model showed smaller quasi-likelihood under the independence model criterion (QIC) for our primary outcome in both shockable and nonshockable cohorts, compared with the spline regression model. Since prior literature recommends using a GEE model with the smallest QIC, we chose the linear model.

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Statistical codes of time-dependent propensity score and risk-set matching

if(0){
  install.packages( "dplyr"      , repos = "http://cran.r-project.org/" )
  install.packages( "plyr"       , repos = "http://cran.r-project.org/" )
  install.packages( "tidyr"      , repos = "http://cran.r-project.org/" )
  install.packages( "Matching"   , repos = "http://cran.r-project.org/" )
}

library( dplyr )
library( plyr )
library( tidyr )
library( Matching )

#------------#
#--- Data ---#
#------------#

# analysisdata: long data with time-dependent covariates
#
# analysisdata has the following variables
# treatment : treatment indicator
# time_to_treatment : duration from time of inclusion to time of treatment
# outcome : outcome variable
# PS : time-dependent propensity score which is estimated by survival model
# start : the starting time for the interval in which the patient has that time-dependent covariates
# stop : the stopped time for the interval in which the patient has that time-dependent covariates
#
# This data has some time-independent variables and time-dependent variables
#
# seed : seed for random numbers
#
# We set only analysisdata and seed.
#
#--- Sequential matching algorithm using time-dependent variable ---#
library( Matching )

j.ind <- sort( unique( analysisdata$time_to_treatment ) )
matchinglist <- list()
exclude.ids <- c()
set.seed( seed )
for( j in j.ind ){  # Interval time is one minute
  subdata <- analysisdata

  #--- treatment data ---#
  subind1 <- ( subdata$treatment == 1 & subdata$time_to_treatment == j )
treatmentcandidates <- subdata[ subind1, ]
if( nrow( treatmentcandidates ) == 0 ){
  matchinglist[[ j + 1 ]] <- NULL
  next
}

  treatmentcandidates$treatment1 <- 1

  #--- control ---#
  if( sum( subind1 ) == 0 ){
    subdata0 <- subdata
  }else{
    subdata0 <- subdata[ !( subdata$id %in% treatmentcandidates$id ), ]
  }
  subind0 <- ( subdata0$start <= j & subdata0$stop > j )
controlcandidates <- subdata0[ subind0, ]
if( nrow( controlcandidates ) == 0 ){
  matchinglist[[ j + 1 ]] <- NULL
  print( j )
  next
}
  controlcandidates$treatment1 <- 0

  rownames( treatmentcandidates ) <- rownames( controlcandidates ) <- NULL

  #--- matching ---#
  predata <- NULL
  predata <- rbind( predata, controlcandidates )
  predata <- rbind( predata, treatmentcandidates )
  predata <- predata[ !is.na( predata$PS ), ]
if( nrow( predata ) != 1 ){
  tryCatch( {
    mout <- Match(
      Y = predata$outcome,
      Tr = predata$treatment1,
      X = predata$PS,
      caliper = 0.2,
    )
  } catch { error } )

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ties = F, replace = F)

if( sum( is.na( mout ) ) >= 1 ) {# stopping rule
  matchinglist[[ j + 1 ]] <- NULL
} else {
  matchinglist[[ j + 1 ]] <- try(
    # "matchinglist" is a list which includes observation number sets of matched pairs
    data.frame(
      cbind(
        predata[ mout$index.treated, ]$obs,
        predata[ mout$index.control, ]$obs
      )
    )
  )
}

if( repstatus == "N" ) exclude.ids <- c( exclude.ids, 
  predata[ mout$index.treated, ]$id, predata[ mout$index.control, ]$id )

} else {
  matchinglist[[ j + 1 ]] <- NULL
}

print( j )

matchinglistpreserve <- matchinglist

names( matchinglist ) <- 1:( length( matchinglist ) )
for( h in (1:length( matchinglist ))[ !sapply( matchinglist, is.null ) ] ) {
  matchinglist[[ h ]]$X3 <- h - 1
}

matchedOBSset <- ldply( matchinglist ) # list to data.frame
matchedOBSset$pair <- 1:nrow( matchedOBSset ) # matching pair indicator
colnames( matchedOBSset ) <- c( "id", "treatedobs", "controledobs", "timing", "pair" )
matchedOBSset.long <- tidyr::gather( matchedOBSset, key = treatment1, value = obs, -timing, -pair, -id ) # convert to long format

matcheddata <- merge(
  x = matchedOBSset.long[, -1],
  y = analysisdata[, -which( names( analysisdata ) == "treatment1" )],
  by = "obs",
  all.x = T
)
matcheddata$w <- rep( rle( matcheddata$obs )$length, rle( matcheddata$obs )$length ) # frequency weight

if(0){
  head( matcheddata )
}

# For the created matched data, the some statistical analysis methods such as
# GEE and conditional logistic methods will be applied by using standard R functions.
#---------------------------------------------------------------#
eFigure 1. Patient Flow

ALS indicates advanced life support; DNR do-not resuscitate; EMS emergency medical services; OHCA out-of-hospital cardiac arrest.
**eFigure 2.** Association of epinephrine administration with survival to hospital discharge (A), favorable functional outcome at hospital discharge (B), and prehospital ROSC (C) by the timing of the administration for patients with shockable OHCA (matching without replacement).

Point estimates of the association of epinephrine with outcomes (solid lines) were reported with 95% CIs (dot lines), treating timing of epinephrine administration after ALS EMS as a continuous variable. Plots indicate point estimates of the association of epinephrine with outcomes with 95% CIs, treating timing as a categorical variable. The plots were placed at median time for each categorized time. We rounded decimal points of the numbers of imputed patients with favorable functional status (eFigure 2B).

eFigure 2A: Change of RR per minute = -4.6% (95% CI -7.7% to -1.4%, p-value for the interaction=0.005). eFigure 2B: Change of RR per minute = -4.8% (95% CI -8.4% to -1.0%, p-value for the interaction=0.02). eFigure 2C: Change of RR per minute = 0.7% (95% CI -1.0% to 2.5%, p-value for the interaction=0.409).

ALS indicates advanced life support; CI confidence interval; EMS emergency medical services; OHCA out-of-hospital cardiac arrest; ROSC return of spontaneous circulation.

| Time after ALS EMS arrival, minutes | 0-5       | 5-10      | 10-15     | 15-20     |
|------------------------------------|-----------|-----------|-----------|-----------|
| Epinephrine                        | 425/1494 (28.4%) | 540/2661 (20.3%) | 40/294 (13.6%) | 4/33 (12.1%) |
| At-risk of receiving epinephrine    | 387/1494 (25.9%) | 538/2661 (20.2%) | 59/294 (20.1%) | 9/33 (27.3%) |
| Risk ratio (95% CI)                 | 1.10 (0.98-1.24) | 1.00 (0.9-1.11) | 0.68 (0.47-0.98) | 0.45 (0.16-1.28) |

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P value for interaction = 0.02

| Time after ALS EMS arrival, minutes | 0-5            | 5-10           | 10-15          | 15-20          |
|-----------------------------------|----------------|----------------|----------------|----------------|
| Epinephrine                       | 340/1494 (22.8%) | 412/2661 (15.5%) | 30/294 (10.2%) | 2/33 (6.1%)    |
| At-risk of receiving epinephrine   | 325/1494 (21.8%) | 438/2661 (16.5%) | 43/294 (14.6%) | 7/33 (21.2%)   |
| Risk ratio (95% CI)               | 1.05 (0.91-1.2)  | 0.94 (0.83-1.07) | 0.70 (0.45-1.1) | 0.29 (0.07-1.28) |
C

Risk ratio for prehospital return of spontaneous circulation

P value for interaction = 0.409

Risk ratio = 1.00

Favors epinephrine

Favors at-risk of receiving epinephrine

| Time after ALS EMS arrival, minutes | 0-5             | 5-10            | 10-15            | 15-20            |
|-----------------------------------|-----------------|-----------------|------------------|------------------|
| Epinephrine                       | 899/1494 (60.2%)| 1333/2661 (50.1%)| 108/294 (36.7%)  | 12/33 (36.4%)    |
| At-risk of receiving epinephrine  | 832/1494 (55.7%)| 1255/2661 (47.2%)| 100/294 (34.0%)  | 6/33 (18.2%)     |
| Risk ratio (95% CI)               | 1.08 (1.02-1.15)| 1.06 (1.01-1.12) | 1.08 (0.87-1.35) | 1.98 (0.87-4.53) |
**eFigure 3.** Association of epinephrine administration with survival to hospital discharge (A), favorable functional outcome at hospital discharge (B), and prehospital ROSC (C) by the timing of the administration for patients with nonshockable OHCA (matching without replacement).

