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A time-dependent propensity score matching approach to assess epinephrine use on patients survival within out-of-hospital cardiac arrest care

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Declarations of competing Interest

None.

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1 **A time-dependent propensity score matching approach to assess epinephrine use on**
2 **patients survival within out-of-hospital cardiac arrest care**

3 **Abstract**

4 **Background:** Epinephrine effectiveness and safety are still questioned. It is well-known
5 **that the effect of epinephrine varies depending of patients' rhythm and of time to**
6 **injection.**

7 **Objectives:** We aimed to assess the association between epinephrine use during out-of-
8 **hospital cardiac arrest (OHCA) care and patient D30 survival.**

9 **Methods:** Between 2011 and 2017, 27,008 OHCA patients were included from the French
10 **OHCA registry. We adjusted populations using a time-dependent propensity score**
11 **matching. Analyses were stratified according to patient's first rhythm. After matching,**
12 **2,837 pairs of patients with a shockable rhythm were created and 20,950 with a**
13 **nonshockable rhythm.**

14 **Results:** Whatever the patients' rhythm (shockable or nonshockable), epinephrine use
15 **was associated with less D30 survival (respectively: OR=0.508 [0.440; 0.586] and**
16 **OR=0.645 [0.549;0.759]). In shockable rhythms, on all outcomes, epinephrine use was**
17 **deleterious. In nonshockable rhythms, no difference was observed regarding ROSC and**
18 **survival at the hospital admission. However, epinephrine use was associated with worse**
19 **neurological prognosis (OR=0.646 [0.549;0.759]).**

20 **Conclusions:** In shockable and nonshockable rhythms populations, epinephrine does not
21 **seem to have any benefit on D30 survival. These results underscore the need to perform**
22 **further studies to define the optimal conditions for using epinephrine in patients with**
23 **OHCA.**

24 **Keywords**

25 **Out-of-hospital Cardiac Arrest, epinephrine, resuscitation, time-dependent propensity score**

26

27

28 INTRODUCTION

29 Out-of-hospital cardiac arrest (OHCA) is a major public health issue. In France, 46,000 cardiac
30 arrests occur each year (1,2). Furthermore, survival rates are dramatically low. Only 5% of
31 victims survive 30 days after the onset of cardiac arrest, and of them, 85% survive with few or
32 no neurological sequelae (3).

33 To improve care practices and survival rates, the International Liaison Committee On
34 Resuscitation (ILCOR) generates guidelines and defines drug strategies for OHCA care (4). These
35 strategies include the epinephrine use for patients who suffer an OHCA. The most recent
36 guidelines update (2015) advises a standard dose of 1 mg every 3 to 5 minutes of resuscitation
37 (5). The advice to use epinephrine was never withdrawn, even if evidence of its effectiveness is
38 not yet conclusive in the literature, as highlighted by the ILCOR (6). Several non-adjusted studies
39 assessing epinephrine effectiveness exist (7-9). These studies have biases that could be avoided
40 by performing prospective randomized controlled trials, but these designs are difficult to
41 implement. As an example, the study by Jacobs *et al.* (10) experienced methodological problems,
42 as they excluded 67.11% of patients after randomization. In addition, Olasveengen *et al.* (11)
43 compared patients who benefited from intravenous cannulation (including epinephrine and
44 other drugs) with patients who did not benefit from such cannulation, so that study did not focus
45 on the use of epinephrine. Finally, we can only rely on a recent reliable randomized study
46 (PARAMEDIC2) (12). Other recent studies used propensity score matching to be as close as
47 possible to a randomized controlled trial, but their results are conflicting (13-15).

48 We assume that the effectiveness of the use of epinephrine in OHCA is not constant and may
49 vary according to the initial rhythm (13) and to the injection time (16,17). On the French
50 national Cardiac Arrest Registry (RéAC) (3), the aim of our study was to assess the associations
51 between the use of epinephrine and patient survival and neurological outcomes in patients with
52 OHCA in the real-world setting (according to their first recorded rhythm, shockable or
53 nonshockable) using a time-dependent propensity score matching.

54 MATERIAL AND METHODS

55 *Ethics approval and consent to participate*

56 This study was approved by the French Advisory Committee on Information Processing in
57 Material Research in the Field of Health (“Comité Consultatif sur le Traitement de l’Information
58 en Matière de Recherche dans le Domaine de la Santé”: CCTIRS) and by the French National Data
59 Protection Commission (“Commission Nationale de l’Informatique et des Libertés”: CNIL;
60 authorization number 910946).

61

62 *Study design*

63 In France, the prehospital emergency medical system is a two-tiered system with a fire
64 department ambulance available for providing a first response and basic life support (BLS) and a
65 mobile emergency and resuscitation service (MERS) including a mobile medical team (MMT) for
66 advanced cardiac life support (ACLS) (18). Medical dispatch centers are responsible for out-of-
67 hospital emergency coordination. All MERSs use a specific RéAC recording form during OHCA
68 interventions to enter patient data, times, care, and immediate survival status. The RéAC form
69 meets the requirements of the French Emergency Medical System (EMS) organizations and is
70 structured according to the universal Utstein style (3,19). Data are reported in the RéAC secure
71 database (www.registreac.org). A 30-day follow-up data collection after the onset of the OHCA
72 or at the time of hospital discharge is performed and entered into the database.

73 *Study population and data*

74 Our comparative, multicenter study used data from the RéAC. Data were collected between July
75 1, 2011, and December 31, 2017.

76 *Inclusion criteria*

- 77 - medical OHCA according to the Utstein template (19)
- 78 - patients aged 18 or older

79 - patients in whom ACLS was attempted.

80 *Exclusion criteria*

81 - physical indications of death (*rigor mortis*)

82 - files lacking data for mandatory criteria (Utstein core data)

83 - for patients who had epinephrine during their care: files lacking data for the time
84 between OHCA and the epinephrine injection (if the RéAC investigator did not recorded
85 the time of the first epinephrine injection during the intervention)

86 - files lacking data for the time between T0 (first call) and the time of death

87 - time between call (T0) and MMT arrival longer than 60 minutes

88 - patients with a return of spontaneous circulation (ROSC) before MMT arrival

89 - patients with a known Do Not Attempt Resuscitation (DNAR) order.

90 The data collected included baseline clinical characteristics, times, history, bystander BLS, first
91 aid provider BLS, first rhythm recorded by the MMT, ACLS, prehospital treatment, patient
92 transport, and admission parameters. Thirty-day follow-up data included patient vital status and
93 neurological outcome.