Point estimates of the association of epinephrine with outcomes (solid lines) were reported with 95% CIs (dot lines), treating timing of epinephrine administration after ALS EMS as a continuous variable. Plots indicate point estimates of the association of epinephrine with outcomes with 95% CIs, treating timing as a categorical variable. The plots were placed at median time for each categorized time. We rounded decimal points of the numbers of imputed patients with favorable functional status (eFigure 3B).

eFigure 3A: Change of RR per minute = -2.0% (95% CI -6.9% to 3.0%, p-value for the interaction=0.425). eFigure 3B: Change of RR per minute = -1.8% (95% CI -9.3% to 6.3%, p-value for the interaction=0.300). eFigure 3C: Change of RR per minute = 0.03% (95% CI -1.3% to 1.4%, p-value for the interaction=0.963). ALS indicates advanced life support; CI confidence interval; EMS emergency medical services; OHCA out-of-hospital cardiac arrest; ROSC return of spontaneous circulation.

| Time after ALS EMS arrival, minutes | 0-5 | 5-10 | 10-15 | 15-20 | > 20 |
|-------------------------------------|-----|------|-------|-------|------|
| Epinephrine                         | 105/3681 (2.9%) | 230/9327 (2.5%) | 29/1594 (1.8%) | 1/131 (0.8%) | 0/20 (0%) |
| At-risk of receiving epinephrine     | 103/3681 (2.8%) | 237/9327 (2.5%) | 30/1594 (1.9%) | 2/131 (1.5%) | 0/20 (0%) |
| Risk ratio (95% CI)                 | 1.02 (0.78-1.33) | 0.97 (0.81-1.16) | 0.97 (0.58-1.60) | 0.50 (0.05-5.44) | 1.00 (0.54-1.86) |

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B

![Graph showing risk ratio for favorable functional status at hospital discharge over time after ALS EMS arrival minutes.]

| Time after ALS EMS arrival, minutes | 0-5     | 5-10    | 10-15   | 15-20   | > 20    |
|------------------------------------|---------|---------|---------|---------|---------|
| Epinephrine                        | 51/3681 (1.4%) | 109/9327 (1.2%) | 13/1594 (0.8%) | 0/131 (0%) | 0/20 (0%) |
| At-risk of receiving epinephrine    | 50/3681 (1.4%) | 114/9327 (1.2%) | 17/1594 (1.1%) | 1/131 (0.8%) | 0/20 (0%) |
| Risk ratio (95% CI)                | 1.03 (0.68-1.56) | 0.96 (0.71-1.30) | 0.77 (0.34-1.70) | 0 (0-0.01) | 1.00 (0.54-1.86) |

P value for interaction = 0.30

Favors epinephrine

Risk ratio = 1.00

Favors at-risk of receiving epinephrine

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The table shows the risk ratio for prehospital return of spontaneous circulation (ROSCI) at different times after Advanced Life Support (ALS) EMS arrival, stratified by epinephrine administration and risk of receiving epinephrine. The risk ratio is calculated using 95% confidence intervals (CI).

| Time after ALS EMS arrival, minutes | 0-5   | 5-10  | 10-15 | 15-20 | > 20 |
|------------------------------------|-------|-------|-------|-------|------|
| Epinephrine                        | 1244/3681 (33.8%) | 2888/9327 (31.0%) | 396/1594 (24.8%) | 21/131 (16.0%) | 1/20 (5.0%) |
| At-risk of receiving epinephrine   | 1017/3681 (27.6%) | 2360/9327 (25.3%) | 298/1594 (18.7%) | 14/131 (10.7%) | 3/20 (15.0%) |
| Risk ratio (95% CI)                | 1.23 (1.08-1.39) | 1.22 (1.17-1.28) | 1.33 (1.16-1.52) | 1.50 (0.80-2.80) | 0.33 (0.04-2.94) |

The P value for interaction is 0.963, indicating no significant interaction between time after ALS EMS arrival and epinephrine administration on the risk of ROSCI.
**eFigure 4.** Association of epinephrine administration with survival to hospital discharge (A), favorable functional outcome at hospital discharge (B), and prehospital ROSC (C) by the timing of the administration for patients with shockable OHCA excluding those who had ROSC or TOR within 5 minutes after ALS EMS arrival on the scene.

Point estimates of the association of epinephrine with outcomes (solid lines) were reported with 95% CIs (dot lines), treating timing of epinephrine administration after ALS EMS as a continuous variable. Plots indicate point estimates of the association of epinephrine with outcomes with 95% CIs, treating timing as a categorical variable. The plots were placed at median time for each categorized time. We rounded decimal points of the numbers of imputed patients with favorable functional status (eFigure 4B).

* eFigure 4A: Change of RR per minute = -6.3% (95% CI -8.5% to -4.1%, p-value for the interaction<0.001).
* eFigure 4B: Change of RR per minute = -7.4% (95% CI -10.1% to -4.7%, p-value for the interaction<0.001).
* eFigure 4C: Change of RR per minute = 0.4% (95% CI -0.9 to 1.7%, p-value for the interaction=0.52).

ALS indicates advanced life support; CI confidence interval; EMS emergency medical services; OHCA out-of-hospital cardiac arrest; ROSC return of spontaneous circulation; TOR termination of resuscitation.

**A**

![Graph showing association of epinephrine administration with outcomes](image)

| Time after ALS EMS arrival, minutes | 0-5       | 5-10      | 10-15     | 15-20     | > 20      |
|------------------------------------|-----------|-----------|-----------|-----------|-----------|
| Epinephrine                        | 420/1572 (26.7%) | 877/4540 (19.3%) | 185/1546 (12.0%) | 27/369 (7.3%) | 5/118 (4.2%) |
| At-risk of receiving epinephrine    | 370/1572 (23.5%) | 898/4540 (19.8%) | 226/1546 (14.6%) | 53/369 (14.4%) | 25/118 (21.2%) |
| Risk ratio (95% CI)                | 1.27 (1.12-1.46) | 1.11 (1.01-1.22) | 0.94 (0.76-1.15) | 0.66 (0.39-1.11) | 0.10 (0.04-0.29) |

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### Figure B

The graph shows the risk ratio for favorable functional status at hospital discharge based on time after ALS EMS arrival, minutes. The risk ratio is compared between receiving epinephrine and being at risk for receiving epinephrine. The P value for interaction is less than 0.001.

The graph illustrates that receiving epinephrine favors a lower risk ratio compared to being at-risk of receiving epinephrine.

### Table

| Time after ALS EMS arrival, minutes | 0-5 | 5-10 | 10-15 | 15-20 | > 20 |
|------------------------------------|-----|------|-------|-------|------|
| Epinephrine                        | 337/1572 (21.4%) | 687/4540 (15.1%) | 132/1546 (8.5%) | 18/369 (4.9%) | 3/118 (2.5%) |
| At-risk of receiving epinephrine    | 307/1572 (19.5%) | 708/4540 (15.6%) | 163/1546 (10.5%) | 40/369 (10.8%) | 24/118 (20.3%) |
| Risk ratio (95% CI)                | 1.23 (1.06-1.44) | 1.13 (1.01-1.26) | 0.93 (0.72-1.20) | 0.60 (0.31-1.15) | 0.06 (0.01-0.26) |
### Table C

| Time after ALS EMS arrival, minutes | 0-5     | 5-10    | 10-15   | 15-20   | > 20    |
|-------------------------------------|---------|---------|---------|---------|---------|
| Epinephrine                         | 922/1572 (58.7%) | 2289/4540 (50.4%) | 579/1546 (37.5%) | 95/369 (25.7%) | 19/118 (16.1%) |
| At-risk of receiving epinephrine     | 832/1572 (52.9%) | 2083/4540 (45.9%) | 473/1546 (30.6%) | 75/369 (20.3%) | 16/118 (13.6%) |
| Risk ratio (95% CI)                  | 1.18 (1.10-1.26) | 1.19 (1.13-1.25) | 1.32 (1.18-1.48) | 1.21 (0.90-1.64) | 0.90 (0.46-1.78) |

P value for interaction = 0.52

- Favors epinephrine
- Risk ratio = 1.00
- Favors at-risk of receiving epinephrine

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**eFigure 5.** Association of epinephrine administration with survival to hospital discharge (A), favorable functional outcome at hospital discharge (B), and prehospital ROSC (C) by the timing of the administration for patients with nonshockable OHCA excluding those who had ROSC or TOR within 5 minutes after ALS EMS arrival on the scene.

Point estimates of the association of epinephrine with outcomes (solid lines) were reported with 95% CIs (dot lines), treating timing of epinephrine administration after ALS EMS as a continuous variable. Plots indicate point estimates of the association of epinephrine with outcomes with 95% CIs, treating timing as a categorical variable. The plots were placed at median time for each categorized time. We rounded decimal points of the numbers of imputed patients with favorable functional status (eFigure 5B).

- **eFigure 5A:** Change of RR per minute = -3.2% (95% CI -6.3% to -0.03%, p-value for the interaction=0.048).
- **eFigure 5B:** Change of RR per minute = -5.0% (95% CI -9.8% to -0.07%, p-value for the interaction=0.03).
- **eFigure 5C:** Change of RR per minute = 1.3% (95% CI 0.4% to 2.3%, p-value for the interaction=0.007).

ALS indicates advanced life support; CI confidence interval; EMS emergency medical services; OHCA out-of-hospital cardiac arrest; ROSC return of spontaneous circulation; TOR termination of resuscitation.

### Table

| Time after ALS EMS arrival, minutes | 0-5         | 5-10        | 10-15       | 15-20       | > 20        |
|-------------------------------------|-------------|-------------|-------------|-------------|-------------|
| Epinephrine                         | 100/3822 (2.6%) | 361/14756 (2.4%) | 117/6650 (1.8%) | 21/1872 (1.1%) | 4/727 (0.6%) |
| At-risk of receiving epinephrine    | 93/3822 (2.4%) | 341/14756 (2.3%) | 134/6650 (2%) | 29/1872 (1.5%) | 7/727 (1.0%) |
| Risk ratio (95% CI)                 | 1.46 (1.09-1.97) | 1.23 (1.04-1.44) | 0.94 (0.72-1.23) | 0.70 (0.37-1.33) | 0.96 (0.23-3.98) |

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| Time after ALS EMS arrival, minutes | 0-5      | 5-10     | 10-15    | 15-20    | > 20     |
|-------------------------------------|----------|----------|----------|----------|----------|
| Epinephrine                         | 49/3822 (1.3%) | 150/14756 (1.0%) | 49/6650 (0.7%) | 9/1872 (0.5%) | 1/727 (0.1%) |
| At-risk of receiving epinephrine    | 52/3822 (1.4%) | 164/14756 (1.1%) | 75/6650 (1.1%) | 16/1872 (0.9%) | 3/727 (0.4%) |
| Risk ratio (95% CI)                 | 1.30 (0.83-2.03) | 1.06 (0.80-1.41) | 0.73 (0.48-1.11) | 0.54 (0.21-1.36) | 0.94 (0.09-9.69) |
The table below shows the risk ratio for prehospital return of spontaneous circulation (ROSC) over time after ALS EMS arrival, comparing epinephrine to at-risk of receiving epinephrine.

| Time after ALS EMS arrival, minutes | 0-5       | 5-10      | 10-15     | 15-20     | > 20    |
|------------------------------------|-----------|-----------|-----------|-----------|---------|
| Epinephrine                        | 1261/3822 (33.0%) | 4531/14756 (30.7%) | 1647/6650 (24.8%) | 348/1872 (18.6%) | 93/727 (12.8%) |
| At-risk of receiving epinephrine    | 1038/3822 (27.2%) | 3520/14756 (23.9%) | 1216/6650 (18.3%) | 218/1872 (11.6%) | 42/727 (5.8%) |
| Risk ratio (95% CI)                | 1.33 (1.23-1.43) | 1.36 (1.31-1.42) | 1.36 (1.26-1.46) | 1.56 (1.31-1.85) | 2.11 (1.44-3.1) |

P value for interaction = 0.007

- Favors epinephrine
- Risk ratio = 1.00
- Favors at-risk of receiving epinephrine
**eFigure 6.** Association of epinephrine administration with survival to hospital discharge (A), favorable functional outcome at hospital discharge (B), and prehospital ROSC (C) by the timing of the administration for patients with bystander witnessed shockable OHCA.

Point estimates of the association of epinephrine with outcomes (solid lines) were reported with 95% CIs (dot lines), treating timing of epinephrine administration after ALS EMS as a continuous variable. Plots indicate point estimates of the association of epinephrine with outcomes with 95% CIs, treating timing as a categorical variable. The plots were placed at median time for each categorized time. We rounded decimal points of the numbers of imputed patients with favorable functional status (eFigure 6B).

*eFigure 6A:* Change of RR per minute = \(-5.4\%\) (95% CI -7.8% to -3.0%, p-value for the interaction<0.001). *eFigure 6B:* Change of RR per minute = \(-6.5\%\) (95% CI -9.3% to -3.5%, p-value for the interaction<0.001). *eFigure 6C:* Change of RR per minute = 0.4% (95% CI -1.1% to 2.0%, p-value for the interaction=0.56).

ALS indicates advanced life support; CI confidence interval; EMS emergency medical services; OHCA out-of-hospital cardiac arrest; ROSC return of spontaneous circulation.

| Time after ALS EMS arrival, minutes | 0-5 | 5-10 | 10-15 | 15-20 | > 20 |
|-------------------------------------|-----|------|-------|-------|------|
| Epinephrine                         | 364/1113 (32.7%) | 656/2967 (22.1%) | 133945 (14.1%) | 21/233 (9.0%) | 4/68 (5.9%) |
| At-risk of receiving epinephrine    | 349/1113 (31.4%) | 718/2967 (24.2%) | 157945 (16.6%) | 47/233 (20.2%) | 16/68 (23.5%) |
| Risk ratio (95% CI)                 | 1.19 (1.04-1.37) | 1.03 (0.92-1.14) | 0.90 (0.70-1.14) | 0.52 (0.30-0.91) | 0.27 (0.08-0.95) |

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### Table 1: Risk Ratio for Favorable Functional Status at Hospital Discharge

| Time after ALS EMS arrival, minutes | 0-5   | 5-10  | 10-15 | 15-20 | > 20  |
|-------------------------------------|-------|-------|-------|-------|-------|
| Epinephrine                         | 296/1113 (26.6%) | 521/2967 (17.6%) | 101,945 (10.7%) | 14/233 (6.0%) | 2/68 (3.0%) |
| At-risk of receiving epinephrine     | 309/1113 (27.8%) | 578/2967 (19.5%) | 121,945 (12.8%) | 37/233 (15.9%) | 15/68 (22.1%) |
| Risk ratio (95% CI)                  | 1.10 (0.95-1.29) | 1.06 (0.93-1.19) | 0.86 (0.64-1.15) | 0.46 (0.23-0.91) | 0.14 (0.03-0.80) |

P value for interaction <0.001

Favors epinephrine

Risk ratio=1.00

Favors at-risk of receiving epinephrine

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| Time after ALS EMS arrival, minutes | 0-5     | 5-10    | 10-15   | 15-20   | > 20   |
|------------------------------------|---------|---------|---------|---------|--------|
| Epinephrine                        | 719/1113 (64.6%) | 1578/2967 (53.2%) | 385/945 (40.7%) | 63/233 (27.0%) | 16/68 (23.5%) |
| At-risk of receiving epinephrine    | 677/1113 (60.8%) | 1455/2967 (49.0%) | 330/945 (34.9%) | 62/233 (26.6%) | 7/68 (10.3%) |
| Risk ratio (95% CI)                | 1.13 (1.05-1.22) | 1.20 (1.14-1.28) | 1.20 (1.05-1.37) | 1.00 (0.70-1.42) | 2.29 (0.87-6.05) |
**eFigure 7.** Association of epinephrine administration with survival to hospital discharge (A), favorable functional outcome at hospital discharge (B), and prehospital ROSC (C) for patients with bystander witnessed nonshockable OHCA.