94 *Endpoints*

95 The primary endpoint was patient survival D30, it corresponded to the patient follow up 30 days
96 after the OHCA, at the patient death or at hospital discharge. The secondary endpoints were the
97 ROSC, the survival at hospital admission (D0) and the neurological outcome at 30 days post-
98 OHCA or hospital discharge assessed by the Cerebral Performance Category score (CPC) for alive
99 patients (20).

100 *Statistical analysis*

101 First, we described and compared two cohorts of patients. Patients who received epinephrine
102 were compared with patients who did not. We stratified the results according to the first patient
103 rhythm recorded by the MMT (shockable or nonshockable).

104 Second, we compared the populations' survival rates according to the primary and secondary
105 endpoints after matching both populations (epinephrine vs. no epinephrine). As the risk of
106 receiving epinephrine varies over time, we considered that a patient receiving epinephrine at a
107 time t cannot be part of the same group as a patient receiving epinephrine at time $t+k$ minutes.
108 Hence, we performed a time-dependent propensity score matching per stratified group (21–23).

109 *Description and comparison of cohorts*

110 The quantitative variables are described as medians and first and third quartiles [Q1; Q3]. The
111 qualitative variables are described as frequencies. Bivariate analysis were assessed using the
112 Pearson Chi-Square test for categorical variables and the non-parametric Wilcoxon rank test for
113 continuous variables. The level of significance was set at a p-value <0.05 .

114

115 *Estimation of the time-dependent propensity score*

116 We estimated the effect of time to injection based on a Cox proportional hazard regression
117 model. We considered as censored; the deceased patients who did not receive epinephrine and
118 patients arriving alive at the hospital. For alive patients at the hospital, the censor time was the
119 arrival time when available or the ROSC. We included 13 covariates in the model: year of OHCA,
120 patients' age, patients' sex, bystander presence, type of bystander, OHCA cause, immediate CPR,
121 during BLS: chest compressions, ventilation, shock by AED; defibrillator shock by MMT,
122 intubation and time between T0 (first call) and MMT arrival. A quadratic effect was used on the
123 age. We tested proportional hazards assumption for each covariate using a chi-squared test on
124 the Schoenfeld's residuals (24). We observed that the ratio of the hazards were not constant
125 over time for type of bystander ($p=0.0009$) and time from T0 to MMT arrival ($p<0.0001$) in the
126 group of shockable rhythm, and for type of bystander ($p=0.0001$), immediate CPR ($p=0.0195$)
127 and time from T0 to MMT arrival ($p<0.0001$) in the group of nonshockable rhythm. These
128 covariates were considered as time dependent with a step function (25) about 5-minute time

129 intervals. The covariates that verified the assumption of proportional risk hazards were selected
130 in the models as time constant. After time stratification, the global test on Schoenfeld's residuals
131 was not significant for the shockable rhythm ($p=0.9914$) and the nonshockable rhythm
132 ($p=0.8380$). Finally, we estimated the time dependent propensity score as the linear predictor
133 for each patient at t time down to the minute.

134

135 *Matching method*

136 Sequential matching of patients was performed between 0 and 65 minutes. The 65-minute
137 threshold corresponded to the quantile at 98% of the time before injection of epinephrine in the
138 overall population. The matching distance used was the nearest neighbor with replacement,
139 within a caliper of 10% of the standard deviation.

140 In the shockable population, 2,837 patients receiving epinephrine at time t were matched to
141 2,837 control patients corresponding to 1,055 patients that did not received epinephrine and
142 1,782 patients receiving epinephrine later. Of those 1,782 patients, 1,262 received epinephrine
143 within 10 minutes after the case and 520 at least 10 minutes later and up to 119 minutes later.
144 Among the control group, 2,131 patients were matched several times with 9 duplicate cases
145 maximum for 9 control patients.

146 In the nonshockable population, 20,950 patients receiving epinephrine at time t were matched
147 to 20,950 control patients corresponding to 5,509 patients that did not received epinephrine
148 and 15,441 patients receiving epinephrine later. Of those 15,441 patients, 10,918 received
149 epinephrine within 10 minutes after and 4,522 at least 10 minutes later and up to 619 minutes
150 later. Among the control group, 16,055 patients were matched several times with 13 duplicate
151 cases maximum for 39 control patients.

152

153 *Quality of matching*

154 We measured the matching quality with the weighted standardized mean difference
155 (Supplementary figure 1 and 2). The time between T0 and the MMT arrival was unbalanced after
156 pairing. In the group of shockable rhythm, the difference was greater than the 10% threshold. In
157 practice, the matching was considered satisfying as the average delay was 22.55 minutes for
158 cases vs 21.16 minutes for control and the standardized difference about 12.6%.

159

160 *Conditional weighted logistic regression*

161 We performed a logistic regression for non-adjusted Odds Ratios (OR) and a conditional
162 weighted logistic regression (26) based on matching pairs for adjusted OR. We supplied 95%
163 confidence interval in both cases.

164

165 Statistical analysis were performed using R 3.5.1 software, with the “survival” package (27) for
166 developing time dependent propensity score algorithms and fitting a conditional logistic
167 regression. The “MatchIt” package (28) for sequential matching. The “tableone” package (29) to
168 compute the standardized differences before and after matching.

169

170 **RESULTS**

171 *Unadjusted population*

172 *Study participants*

173

174 Between July 1, 2011, and December 31, 2017, we identified 81,780 patients with OHCAs during
175 the study period (Fig. 1), of whom 27,008 met the inclusion criteria of the study. An epinephrine

176 injection was administered to 90.0% of the patients. A shockable rhythm was found in 3,448
177 patients and a nonshockable rhythm in 23,560 patients.

178 *Description of the studied population*

179 Our studied population was mainly male (68.9%), and the median age was 68. A bystander was
180 present at the onset of the OHCA in 73.1% of cases. The first recorded rhythm by MMT was
181 nonshockable in 87.2% of patients. A ROSC occurred in 28.5% of patients, and 22.7% of patients
182 were admitted to the hospital alive. Thirty days after the OHCA, 5.1% of the patients were alive,
183 and among them, 72.9% had a good neurological outcome. The detailed results are presented in
184 Table 1.

185 *Comparison between the epinephrine and no epinephrine groups in the studied population*

186 We observed significant differences for almost every descriptive criterion between our two
187 groups, except the presence of a bystander and a shock delivered during BLS (Table 1).
188 At 30 days, a lower survival rate was observed when epinephrine was used (3.5% vs. 19.3%, $P <$
189 0.001). The ROSC rate was not different between our two groups (28.5% vs. 28.3%, $P = 0.898$),
190 whereas the survival rate at the time of hospital admission was higher in the no epinephrine
191 group than in the epinephrine group (22.2% vs. 27.2%, $P < 0.001$). At 30 days, we recorded a
192 worse neurological outcome in the epinephrine group than in the no epinephrine group (65.3%
193 vs. 85.3%, $P < 0.001$) (Table 1).

194 *Comparison between epinephrine and no epinephrine groups in patients with shockable rhythms*

195 Epinephrine was used in 83.5% of patients who had a shockable rhythm at the time of MMT
196 arrival (VF/pulseless VT). When epinephrine was injected, the population was significantly,
197 older, more likely to be male, with less bystander presence, the bystander was more a family
198 member. During ACLS, in the epinephrine population we observed significantly more shock and
199 the time from call (T0) to ROSC or death was longer. Regarding survival at 30 days, lower rate

200 was observed in the epinephrine group (15.1 vs. 69.1, $P < .001$). All other survival rates (ROSC
201 and hospital admission) and good neurological outcome rates were significantly lower in the
202 epinephrine group (Table 2).

203 *Comparison between epinephrine and no epinephrine groups in patients with nonshockable*
204 *rhythms*

205 Among patients in whom the initial rhythm on MMT arrival was not shockable, in the
206 epinephrine group the population was older and more often male, with more bystander
207 presence and OHCA etiology was more cardiac. The time from the call to ROSC or death was
208 longer in the epinephrine group than in the no epinephrine group. The MMT delivered a shock
209 four times more often in the epinephrine group than in the no epinephrine group.

210 The D30 survival was lower in the epinephrine group (2.0 vs. 6.2, $P < .001$). Rates of ROSC and
211 survival at hospital admission were higher in the epinephrine group than in the no epinephrine
212 group. However, the rate of good neurological outcome was significantly lower in the
213 epinephrine group (Table 2).

214

215 *Adjusted population*

216 *Comparison when the initial rhythm was shockable*

217 On D30 survival we observed significantly less survival in the epinephrine group compared to
218 the no epinephrine group on unadjusted results (OR = 0.080 [0.065;0.098]). Less D30 survival
219 was also observed in the epinephrine group compared to controls in the matched populations
220 (OR = 0.508 [0.440;0.586]). On all other secondary outcomes, regardless whether of populations
221 were matched, epinephrine was always associated with less survival and worse neurological
222 outcome (Fig. 2).

223 *Comparison when the initial rhythm was nonshockable*

224 Regardless of whether the population was adjusted, epinephrine use was associated with a
225 lower survival rate at 30 days compared to the no epinephrine group for unadjusted results and
226 to controls for adjusted results (OR (unadjusted)=0.307 [0.251;0.375] and OR (adjusted)=0.645
227 [0.549;0.759]). On non-adjusted results, epinephrine was associated with more ROSC and D0
228 survival. By comparing the epinephrine group with controls on adjusted results, no difference
229 was observed on ROSC and D0 survival (respectively: OR = 1.048 [0.997;1.101] and OR = 1.037
230 [0.980;1.098]). Regarding good neurological outcome at D30, in non-adjusted and adjusted
231 results, epinephrine was significantly associated with lower rates (respectively: OR = 2.163
232 [1.908;2.452] and OR = 1.048 [0.997; 1.101]) (Fig. 3).

233 **DISCUSSION**

234 Our study was performed with a large cohort of OHCA patients and based on a time-dependent
235 propensity score-matched analysis. This methodology enabled us to assess the link between
236 epinephrine use and survival in the real-world setting by limiting the inherent bias of the impact
237 of time to injection on patient survival. Regarding survival, in both groups with nonshockable
238 rhythms or with shockable rhythms, we observed that the epinephrine use was associated with
239 a decrease in 30-day survival compared to controls. Some other studies have also highlighted
240 negative impacts of epinephrine on 30-day survival (9,15,30), while others did not (7,12,13).
241 However, previous findings did not support robust conclusions regarding the efficacy of
242 epinephrine due to methodological issues (10,11) or conflicting results (13–15).

243 In our adjusted analysis, epinephrine use was never associated with a better outcome. We
244 always observed deleterious effects of epinephrine 30 days after OHCA. The results regarding
245 D30 survival are in agreement with those of the studies by Hagihara *et al.* (15) and Olasveengen
246 *et al.* (11). Those studies also found deleterious effects of epinephrine 30 days after the OHCA. In
247 the Olasveengen *et al.* study, they reported a 48% lower change of survival when epinephrine
248 was injected than when epinephrine was not injected (11). However, some recent studies noted

249 results that conflicted with ours. The Perkins *et al.*(12), Holmberg *et al* (31) and Finn *et al.* (32)
250 studies observed a better 30-day survival among patients who received epinephrine than among
251 those who did not receive epinephrine. However, they did not notice any difference in
252 neurological outcomes.

253 If we focus on shockable rhythms, in our study, a deleterious effect of epinephrine use is evident
254 for all endpoints (ROSC, D0 survival, 30-day survival, and neurological outcome) in the adjusted
255 population. In general, other studies' results conflicted with ours (7,8,13). For example,
256 Nakahara *et al* .who also used a time-dependent propensity score matching found a positive
257 impact of epinephrine on 30-day survival but no significant difference with regard to the
258 neurological outcome (13). In the recent randomized Perkins *et al.* study, in shockable rhythms,
259 they observed a better rate of ROSC and survival at the hospital admission in the epinephrine
260 group. However, they did not highlighted any significant difference regarding survival and
261 neurological outcome 30 days after the OHCA when epinephrine was injected (33).

262 However, regarding patients with nonshockable rhythms, we observe more survival on
263 unadjusted results regarding ROSC and D0 survival. However, on adjusted population, this
264 beneficial effect became non-significant. Nevertheless, there was a negative association between
265 epinephrine use and 30-day outcomes. In studies that investigated the subpopulation of patients
266 with nonshockable rhythms, better short-term survival was largely observed among those who
267 received epinephrine than among those who did not (7,14,33). However, Goto *et al.* and Perkins
268 *et al.* noticed an absence of significance regarding the difference in neurological outcomes
269 between the two groups (7,33). Tomio *et al.* observed a better neurological outcome in their
270 asystole group and no significant difference in their PEA group (14).