Point estimates of the association of epinephrine with outcomes (solid lines) were reported with 95% CIs (dot lines), treating timing of epinephrine administration after ALS EMS as a continuous variable. Plots indicate point estimates of the association of epinephrine with outcomes with 95% CIs, treating timing as a categorical variable. The plots were placed at median time for each categorized time. We rounded decimal points of the numbers of imputed patients with favorable functional status (eFigure 7B).

- **eFigure 7A:** Change of RR per minute = -2.8% (95% CI -7.2% to 1.8%, p-value for the interaction=0.23).
- **eFigure 7B:** Change of RR per minute = -5.8% (95% CI -11.7% to 0.4%, p-value for the interaction=0.09).
- **eFigure 7C:** Change of RR per minute = 1.6% (95% CI 0.4% to 2.9%, p-value for the interaction=0.01)

ALS indicates advanced life support; CI confidence interval; EMS emergency medical services; OHCA out-of-hospital cardiac arrest; ROSC return of spontaneous circulation.

| Time after ALS EMS arrival, minutes | 0-5 | 5-10 | 10-15 | 15-20 | > 20 |
|-------------------------------------|-----|------|-------|-------|------|
| Epinephrine                         | 63/1366 (4.6%) | 183/4955 (3.7%) | 65/2250 (2.9%) | 10/607 (1.6%) | 2/240 (0.8%) |
| At-risk of receiving epinephrine    | 75/1366 (5.5%) | 209/4955 (4.2%) | 70/2250 (3.1%) | 19/607 (3.1%) | 7/240 (2.9%) |
| Risk ratio (95% CI)                 | 1.00 (0.71-1.42) | 1.06 (0.85-1.31) | 1.05 (0.72-1.51) | 0.40 (0.17-0.95) | 0.44 (0.08-2.51) |

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B

![Graph showing risk ratio for favorable functional status at hospital discharge over time after ALS EMS arrival, minutes. P value for interaction = 0.09.]

| Time after ALS EMS arrival, minutes | 0-5     | 5-10    | 10-15   | 15-20   | > 20    |
|------------------------------------|---------|---------|---------|---------|---------|
| Epinephrine                        | 34/1366 (2.5%) | 76/4955 (1.5%) | 33/2250 (1.5%) | 5/607 (0.8%) | 0/240 (0%) |
| At-risk of receiving epinephrine    | 42/1366 (3.1%) | 122/4955 (2.5%) | 43/2250 (1.9%) | 14/607 (2.3%) | 3/240 (1.3%) |
| Risk ratio (95% CI)                | 1.00 (0.60-1.65) | 0.75 (0.52-1.07) | 0.79 (0.46-1.36) | 0.37 (0.12-1.19) | 0 (0-34816756) |

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C

P value for interaction=0.01

Favors epinephrine

Risk ratio=1.00

Favors at-risk of receiving epinephrine

| Time after ALS EMS arrival, minutes | 0-5   | 5-10  | 10-15 | 15-20 | > 20  |
|-----------------------------------|-------|-------|-------|-------|-------|
| Epinephrine                       | 636/1366 (46.6%) | 2137/4955 (43.1%) | 751/2250 (33.4%) | 151/607 (24.9%) | 33/240 (13.8%) |
| At-risk of receiving epinephrine   | 546/1366 (40%)   | 1706/4955 (34.4%) | 562/2250 (25.0%) | 86/607 (14.2%) | 16/240 (6.7%)  |
| Risk ratio (95% CI)               | 1.26 (1.15-1.39) | 1.32 (1.25-1.40)  | 1.39 (1.26-1.55) | 1.78 (1.36-2.32) | 1.91 (1.02-3.60) |
**Table 1.** Characteristics of adult patients with out-of-hospital cardiac arrest with epinephrine and at risk of receiving epinephrine in time-dependent propensity score matched cohort (matching without replacement)

|                                | Shockable rhythms |                      | Nonshockable rhythms |                      |
|--------------------------------|-------------------|----------------------|----------------------|----------------------|
|                                | At-risk of        | Epinephrine          |                      | At-risk of           | Epinephrine          |
|                                | receiving         | (n=4482)             |                      | receiving           | (n=14753)            |
|                                | epinephrine       | (n=4482)             | standardized         |                      |                      |
|                                | standardized      | difference            |                      | difference            |
| Age, median (IQR), y           | 65 (55-76)        | 64 (54-75)           | 0.053                | 68 (55-80)           | 68 (55-81)           | 0.01                |
| Sex                            |                   |                      | 0.068                |                      |                      | 0.021               |
| Male                           | 3413 (76.1)       | 3530 (78.8)          | 0.032                | 9021 (61.1)          | 8981 (60.9)          | 0.004               |
| Unknown                        | 4 (0.1)           | 1 (0.0)              |                      | 3 (0.0)              | 9 (0.1)              |                    |
| Race                           |                   |                      |                      |                      |                      |                    |
| White                          | 1105 (24.7)       | 1167 (26.0)          |                      | 3541 (24.0)          | 3567 (24.2)          |                    |
| Non-white                      | 3377 (75.3)       | 3315 (74.0)          |                      | 11212 (76.0)         | 11186 (75.8)         |                    |
| Etiology                       |                   |                      | 0.025                |                      | 0.025                |                    |
| Cardiac                        | 4392 (98.0)       | 4407 (98.3)          |                      | 13671 (92.7)         | 13573 (92.0)         |                    |
| Non-cardiac                    | 89 (2.0)          | 74 (1.7)             |                      | 1082 (7.3)           | 1180 (8.0)           |                    |
| Unknown                        | 1 (0.0)           | 1 (0.0)              |                      |                      |                      |                    |
| Initial rhythm                 |                   |                      | 0.055                |                      |                      |                    |
| PEA                            | N/A               | N/A                  |                      | 4216 (28.6)          | 4585 (31.1)          |                    |
| Asystole                       | N/A               | N/A                  |                      | 10537 (71.4)         | 10168 (68.9)         |                    |
| Location                       |                   |                      | 0.117                |                      | 0.055                |                    |
| Street/highway                 | 405 (9.0)         | 426 (9.5)            |                      | 420 (2.8)            | 433 (2.9)            |                    |
| Public building                | 91 (2.0)          | 97 (2.2)             |                      | 97 (0.7)             | 93 (0.6)             |                    |
| Place of recreation            | 171 (3.8)         | 205 (4.6)            |                      | 193 (1.3)            | 161 (1.1)            |                    |
| Industrial place               | 97 (2.2)          | 100 (2.2)            |                      | 69 (0.5)             | 65 (0.4)             |                    |
| Home                           | 2910 (64.9)       | 2824 (63.0)          |                      | 11129 (75.4)         | 11186 (75.8)         |                    |
| Farm/ranch                     | 7 (0.2)           | 0 (0.0)              |                      | 16 (0.1)             | 12 (0.1)             |                    |
| Healthcare facility            | 73 (1.6)          | 74 (1.7)             |                      | 276 (1.9)            | 329 (2.2)            |                    |