271 Our results may be explained by the pharmacology of epinephrine. The α_1 and β stimulation
272 increases myocardial perfusion pressure. Hence, the higher rate of immediate survival in
273 patients with nonshockable rhythms in unadjusted populations can at least partially be
274 explained by these effects (34). However, the action of epinephrine has deleterious effects on
275 mid-term survival and neurological outcomes (35,36) (myocardial dysfunction (37,38),

276 development of new arrhythmias (37,38), cerebral microcirculation impairment) (30,34,39).
277 Our results related to mid-term survival can also be partially explained by these effects.
278 Our study was based on reliable French national registry-based data. The RéAC registry
279 provided an overview of real-life professional practices and conditions regarding OHCA (2). We
280 used a validated time-dependent propensity-score matching method to reduce bias. Our study
281 provided consistent results that bolstered the limited literature regarding the issue of
282 epinephrine efficacy. In addition, we stratified our results according to the initial patient rhythm
283 on MMT arrival. Guidelines regarding epinephrine use differ based on if the initial patient
284 rhythm is shockable or not (20). Furthermore, some studies have suggested that the impact of
285 epinephrine differs according to the initial rhythm identified (7,16). Hence, our results were not
286 influenced by the time to epinephrine injection and the patient's rhythm.

287 *Limitations*

288 Our study has some limitations. The first is linked to the use of the French National Cardiac
289 Arrest Registry (RéAC), which is based on the voluntary participation of the MMT; the list of
290 participating MMTs was not exhaustive during the study period. However, the participating
291 MERS are spread over the entire French territory and provide an overview of guideline
292 implementation. A further limitation concerns the epinephrine use; it was not randomly
293 administered. To mimic as much as possible a randomized controlled study, we used time-
294 dependent propensity score matching. The retrospective nature of this study is another
295 limitation. However, the data were collected through the use of a standardized form. The last
296 limitation is that we did not take into account differences in postresuscitation care that could
297 influence D30 survival and neurological outcomes. However, other studies did not consider
298 these in-hospital parameters either.

299 Our study was based on data from a national registry. The French emergency system is based on
300 the “stay and play” model. Hence, our results are not fully generalizable to countries applying
301 the “scoop and run” model (40). Additionally, the study population was predominantly

302 Caucasian and had specific characteristics that prevent us from generalizing our results to the
303 whole world.

304

305 **CONCLUSIONS**

306 The currently recommended use of epinephrine does not seem to have any benefit on mid-term
307 outcomes, regardless of the patients' initial rhythm and after adjustment for time imbalances.

308 Questions such as the optimal epinephrine dose or the association with other drugs still have to
309 be investigated within the context of a global therapeutic strategy surrounding the use of
310 epinephrine.

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313 **REFERENCES**

- 314 1. Gräsner J-T, Lefering R, Koster RW, Masterson S, Böttiger BW, Herlitz J, et al.
315 EuReCa ONE-27 Nations, ONE Europe, ONE Registry: A prospective one month
316 analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe.
317 Resuscitation. 2016;105:188-95.
- 318 2. Luc G, Baert V, Escutnaire J, Genin M, Vilhelm C, Di Pompéo C, et al. Epidemiology
319 of out-of-hospital cardiac arrest: A French national incidence and mid-term survival rate
320 study. *Anaesth Crit Care Pain Med.* 2019;38:131-5.
- 321 3. Hubert H, Tazarourte K, Wiel E, Zitouni D, Vilhelm C, Escutnaire J, et al. Rationale,
322 methodology, implementation, and first results of the French out-of-hospital cardiac
323 arrest registry. *Prehospital Emerg Care Off J Natl Assoc EMS Physicians Natl Assoc*
324 *State EMS Dir.* 2014;18:511-9.
- 325 4. Perkins GD, Neumar R, Monsieurs KG, Lim SH, Castren M, Nolan JP, et al. The
326 International Liaison Committee on Resuscitation—Review of the last 25 years and
327 vision for the future. *Resuscitation.* 2017;121:104–116.
- 328 5. Callaway CW, Soar J, Aibiki M, Böttiger BW, Brooks SC, Deakin CD, et al. Part 4:
329 Advanced Life Support: 2015 International Consensus on Cardiopulmonary
330 Resuscitation and Emergency Cardiovascular Care Science With Treatment
331 Recommendations. *Circulation.* 2015;132:S84-145.
- 332 6. Soar J, Nolan JP, Böttiger BW, Perkins GD, Lott C, Carli P, et al. European
333 Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life
334 support. *Resuscitation.* 2015;95:100-47.

- 335 7. Goto Y, Maeda T, Goto YN. Effects of prehospital epinephrine during out-of-hospital
336 cardiac arrest with initial non-shockable rhythm: an observational cohort study. *Crit*
337 *Care*. 2013;17:R188.
- 338 8. Herlitz J, Ekström L, Wennerblom B, Axelsson A, Bang A, Holmberg S. Adrenaline in
339 out-of-hospital ventricular fibrillation. Does it make any difference? *Resuscitation*.
340 1995;29:195–201.
- 341 9. Holmberg M, Holmberg S, Herlitz J. Low chance of survival among patients requiring
342 adrenaline (epinephrine) or intubation after out-of-hospital cardiac arrest in Sweden.
343 *Resuscitation*. 2002;54:37–45.
- 344 10. Jacobs IG, Finn JC, Jelinek GA, Ozer HF, Thompson PL. Effect of adrenaline on
345 survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled
346 trial. *Resuscitation*. 2011;82:1138–1143.
- 347 11. Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug
348 administration during out-of-hospital cardiac arrest: a randomized trial. *Jama*.
349 2009;302:2222–2229.
- 350 12. Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scopin C, et al. A randomized
351 trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med*. 2018;379:711–721.
- 352 13. Nakahara S, Tomio J, Takahashi H, Ichikawa M, Nishida M, Morimura N, et al.
353 Evaluation of pre-hospital administration of adrenaline (epinephrine) by emergency
354 medical services for patients with out of hospital cardiac arrest in Japan: controlled
355 propensity matched retrospective cohort study. *BMJ*. 10 2013;347:f6829.