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| Category                              | Yes       | No        | Unknown |
|---------------------------------------|-----------|-----------|---------|
| Residential institution               | 1891 (12.8) | 1730 (11.7) | 28 (0.2) |
| Other public property                 | 587 (4.0) | 676 (4.6) | 28 (0.2) |
| Other non-public property             | 47 (0.3)  | 40 (0.3)  | 28 (0.2) |
| Unknown                               | 11 (0.2)  | 28 (0.2)  | 28 (0.2) |
| Witnessed collapse                    | 0.058     | 0.021     |         |
| Bystander                             | 4916 (33.3) | 5060 (34.3) |        |
| None                                  | 9429 (63.9) | 9288 (63.0) |        |
| Unknown                               | 408 (2.8)  | 405 (2.7)  |         |
| Layperson CPR                         | 0.033     |           |         |
| Yes                                   | 2460 (54.9) | 2705 (60.4) |        |
| No                                    | 1932 (43.1) | 1707 (38.1) |        |
| Unknown                               | 90 (2.0)  | 70 (1.6)  |         |
| Shock delivery before ALS arrival    | 0.119     | 0.023     |         |
| Yes                                   | 1178 (26.3) | 1419 (31.7) |        |
| No                                    | 3304 (73.7) | 3063 (68.3) |        |
| EMS response time (interval between 9-1-1 call and first EMS arrival), median (IQR), minutes | 5.5 (4.3-7.0) | 5.5 (4.2-7.0) | 5.4 (4.2-7.0) |
| Shock delivery after ALS arrival     | 0.155     | 0.017     |         |
| Yes                                   | 3263 (72.8) | 2944 (65.7) |        |
| Interval between ALS arrival and shock delivery, median (IQR), minutes | 14.6 (8.7-21.0) | 12.5 (8.2-18.5) |         |
| Yes                                   | 3445 (76.9) | 3580 (79.9) |        |
| Advanced airway management            | 10933 (74.1) | 11473 (77.8) |         |
| Yes                                   | 11.0 (7.1-16.0) | 10.0 (6.7-14.0) |        |
| Interval between ALS arrival and AAM, median (IQR), minutes | 11.2 (8.0-13.0) | 10.0 (7.0-13.6) |         |
| Yes                                   | 3606 (80.5) | 3546 (79.1) |        |
| Departure from the scene              | 7457 (50.5) | 7081 (48.0) |         |

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| Interval between ALS arrival and departure from the scene, median (IQR), minutes | 24.8 (19.0-32.0) | 24.0 (18.9-30.4) | 0.097 | 25.5 (19.2-33.1) | 24.9 (19.1-31.5) | 0.09 |

IQR indicates interquartile range; PEA, pulseless electrical activity; CPR, cardiopulmonary resuscitation; ALS, advanced life support; EMS, emergency medical services; and AAM, advanced airway management
**eTable 2. Outcomes in time-dependent propensity score matched cohort (matching without replacement)**

| Outcomes                                      | No (%) patients with outcome/total patients | Risk ratio (95% CI) |
|-----------------------------------------------|---------------------------------------------|---------------------|
|                                               | At-risk of receiving epinephrine            | Epinephrine         |                     |
| Shockable rhythms                             |                                             |                     |                     |
| Survival to hospital discharge                | 993/4482 (22.2%)                            | 1009/4482 (22.5%)   | 1.02 (0.94-1.10)    |
| Favorable functional outcome at hospital discharge | 813/4482 (18.1%)                           | 784/4482 (17.5%)    | 0.96 (0.88-1.06)    |
| Prehospital ROSC                              | 2193/4482 (48.9%)                           | 2352/4482 (52.5%)   | 1.07 (1.03-1.12)    |
| Nonshockable rhythms                          |                                             |                     |                     |
| Survival to hospital discharge                | 372/14753 (2.5%)                            | 365/14753 (2.5%)    | 0.98 (0.85-1.13)    |
| Favorable functional outcome at hospital discharge | 182/14753 (1.2%)                           | 173/14753 (1.2%)    | 0.95 (0.76-1.20)    |
| Prehospital ROSC                              | 3692/14753 (25.0%)                          | 4550/14753 (30.8%)  | 1.23 (1.19-1.28)    |

ROSC indicates return of spontaneous circulation.
### eTable 3. Characteristics of adult patients with out-of-hospital cardiac arrest with and without epinephrine in original cohort, excluding those who had ROSC or TOR within 5 minutes after ALS EMS arrival

|                        | No epinephrine (n=1051) | Epinephrine (n=8158) | standardized difference | No epinephrine (n=2223) | Epinephrine (n=27841) | standardized difference |
|------------------------|--------------------------|----------------------|-------------------------|--------------------------|------------------------|-------------------------|
| Age, median (IQR), y   | 63 (53-72)               | 65 (55-76)           | 0.164                   | 70 (56-82)               | 68 (55-80)             | 0.08                    |
| Sex                    |                          |                      | 0.167                   |                          |                        | 0.149                   |
| Male                   | 744 (70.8)               | 6368 (78.1)          |                         | 1200 (54.0)              | 17071 (61.3)           |                         |
| Unknown                | 1 (0.1)                  | 4 (0.0)              |                         | 2 (0.1)                  | 12 (0.0)               |                         |
| Race                   |                          |                      | 0.006                   |                          |                        | 0.174                   |
| White                  | 264 (25.1)               | 2071 (25.4)          |                         | 388 (17.5)               | 6830 (24.5)            |                         |
| Non-white              | 787 (74.9)               | 6087 (74.6)          |                         | 1835 (82.5)              | 21011 (75.5)           |                         |
| Etiology               |                          |                      | 0.051                   |                          |                        | 0.151                   |
| Cardiac                | 1026 (97.6)              | 8013 (98.2)          |                         | 1960 (88.2)              | 25766 (92.5)           |                         |
| Non-cardiac            | 24 (2.3)                 | 144 (1.8)            |                         | 262 (11.8)               | 2075 (7.5)             |                         |
| Unknown                | 1 (0.1)                  | 1 (0.0)              |                         | 1 (0.0)                  | 0 (0.0)                |                         |
| Initial rhythm         |                          |                      |                         |                          |                        | 0.155                   |
| PEA                    | N/A                      | N/A                  |                         | 819 (36.8)               | 8226 (29.5)            |                         |
| Asystole               | N/A                      | N/A                  |                         | 1404 (63.2)              | 19615 (70.5)           |                         |
| Location               |                          |                      | 0.25                    |                          |                        | 0.119                   |
| Street/highway         | 120 (11.4)               | 738 (9.0)            |                         | 86 (3.9)                 | 790 (2.8)              |                         |
| Public building        | 39 (3.7)                 | 168 (2.1)            |                         | 18 (0.8)                 | 177 (0.6)              |                         |
| Place of recreation    | 63 (6.0)                 | 339 (4.2)            |                         | 37 (1.7)                 | 324 (1.2)              |                         |
| Industrial place       | 20 (1.9)                 | 179 (2.2)            |                         | 2 (0.1)                  | 131 (0.5)              |                         |
| Home                   | 564 (53.7)               | 5282 (64.7)          |                         | 1644 (74.0)              | 21074 (75.7)           |                         |
| Farm/ranch             | 0 (0.0)                  | 7 (0.1)              |                         | 2 (0.1)                  | 26 (0.1)               |                         |
| Healthcare facility    | 24 (2.3)                 | 131 (1.6)            |                         | 57 (2.6)                 | 564 (2.0)              |                         |
| Residential institution| 46 (4.4)                 | 300 (3.7)            |                         | 276 (12.4)               | 3429 (12.3)            |                         |
| Other public property  | 159 (15.1)               | 946 (11.6)           |                         | 89 (4.0)                 | 1191 (4.3)             |                         |
| Feature                                | Yes          | No           | Unknown     | Yes          | No           | Unknown     |
|----------------------------------------|--------------|--------------|-------------|--------------|--------------|-------------|
| Other non-public property              | 11 (1.0)     | 49 (0.6)     | 4 (0.2)     | 84 (0.3)     | 5 (0.5)      | 19 (0.2)    |
| Witnessed collapse                     |              |              |             | 0.259        |              |             |
| Bystander                              | 801 (76.2)   | 5297 (64.9)  | 784 (35.3)  | 9413 (33.8)  |              |             |
| None                                   | 225 (21.4)   | 2677 (32.8)  | 1383 (62.2) | 17656 (63.4) |              |             |
| Unknown                                | 25 (2.4)     | 184 (2.3)    | 56 (2.5)    | 772 (2.8)    |              |             |
| Layperson CPR                          |              |              |             | 0.208        |              |             |
| Yes                                    | 700 (66.6)   | 4641 (56.9)  | 906 (40.8)  | 13155 (47.3) |              |             |
| No                                     | 330 (31.4)   | 3373 (41.3)  | 1270 (57.1) | 14086 (50.6) |              |             |
| Unknown                                | 21 (2.0)     | 144 (1.8)    | 47 (2.1)    | 600 (2.2)    |              |             |
| Shock delivery before ALS arrival      |              |              |             | 0.217        |              |             |
| Yes                                    | 255 (24.3)   | 2342 (28.7)  | 22 (1.0)    | 306 (1.1)    |              |             |
| No                                     | 796 (75.7)   | 5816 (71.3)  | 2201 (99.0) | 27535 (98.9) |              |             |
| EMS response time (interval between 9-1-1 call and first EMS arrival), median (IQR), minutes | 5.2 (4.0-6.6) | 5.5 (4.3-7.0) | 5.6 (4.4-7.0) | 5.4 (4.2-7.0) | 0.148 | 0.109 |
| Shock delivery after ALS arrival       |              |              |             |              | 0.138        | 0.109       |
| Yes                                    | 793 (75.5)   | 5654 (69.3)  | 128 (5.8)   | 4483 (16.1)  |              |             |
| Interval between ALS arrival and shock delivery, median (IQR), minutes | 3.9 (2.6-5.1) | 4.0 (2.5-5.9) | 10.0 (4.4-17.1) | 13.5 (8.5-19.9) | 0.109 | 0.109 |
| Advanced airway management             |              |              |             |              | 0.853        | 0.109       |
| Yes                                    | 455 (43.3)   | 6635 (81.3)  | 663 (29.8)  | 21857 (78.5) |              |             |

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|                                      | ALS     | AAM     | PEA     | CPR     | EMS     | AAM     |
|--------------------------------------|---------|---------|---------|---------|---------|---------|
| Interval between ALS arrival and AAM, | 11.0 (7.0-16.9) | 10.5 (7.0-15.0) | 10.0 (6.5-15.3) | 10.5 (7.1-14.7) | 0.116 | 0.04 |
| median (IQR), minutes                |         |         |         |         |         |         |
| Departure from the scene             |         |         |         |         |         |         |
| Yes                                  | 1001 (95.2) | 6394 (78.4) | 1016 (45.7) | 13753 (49.4) | 0.515 | 0.074 |
| Interval between ALS arrival and     | 19.7 (15.1-25.7) | 24.9 (19.5-31.8) | 19.9 (14.3-26.2) | 25.5 (19.6-32.7) | 0.586 | 0.563 |
| departure from the scene, median     |         |         |         |         |         |         |
| (IQR), minutes                       |         |         |         |         |         |         |

ROSC indicates return of spontaneous circulation; TOR, termination of resuscitation; IQR, interquartile range; PEA, pulseless electrical activity; CPR, cardiopulmonary resuscitation; ALS, advanced life support; EMS, emergency medical services; and AAM, advanced airway management.
**eTable 4.** Characteristics of adult patients with out-of-hospital cardiac arrest with epinephrine and at risk of receiving epinephrine in time-dependent propensity score matched cohort, excluding those who had ROSC or TOR within 5 minutes after ALS EMS arrival

|                          | Shockable rhythm |                                          | Nonshockable rhythm |                                          |
|--------------------------|------------------|-------------------------------------------|---------------------|-------------------------------------------|
|                          | At-risk of       | Epinephrine (n=8145)                      | At-risk of          | Epinephrine (n=27827)                      |
|                          | receiving        | standardized difference                   | receiving           | standardized difference                   |
|                          | epinephrine      |                                           | epinephrine         |                                           |
|                          | (n=8145)         |                                           | (n=27827)           |                                           |
| Age, median (IQR), y     | 65 (55-76)       | 65 (55-76)                                | 67 (55-80)          | 68 (55-80)                                |
|                          | 0.014            | 0.014                                     | 0.021               | 0.021                                     |
| Sex                      | 0.032            |                                           | 0.006               |                                           |
| Male                     | 6251 (76.7)      | 6360 (78.1)                               | 17132 (61.6)        | 17060 (61.3)                              |
| Unknown                  | 4 (0.0)          | 4 (0.0)                                   | 11 (0.0)            | 12 (0.0)                                  |
| Race                     | 0.053            |                                           | 0.002               |                                           |
| White                    | 1883 (23.1)      | 2069 (25.4)                               | 6852 (24.6)         | 6828 (24.5)                               |
| Non-white                | 6262 (76.9)      | 6076 (74.6)                               | 20975 (75.4)        | 20999 (75.5)                              |
| Etiology                 | 0.008            |                                           | 0.009               |                                           |
| Cardiac                  | 7992 (98.1)      | 8001 (98.2)                               | 25823 (92.8)        | 25759 (92.6)                              |
| Non-cardiac              | 152 (1.9)        | 143 (1.8)                                 | 2004 (7.2)          | 2068 (7.4)                                |
| Unknown                  | 1 (0.0)          | 1 (0.0)                                   |                     |                                           |
| Initial rhythm           |                  |                                           | 0.025               |                                           |
| PEA                      | N/A              | N/A                                       | 7905 (28.4)         | 8223 (29.6)                               |
| Asystole                 | N/A              | N/A                                       | 19922 (71.6)        | 19604 (70.4)                              |
| Location                 |                  |                                           | 0.061               | 0.029                                     |
| Street/highway           | 748 (9.2)        | 738 (9.1)                                 | 806 (2.9)           | 790 (2.8)                                 |
| Public building          | 141 (1.7)        | 167 (2.1)                                 | 162 (0.6)           | 177 (0.6)                                 |
| Place of recreation      | 301 (3.7)        | 339 (4.2)                                 | 386 (1.4)           | 320 (1.1)                                 |
| Industrial place         | 182 (2.2)        | 178 (2.2)                                 | 121 (0.4)           | 131 (0.5)                                 |
| Home                     | 5403 (66.3)      | 5275 (64.8)                               | 21036 (75.6)        | 21067 (75.7)                              |
| Farm/ranch               | 8 (0.1)          | 6 (0.1)                                   | 23 (0.1)            | 26 (0.1)                                  |
| Healthcare facility      | 135 (1.7)        | 129 (1.6)                                 | 550 (2.0)           | 564 (2.0)                                 |
| Category                        | 305 (3.7) | 299 (3.7) | 3383 (12.2) | 3429 (12.3) |
|--------------------------------|-----------|-----------|-------------|-------------|
| Residential institution        | 873 (10.7)| 946 (11.6)| 1197 (4.3)  | 1188 (4.3)  |
| Other public property          | 28 (0.3)  | 49 (0.6)  | 94 (0.3)    | 84 (0.3)    |
| Other non-public property      | 21 (0.3)  | 19 (0.2)  | 69 (0.2)    | 51 (0.2)    |
| Witnessed collapse             | 0.036     |           | 0.017       |
| Bystander                      | 5192 (63.7)| 5289 (64.9)| 9206 (33.1) | 9410 (33.8) |
| None                           | 2793 (34.3)| 2672 (32.8)| 17807 (64.0)| 17645 (63.4)|
| Unknown                        | 160 (2.0) | 184 (2.3) | 814 (2.9)   | 772 (2.8)   |
| Layperson CPR                  | 0.047     |           | 0.008       |
| Yes                            | 4450 (54.6)| 4635 (56.9)| 13048 (46.9)| 13145 (47.2)|
| No                             | 3555 (43.6)| 3367 (41.3)| 14191 (51.0)| 14082 (50.6)|
| Shock delivery before ALS arrival | 140 (1.7) | 143 (1.8) | 588 (2.1)   | 600 (2.2)   |
| Yes                            | 2452 (30.1)| 2336 (28.7)| 336 (1.2)   | 304 (1.1)   |
| No                             | 5693 (69.9)| 5809 (71.3)| 27491 (98.8)| 27523 (98.9)|
| EMS response time              | 5.6 (4.3-7.1)| 5.5 (4.3-7.0)| 5.4 (4.2-7.0)| 5.4 (4.2-7.0)|
| Shock delivery after ALS arrival | 0.041     |           | 0.014       |
| Yes                            | 5714 (70.2)| 5646 (69.3)| 4066 (14.6) | 4481 (16.1) |
| Interval between ALS arrival and shock delivery | 4.1 (2.7-5.9)| 4.0 (2.5-5.9) | 15.3 (8.6-22.9)| 13.5 (8.5-19.9)|
| Advanced airway management     | 6258 (76.8)| 6625 (81.3)| 20775 (74.7)| 21845 (78.5)|