- 356 14. Tomio J, Nakahara S, Takahashi H, Ichikawa M, Nishida M, Morimura N, et al.
357 Effectiveness of prehospital epinephrine administration in improving long-term
358 outcomes of witnessed out-of-hospital cardiac arrest patients with initial non-shockable
359 rhythms. *Prehosp Emerg Care*. 2017;21:432–441.
- 360 15. Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S. Prehospital
361 Epinephrine Use and Survival Among Patients With Out-of-Hospital Cardiac Arrest.
362 *JAMA*. 21 2012;307:1161-8.
- 363 16. Dumas F, Bougouin W, Geri G, Lamhaut L, Bougle A, Daviaud F, et al. Is epinephrine
364 during cardiac arrest associated with worse outcomes in resuscitated patients? *J Am Coll*
365 *Cardiol*. 2014;64:2360–2367.
- 366 17. Hayashi Y, Iwami T, Kitamura T, Nishiuchi T, Kajino K, Sakai T, et al. Impact of early
367 intravenous epinephrine administration on outcomes following out-of-hospital cardiac
368 arrest. *Circ J*. 2012;76:1639–1645.
- 369 18. Adnet F, Lapostolle F. International EMS systems: France. *Resuscitation*. 2004;63:7-9.
- 370 19. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, et al. Cardiac
371 arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein
372 Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for
373 healthcare professionals from a task force of the International Liaison Committee on
374 Resuscitation (American Heart Association, European Resuscitation Council, Australian
375 and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada,
376 InterAmerican Heart Foundation, Resuscitation Council of Southern Africa,
377 Resuscitation Council of Asia); and the American Heart Association Emergency

- 378 Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care,
379 Perioperative and Resuscitation. *Circulation*. 29 2015;132:1286-300.
- 380 20. Roger C, Palmier L, Louart B, Molinari N, Claret P-G, de la Coussaye J-E, et al. Neuron
381 specific enolase and Glasgow motor score remain useful tools for assessing neurological
382 prognosis after out-of-hospital cardiac arrest treated with therapeutic hypothermia.
383 *Anaesth Crit Care Pain Med*. 2015;34:231-7.
- 384 21. Wang SV, He M, Jin Y, Wyss R, Shin H, Ma Y, et al. A review of the performance of
385 different methods for propensity score matched subgroup analyses and a summary of
386 their application in peer-reviewed research studies. *Pharmacoepidemiol Drug Saf*.
387 2017;26:1507–1512.
- 388 22. Izawa J, Komukai S, Gibo K, Okubo M, Kiyohara K, Nishiyama C, et al. Pre-hospital
389 advanced airway management for adults with out-of-hospital cardiac arrest: nationwide
390 cohort study. *bmj*. 2019;364:l430.
- 391 23. Lu B. Propensity score matching with time-dependent covariates. *Biometrics*.
392 2005;61:721–728.
- 393 24. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on
394 weighted residuals. *Biometrika*. 1994;81:515–526.
- 395 25. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CG. Time-
396 varying covariates and coefficients in Cox regression models. *Ann Transl Med*. 2018;6.
- 397 26. Muller CJ, MacLehose RF. Estimating predicted probabilities from logistic regression:
398 different methods correspond to different target populations. *Int J Epidemiol*.
399 2014;43:962–970.

- 400 27. Therneau TM. A package for survival analysis in S, v. 2.38. 2015; Disponible sur:
401 <https://CRAN.R-project.org/package=survival>
- 402 28. Ho DE, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for
403 parametric causal inference. *J Stat Softw* [Internet]. 2011; Disponible sur:
404 <http://gking.harvard.edu/matchit>
- 405 29. Yoshida K, Bohn J, Yoshida MK. Package ‘tableone’. *R Found Stat Comput Vienna*
406 *Austria* 30 Novemb 2016. 2019;
- 407 30. Loomba RS, Nijhawan K, Aggarwal S, Arora RR. Increased return of spontaneous
408 circulation at the expense of neurologic outcomes: is prehospital epinephrine for out-of-
409 hospital cardiac arrest really worth it? *J Crit Care*. 2015;30:1376–1381.
- 410 31. Holmberg MJ, Issa MS, Moskowitz A, Morley P, Welsford M, Neumar R, et al.
411 Vasopressors during adult cardiac arrest: A systematic review and meta-analysis.
412 *Resuscitation*. 2019;
- 413 32. Finn J, Jacobs I, Williams TA, Gates S, Perkins GD. Adrenaline and vasopressin for
414 cardiac arrest. *Cochrane Database Syst Rev*. 2019;1:CD003179.
- 415 33. Perkins GD, Kenna C, Ji C, Deakin CD, Nolan JP, Quinn T, et al. The effects of
416 adrenaline in out of hospital cardiac arrest with shockable and non-shockable rhythms:
417 Findings from the PACA and PARAMEDIC-2 randomised controlled trials.
418 *Resuscitation*. 19 2019;140:55-63.
- 419 34. Long B, Koyfman A. Emergency medicine myths: epinephrine in cardiac arrest. *J Emerg*
420 *Med*. 2017;52:809–814.

- 421 35. Attaran RR, Ewy GA. Epinephrine in resuscitation: curse or cure? *Future Cardiol.*
422 2010;6:473–482.
- 423 36. Lehnart SE, Wehrens XH, Marks AR. Calstabin deficiency, ryanodine receptors, and
424 sudden cardiac death. *Biochem Biophys Res Commun.* 2004;322:1267–1279.
- 425 37. Tang W, Weil MH, Gazmuri RJ, Sun S, Duggal C, Bisera J. Pulmonary
426 ventilation/perfusion defects induced by epinephrine during cardiopulmonary
427 resuscitation. *Circulation.* 1991;84:2101–2107.
- 428 38. Tang W, Weil MH, Sun S, Noc M, Yang L, Gazmuri RJ. Epinephrine increases the
429 severity of postresuscitation myocardial dysfunction. *Circulation.* 1995;92:3089–3093.
- 430 39. Ristagno G, Sun S, Tang W, Castillo C, Weil MH. Effects of epinephrine and
431 vasopressin on cerebral microcirculatory flows during and after cardiopulmonary
432 resuscitation. *Crit Care Med.* 2007;35:2145–2149.
- 433 40. Liberman M, C Branas C, Mulder DS, Lavoie A, Sampalis JS. Advanced Versus Basic
434 Life Support in the Pre-Hospital Setting—The Controversy between the ‘Scoop and
435 Run’ and the ‘Stay and Play’ Approach to the Care of the Injured Patient. *Int J Disaster*
436 *Med.* 2004;2:9–17.
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439 ARTICLE SUMMARY

440 1. Why is this topic important?