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|                          | median (IQR), minutes |  | median (IQR), minutes |  |  |
|--------------------------|-----------------------|--|--|-----------------------|--|--|
| **Interval between ALS** | **arrival and AAM,**  |  | **departure from the scene** |  |  |
| arrival and AAM, median  | 11.0 (7.0-16.0)       |  | 6392 (78.5)             |  | 6 |
| (IQR), minutes           | 10.5 (7.0-15.0)       |  | 6385 (78.4)             |  | 392 |
|                          | 0.068                 |  | 0.002                  |  | 0.002 |
|                          | 11.0 (7.0-16.0)       |  | 14421 (51.8)           |  | 6385 |
|                          | 10.5 (7.0-14.7)       |  | 13740 (49.4)           |  | 6385 |
|                          | 0.105                 |  | 0.049                  |  | 0.049 |
|                          | 24.9 (19.1-32.3)      |  | 24.9 (19.5-31.8)       |  | 14421 |
|                          | 0.002                 |  | 0.002                  |  | 13740 |
|                          | 25.3 (19.0-33.3)      |  | 25.5 (19.6-32.6)       |  | 14421 |
|                          | 0.021                 |  | 0.021                  |  | 13740 |

ROSC indicates return of spontaneous circulation; TOR, termination of resuscitation; IQR, interquartile range; PEA, pulseless electrical activity; CPR, cardiopulmonary resuscitation; ALS, advanced life support; EMS, emergency medical services; and AAM, advanced airway management.

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**eTable 5. Outcomes in time-dependent propensity score matched cohort, excluding those who had ROSC or TOR within 5 minutes after ALS EMS arrival**

| Outcomes                                      | No (%) patients with outcome/total patients | Risk ratio (95% CI) |
|-----------------------------------------------|---------------------------------------------|--------------------|
|                                               | At-risk of receiving epinephrine Epinephrine |                    |
| Shockable rhythms                              |                                             |                    |
| Survival to hospital discharge                 | 1572/8145 (19.3%) 1514/8145 (18.6%)         | 1.03 (0.95-1.11)   |
| Favorable functional outcome at hospital discharge | 1242/8145 (15.2%) 1176/8145 (14.4%)         | 1.02 (0.94-1.11)   |
| Prehospital ROSC                               | 3479/8145 (42.7%) 3904/8145 (47.9%)         | 1.17 (1.12-1.22)   |
| Nonshockable rhythms                           |                                             |                    |
| Survival to hospital discharge                 | 604/27827 (2.2%) 603/27827 (2.2%)            | 1.09 (0.96-1.23)   |
| Favorable functional outcome at hospital discharge | 310/27827 (1.1%) 258/27827 (0.9%)            | 0.91 (0.74-1.12)   |
| Prehospital ROSC                               | 6034/27827 (21.7%) 7880/27827 (28.3%)        | 1.33 (1.29-1.38)   |

ROSC indicates return of spontaneous circulation; TOR, termination of resuscitation; ALS, advanced life support; and EMS, emergency medical services.
**eTable 6.** Characteristics of adult patients with bystander witnessed out-of-hospital cardiac arrest with and without epinephrine

|                          | Shockable rhythm | Nonshockable rhythm | Sex | Etiology | Location |
|--------------------------|------------------|---------------------|-----|----------|----------|
|                          | No epinephrine   | Epinephrine         |     | Cardiac  | Street/highway |
| Age, median (IQR), y     | 62 (53-72)       | 65 (55-76)         | 0.188 | 1443 (97.9) | 738 (50.1) |
|                          | 70 (58-82)       | 71 (58-82)         | 0.007 | 1002 (87.1) | 789 (68.5) |
| Male                     | 1082 (73.4)      | 4259 (79.7)        | 0.149 | 5269 (98.6) | 483 (9.0) |
| Unknown                  | 1 (0.1)          | 2 (0.0)            | 0.034 | 1323 (24.8) | 122 (2.3) |
| Race                     |                  |                    | 0.05  |          |          |
| White                    | 387 (26.3)       | 1323 (24.8)        | 0.058 |          |          |
| Non-white                | 1087 (73.7)      | 4021 (75.2)        | 0.226 |          |          |
| Etiology                 |                  |                    |       |          |          |
| Cardiac                  | 1443 (97.9)      | 5269 (98.6)        | 0.331 |          |          |
| Non-cardiac              | 31 (2.1)         | 74 (1.4)           |       |          |          |
| Unknown                  | 0 (0.0)          | 1 (0.0)            |       |          |          |
| Initial rhythm           |                  |                    |       |          | 0.331    |
| PEA                      | N/A              | N/A                | 0.331 |          |          |
| Asystole                 | N/A              | N/A                |       |          |          |
| Location                 |                  |                    | 0.275 |          | 0.153    |
| Street/highway           | 159 (10.8)       | 483 (9.0)          |       |          |          |
| Public building          | 54 (3.7)         | 122 (2.3)          |       |          |          |
| Place of recreation      | 117 (7.9)        | 269 (5.0)          |       |          |          |
| Industrial place         | 45 (3.1)         | 121 (2.3)          |       |          |          |
| Home                     | 738 (50.1)       | 3345 (62.6)        |       |          |          |
| Farm/ranch               | 0 (0.0)          | 7 (0.1)            |       |          |          |
| Healthcare facility      | 30 (2.0)         | 99 (1.9)           |       |          |          |
| Residential institution  | 45 (3.1)         | 127 (2.4)          |       |          |          |
| Other public property    | 261 (17.7)       | 721 (13.5)         |       |          |          |

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| Other non-public property | 20 (1.4) | 33 (0.6) | 2 (0.2) | 31 (0.3) |
|---------------------------|---------|---------|--------|---------|
| Unknown                   | 5 (0.3) | 17 (0.3) | 4 (0.3) | 16 (0.2) |
| Layperson CPR             |         |         | 0.224  |         |
| Yes                       | 1060 (71.9) | 3284 (61.5) | 567 (49.3) | 4880 (51.7) |
| No                        | 394 (26.7) | 1972 (36.9) | 570 (49.5) | 4376 (46.4) |
| Shock delivery before ALS arrival |         |         | 0.215  |         |
| Yes                       | 584 (39.6) | 1614 (30.2) | 15 (1.3) | 129 (1.4) |
| No                        | 890 (60.4) | 3730 (69.8) | 1136 (98.7) | 9306 (98.6) |
| EMS response time (interval between 9-1-1 call and first EMS arrival), median (IQR), minutes | 5.1 (4.0-6.6) | 5.6 (4.4-7.1) | 0.192  | 5.5 (4.2-7.0) | 5.5 (4.4-7.2) | 0.056 |
| Shock delivery after ALS arrival |         |         |         |         |
| Yes                       | 889 (60.3) | 3686 (69.0) | 0.182  | 80 (7.0) | 1898 (20.1) |
| Interval between ALS arrival and shock delivery, median (IQR), minutes | 3.1 (1.9-4.5) | 3.9 (2.5-5.7) | 0.306  | 9.4 (4.4-18.1) | 13.3 (8.3-19.7) |
| Advanced airway management |         |         |         |         |
| Yes                       | 662 (44.9) | 4315 (80.7) | 0.798  | 491 (42.7) | 7655 (81.1) |
| Interval between ALS arrival and AAM, median (IQR), minutes | 10.9 (6.6-16.0) | 10.3 (6.9-15.0) | 0.088  | 10.0 (6.3-15.5) | 10.4 (7.0-14.8) |
| Departure from the scene |         |         |         |         |
| Yes                       | 1434 (97.3) | 4354 (81.5) | 0.531  | 808 (70.2) | 5857 (62.1) |

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|                | 19.2 (14.5-25.2) | 24.9 (19.5-31.6) | 0.636 | 20.8 (15.5) | 25.5 (19.7-32.8) | 0.520 |
|----------------|------------------|------------------|-------|-------------|------------------|-------|

IQR indicates interquartile range; PEA, pulseless electrical activity; CPR, cardiopulmonary resuscitation; ALS, advanced life support; EMS, emergency medical services; and AAM, advanced airway management
**eTable 7.** Characteristics of adult patients with bystander witnessed out-of-hospital cardiac arrest out-of-hospital cardiac arrest with epinephrine and at risk of receiving epinephrine in time-dependent propensity score matched cohort

|                        | Shockable rhythm | Nonshockable rhythm |                     |                     |                     |                     |
|------------------------|------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
|                        | At-risk of       | Epinephrine         | At-risk of          | Epinephrine         | standardised        | standardised        |
|                        | receiving        | (n=5326)            | receiving           | (n=9418)            | difference          | difference          |
| Age, median (IQR), y   | 65 (55-76)       | 65 (55-76)          | 0.027               | 70 (58-82)          | 71 (58-82)          | 0.024               |
| Sex                    |                  |                     | 0.032               |                     |                     | 0.025               |
| Male                   | 4177 (78.4)      | 4246 (79.7)         | 5673 (60.2)         | 5766 (61.2)         |                    |
| Unknown                | 2 (0.0)          | 2 (0.0)             | 1 (0.0)             | 3 (0.0)             |                    |
| Race                   |                  |                     | 0.038               |                     |                     | 0.008               |
| White                  | 1232 (23.1)      | 1318 (24.7)         | 2232 (23.7)         | 2263 (24.0)         |                    |
| Non-white              | 4094 (76.9)      | 4008 (75.3)         | 7186 (76.3)         | 7155 (76.0)         |                    |
| Etiology               |                  |                     | 0.019               |                     |                     | 0.019               |
| Cardiac                | 5240 (98.4)      | 5251 (98.6)         | 8864 (94.1)         | 8821 (93.7)         |                    |
| Non-cardiac            | 84 (1.6)         | 74 (1.4)            | 554 (5.9)           | 597 (6.3)           |                    |
| Unknown                | 2 (0.0)          | 1 (0.0)             | 0 (0)               | 0 (0)               |                    |
| Initial rhythm         |                  |                     | 0.047               |                     |                     |                    |
| PEA                    | N/A              | N/A                 | 4134 (43.9)         | 4355 (46.2)         |                    |
| Asystole               | N/A              | N/A                 | 5284 (56.1)         | 5063 (53.8)         |                    |
| Location               |                  |                     | 0.078               |                     |                     | 0.027               |
| Street/highway         | 477 (9.0)        | 483 (9.1)           | 412 (4.4)           | 415 (4.4)           |                    |
| Public building        | 102 (1.9)        | 120 (2.3)           | 98 (1.0)            | 89 (0.9)            |                    |
| Place of recreation    | 238 (4.5)        | 269 (5.1)           | 155 (1.6)           | 141 (1.5)           |                    |
| Industrial place       | 101 (1.9)        | 120 (2.3)           | 54 (0.6)            | 56 (0.6)            |                    |
| Home                   | 3427 (64.3)      | 3334 (62.6)         | 6826 (72.5)         | 6821 (72.4)         |                    |
| Farm/ranch             | 13 (0.2)         | 6 (0.1)             | 12 (0.1)            | 12 (0.1)            |                    |
| Healthcare facility    | 109 (2.0)        | 97 (1.8)            | 264 (2.8)           | 281 (3.0)           |                    |

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| Category                               | Yes          | No           | Unknown   | Yes          | No           |
|----------------------------------------|--------------|--------------|-----------|--------------|--------------|
| Residential institution                | 151 (2.8)    | 127 (2.4)    | 1009 (10.7) | 983 (10.4)   |              |
| Other public property                  | 657 (12.3)   | 720 (13.5)   | 546 (5.8)  | 575 (6.1)    |              |
| Other non-public property              | 27 (0.5)     | 33 (0.6)     | 31 (0.3)   | 30 (0.3)     |              |
| Unknown                                | 24 (0.5)     | 17 (0.3)     | 11 (0.1)   | 15 (0.2)     |              |
| Layperson CPR                          |              |              |           | 0.071        | 0.027        |
| Yes                                    | 3093 (58.1)  | 3277 (61.5)  | 4744 (50.4) | 4870 (51.7)  |              |
| No                                     | 2139 (40.2)  | 1962 (36.8)  | 4484 (47.6) | 4370 (46.4)  |              |
| Unknown                                | 94 (1.8)     | 87 (1.6)     | 190 (2.0)  | 178 (1.9)    |              |
| Shock delivery before ALS arrival      |              |              |           | 0.078        | 0.024        |
| Yes                                    | 1420 (26.7)  | 1606 (30.2)  | 106 (1.1)  | 129 (1.4)    |              |
| No                                     | 3906 (73.3)  | 3720 (69.8)  | 9312 (98.9) | 9289 (98.6)  |              |
| EMS response time                      |              |              |           | 0.010        | 0.007        |
| (interval between 9-1-1 call and first | 5.7 (4.4-7.0)| 5.6 (4.4-7.1)| 5.8 (4.4-7.2)| 5.7 (4.4-7.2)|              |
| EMS arrival), median (IQR), minutes    |              |              |           |              |              |
| Shock delivery after ALS arrival       |              |              |           | 0.104        | 0.155        |
| Yes                                    | 3925 (73.7)  | 3674 (69.0)  | 1694 (18.0)| 1889 (20.1)  |              |
| No                                     | 3906 (73.3)  | 3720 (69.8)  | 9312 (98.9)| 9289 (98.6)  |              |
| Interval between ALS arrival and shock |              |              |           |              |              |
| delivery, median (IQR), minutes        | 4.0 (2.6-5.9)| 3.9 (2.4-5.7)| 15.0 (8.4-22.4)| 13.3 (8.3-19.7)|              |
| Advanced airway management             |              |              |           | 0.111        | 0.111        |
| Yes                                    | 4059 (76.2)  | 4302 (80.8)  | 7214 (76.6)| 7640 (81.1)  |              |
| Interval between ALS arrival and AAM,  |              |              |           |              |              |
| median (IQR), minutes                  | 11.0 (6.7-16.0)| 10.3 (6.9-15.0)| 10.9 (7.0-15.8)| 10.4 (7.0-14.8)|              |
| Departure from the scene               |              |              |           | 0.020        | 0.006        |
| Yes                                    | 4381 (82.3)  | 4339 (81.5)  | 5870 (62.3)| 5841 (62.0)  |              |

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| Interval between ALS arrival and departure from the scene, median (IQR), minutes | 25.0 (19.1-32.4) | 24.8 (19.5-31.6) | 0.012 | 25.7 (19.0-33.0) | 25.5 (19.7-32.8) | 0.014 |

IQR indicates interquartile range; PEA, pulseless electrical activity; CPR, cardiopulmonary resuscitation; ALS, advanced life support; EMS, emergency medical services; and AAM, advanced airway management
**eTable 8.** Outcomes in time-dependent propensity score matched cohort of bystander witnessed out-of-hospital cardiac arrest

| Outcomes                                      | No (%) patients with outcome/total patients | Risk ratio (95% CI) |
|-----------------------------------------------|---------------------------------------------|-------------------|
|                                               | At-risk of receiving epinephrine Epinephrine |                   |
| **Shockable rhythm**                         |                                             |                   |
| Survival to hospital discharge                | 1287/5326 (24.2%) 1178/5326 (22.1%)        | 0.97 (0.89-1.05)  |
| Favorable functional outcome at hospital discharge | 1059/5326 (19.9%) 935/5326 (17.6%)        | 0.95 (0.87-1.05)  |
| Prehospital ROSC                              | 2531/5326 (47.5%) 2761/5326 (51.8%)        | 1.15 (1.10-1.21)  |
| **Nonshockable rhythm**                       |                                             |                   |
| Survival to hospital discharge                | 380/9418 (4.0%) 323/9418 (3.4%)             | 0.94 (0.8.0-1.11) |
| Favorable functional outcome at hospital discharge | 224/9418 (2.4%) 148/9418 (1.6%)            | 0.72 (0.56-0.94)  |
| Prehospital ROSC                              | 2916/9418 (31.0%) 3708/9418 (39.4%)        | 1.31 (1.25-1.37)  |