441 Epinephrine is used for Out-of-Hospital cardiac arrest care since 1960's, nevertheless, its
442 effectiveness is still questioned. Identify for which patients and how epinephrine is effective
443 seems to be a priority.

444 2. What does this study attempt to show?

445 The objective of this study was to determine if epinephrine was effective for all patients
446 (according to patients' cardiac rhythm) by taking into account the time of the injection.

447 3. What are the key findings?

448 We observed that epinephrine does not seem to improve patients' survival 30 days after their
449 cardiac arrest. Further studies need to be carried out in order to find the optimal use of
450 epinephrine.

451 4. How is patient care impacted?

452 Patients should be cared separately according to their cardiac rhythm. The optimal use of
453 epinephrine should improve survival rates and limit neurological outcome.

454

455

456 **Legends to figures**

457 **Fig. 1** Flow chart

458 *OHCA: out-of-hospital cardiac arrest, DNAR: do not attempt resuscitation, MMT: mobile*
459 *medical team, ROSC: return of spontaneous circulation, MERS: mobile emergency and*
460 *resuscitation service*

461

462 **Fig. 2** Comparison of endpoints in shockable group

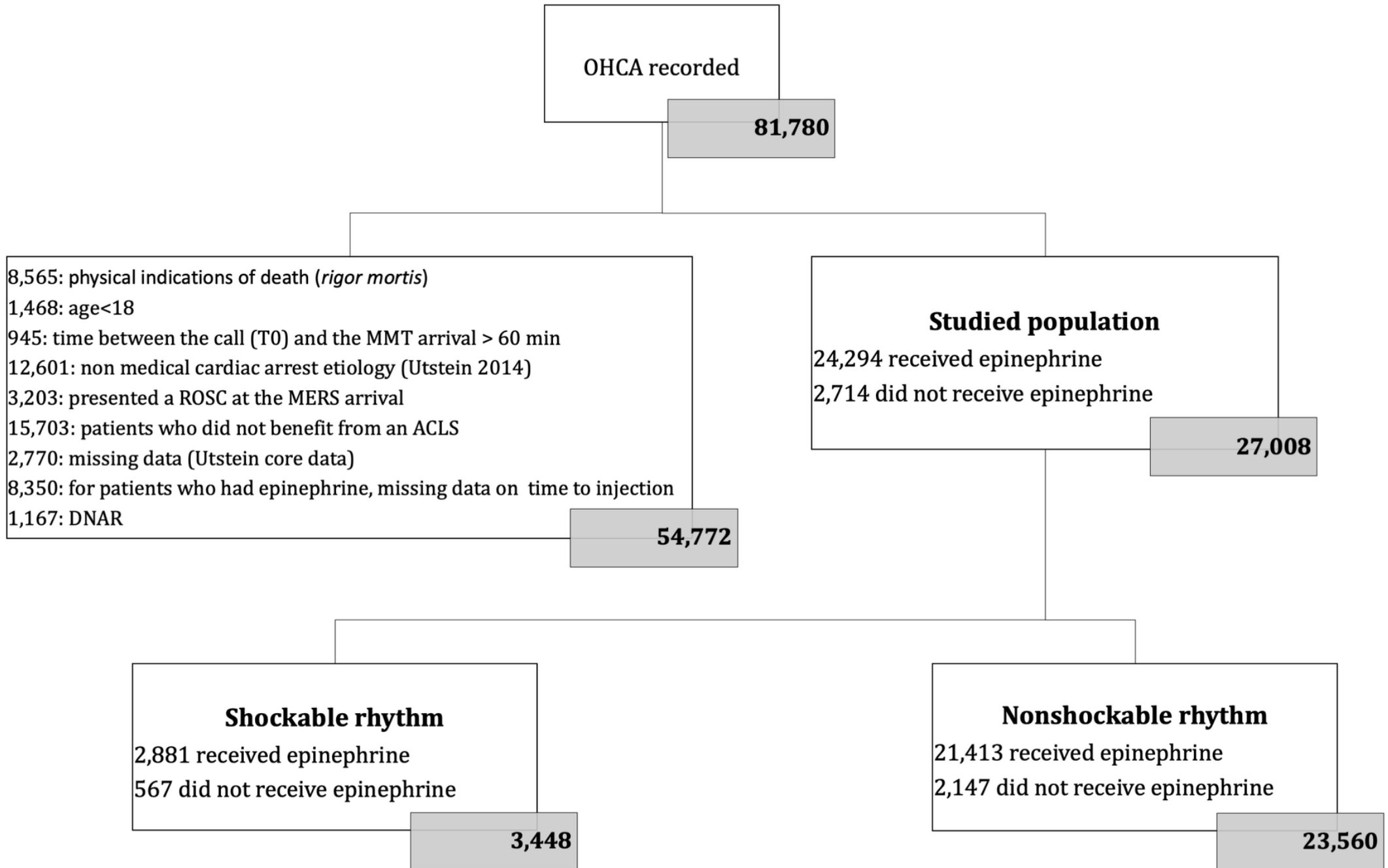
463 *ROSC: return of spontaneous circulation; D30: 30 days*

464

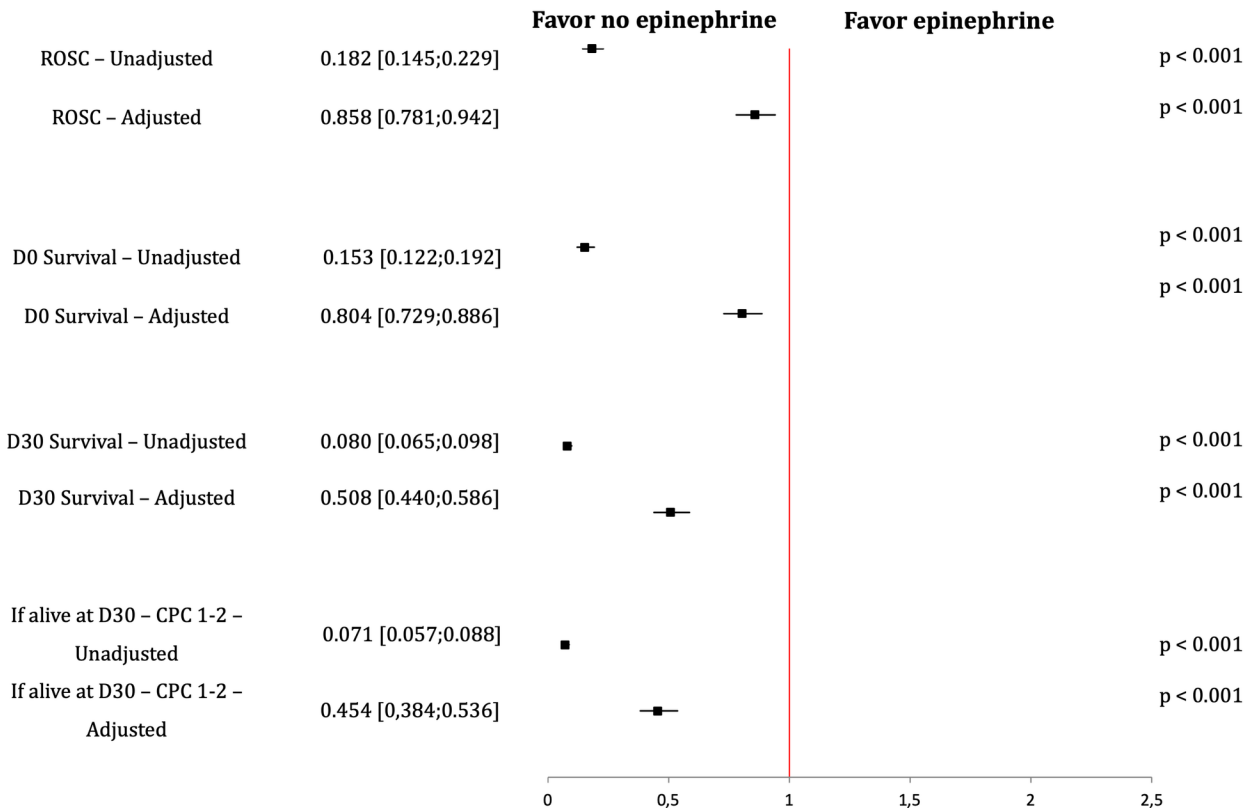
465 **Fig. 3** Comparison of endpoints in nonshockable group

466 *ROSC: return of spontaneous circulation; D30: 30 days*

467



Shockable rhythm – OR (95% CI)



Nonshockable rhythm – OR (95% CI)

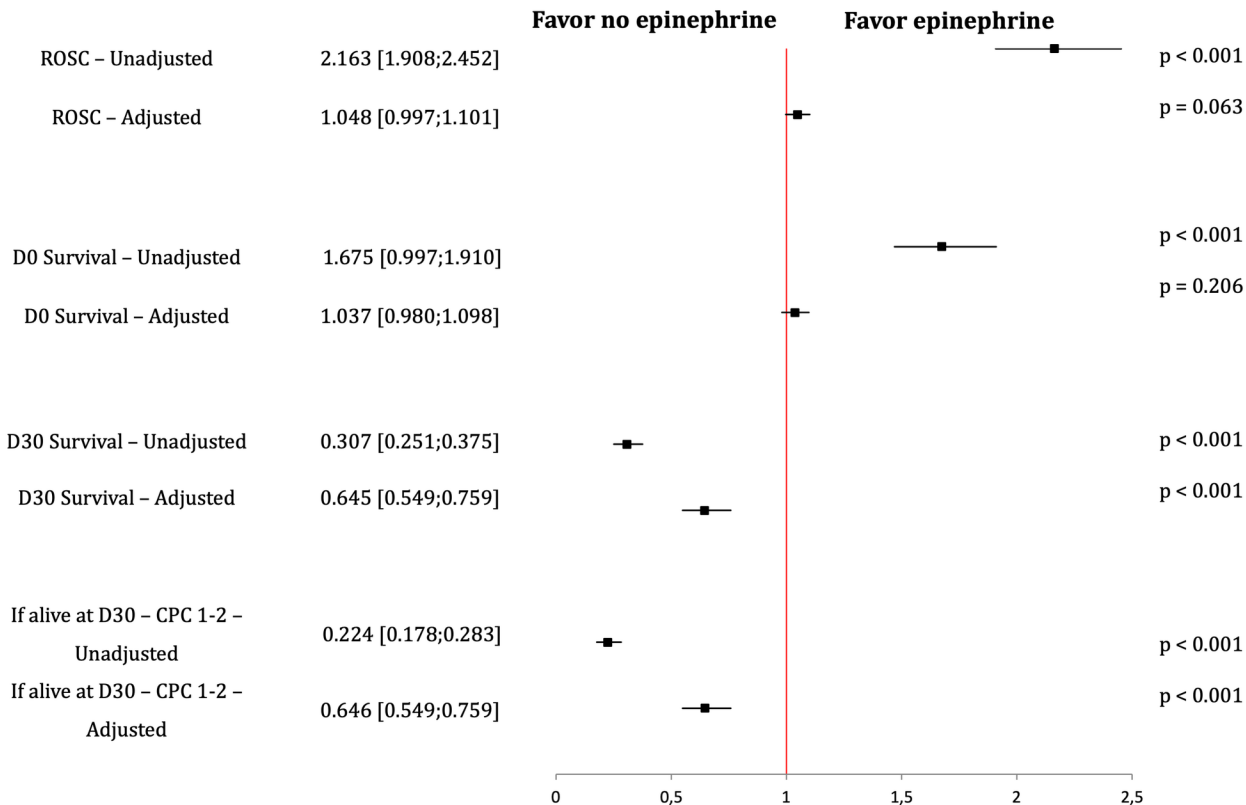


Table 1. Population characteristics and global analysis^a

Characteristics	Description Studied Population 27,008	Comparison		
		Epinephrine 24,294	No Epinephrine 2,714	<i>P</i>
Cases per year				
- 2011	349 (1.3)	326 (1.3)	23 (0.9)	<0.001
- 2012	2699 (10.0)	2421 (10.0)	278 (10.2)	
- 2013	5120 (19.0)	4585 (18.9)	535 (19.7)	
- 2014	5216 (19.3)	4655 (19.2)	561 (20.7)	
- 2015	5339 (19.8)	4896 (20.2)	443 (16.3)	
- 2016	4374 (16.2)	3965 (16.3)	409 (15.1)	
- 2017	3911 (14.5)	3446 (14.2)	465 (17.1)	
Age (years)	68 (57;78)	67 (56;78)	74 (60;84)	< 0.001
Gender (male)	18,613 (68.9)	16,931 (69.7)	1,682 (62.0)	< 0.001
Bystander presence	19,735 (73.1)	17,743 (73.0)	1,992 (73.4)	0.703
Type of bystander (% family)	16,863 (62.4)	15,287 (62.9)	1,576 (58.1)	< 0.001
OHCA etiology (% cardiac)	19,688 (72.9)	17,760 (73.1)	1,928 (71.0)	0.023
BLS				
- Immediate CPR	10,534 (39.0)	9,421 (38.8)	1,113 (41.0)	0.025
- Chest compressions	25,473 (94.3)	22,940 (94.4)	2,533 (93.3)	0.022
- Ventilation	23,112 (85.6)	20,839 (85.8)	2,273 (83.8)	0.005
- AED shock	5,190 (19.2)	4,682 (19.3)	508 (18.7)	0.503
Times				
- call (T0) to MMT arrival	19 (14;26)	19 (14;27)	19 (13;26)	0.032
- call (T0) to ROSC or death	47 (35;60)	48 (37;60)	35 (25;48)	< 0.001
ACLS				
Initial cardiac rhythm:				<0.001
- Asystole/PEA (shockable)	3,448 (12.8)	2,881 (11.9)	567 (20.9)	
- VF/pulseless VT (non-shockable)	23,560 (87.2)	21,413 (88.1)	2,147 (79.1)	
Defibrillator shock by MMT	6,749 (25.0)	6,206 (25.55)	543 (20.01)	< 0.001
Intubation	25,058 (92.8)	22,923 (94.36)	2,135 (78.67)	< 0.001
Insertion of an injection route	26,687 (98.8)	24,294 (100.00)	2,393 (88.17)	< 0.001
Survival				
- ROSC	7,686 (28.5)	6,917 (28.5)	769 (28.3)	0.898
- Vital status at hospital admission (alive)	6,138 (22.7)	5,399 (22.2)	739 (27.2)	< 0.001
- Vital status at D30 (alive)	1,382 (5.1)	858 (3.5)	524 (19.3)	< 0.001
- If alive, CPC 1-2 at 30 days ^b	1,007 (72.9)	560 (65.3)	447 (85.3)	< 0.001

OHCA: out-of-hospital cardiac arrest, BLS: basic life support, CPR: cardiopulmonary resuscitation, AED: automated external defibrillator, ACLS: advanced cardiac life support, MMT: mobile medical team, ROSC: return of spontaneous circulation, PEA: pulseless electrical activity, VF/pulseless VT: ventricular fibrillation/pulseless ventricular tachycardia, D30: day 30, CPC: cerebral performance categories.

^aData are expressed as frequencies. (%) for qualitative variables or median (Q1;Q3) for quantitative variables

^b140 missing values

Table 2 Comparison between epinephrine and no epinephrine according to cardiac rhythms^a

	Shockable rhythm			Non-shockable rhythm		
	Epinephrine N = 2,881	No epinephrine N = 567	P	Epinephrine N = 21,413	No epinephrine N = 2,147	P
Cases per year						
2011	41 (1.4)	3 (0.5)		285 (1.3)	20 (0.9)	
2012	323 (11.2)	59 (10.4)		2,098 (9.8)	219 (10.2)	
2013	600 (20.8)	92 (16.2)		3,985 (18.6)	443 (20.6)	
2014	771 (19.8)	112 (19.8)	0.659	4,084 (19.1)	449 (20.9)	<0.001
2015	740 (18.7)	102 (18.0)		4,356 (20.3)	341 (15.9)	
2016	426 (14.8)	99 (17.5)		3,539 (16.5)	310 (14.4)	
2017	380 (13.2)	100 (17.6)		3,066 (14.3)	365 (17.0)	
Age (years)	63 (54;74)	61 (50;74)	0.041	68 (57;78)	77 (65;85)	<0.001
Gender (male)	2,280 (79.1)	414 (73.0)	0.002	14,651 (68.4)	1,268 (59.1)	< 0.001
Bystander presence	2,510 (87.1)	529 (93.3)	<0.001	15,233 (71.1)	1,463 (68.1)	0.004
Type of bystander (% family)	1,675 (58.1)	208 (36.7)	< 0.001	13,612 (63.6)	1,368 (63.7)	0.911
OHCA etiology (% cardiac)	2,460 (85.4)	499 (88.0)	0.117	15,300 (71.5)	1,429 (66.6)	< 0.001
BLS						
- Immediate CPR	1,507 (52.3)	396 (69.8)	<0.001	7,914 (37.0)	717 (33.4)	0.001
- Chest Compression	2,749 (95.4)	534 (94.2)	0.248	20,191 (94.3)	1,999 (93.1)	0.028
- Ventilation	2,411 (83.7)	456 (80.4)	0.066	18,428 (86.1)	1,817 (84.6)	0.074
- AED shock	1,793 (62.2)	314 (55.4)	0.003	2,889 (13.5)	194 (9.0)	<0.001
Times						
- call (T0) to MMT arrival	17 (12;23)	16 (11;23)	0.083	20 (14;27)	19 (13;27)	0.763
- call (T0) to ROSC or death	49 (34;62)	25 (17;43)	<0.001	48 (37;60)	37 (28;49)	<0.001
ACLS						
- Defibrillator shock by MMT	2,536 (88.0)	442 (77.95)	<0.001	3,670 (17.1)	101 (4.7)	<0.001
- Intubation	2,778 (96.4)	423 (74.60)	<0.001	20,145 (94.1)	1,712 (79.7)	<0.001
- Insertion of an injection route	2,881 (100.0)	549 (96.83)	<0.001	21,413 (100.0)	1,844 (85.9)	<0.001
Survival						
- ROSC	1,334 (46.3)	468 (82.5)	<0.001	5,583 (26.1)	301 (14.0)	<0.001
- Vital status at hospital admission (alive)	1,185 (41.1)	465 (82.0)	<0.001	4,214 (19.7)	274 (12.8)	<0.001
- Vital status at D30 (alive)	436 (15.1)	392 (69.1)	<0.001	422 (2.0)	132 (6.2)	<0.001
- If alive, CPC at 30 days	312 (71.56)	341 (86.99)	<0.001	248 (58.8)	106 (80.3)	<0.001

OHCA: out-of-hospital cardiac arrest, BLS: basic life support, CPR: cardiopulmonary resuscitation, CC: chest compression, AED: automated external defibrillator, ACLS: advanced cardiac life support, MMT: mobile medicalteam, ROSC: return of spontaneous circulation, D30: day 30, CPC: cerebral performance categories.

^aData are expressed as frequencies (%) for qualitative variables or median (Q1;Q3) for quantitative variables