

## Additional file 1

**Table S1**

Characteristics of study population according to epinephrine dose administered during CPR

Variables n (%) or mean $\pm$ SD	0 mg (n = 243)	1 mg (n = 445)	2 – 5 mg (n = 1586)	> 5 mg (n = 518)	<i>p</i> -value Chi2 or ANOVA
Male	138 (56.8%)	272 (61.1%)	958 (60.4%)	334 (64.5%)	0.20
Age (years)	67.3 $\pm$ 17.3	64.3 $\pm$ 16.1	63.8 $\pm$ 14.8	59.8 $\pm$ 14.6	< 0.001
Home location	181 (74.5%)	316 (71.2%)	1159 (73.1%)	353 (68.3%)	0.15
Witnessed	210 (86.4%)	366 (82.4%)	1297 (82.0%)	440 (84.9%)	0.20
Bystander CPR	141 (58.8%)	233 (52.6%)	902 (57.6%)	335 (64.9%)	0.001
No-flow duration (min)	4.1 $\pm$ 5.0	7.1 $\pm$ 9.3	6.9 $\pm$ 8.4	5.2 $\pm$ 7.1	< 0.001
First recorded rhythm					< 0.001
Asystole	193 (79.4%)	352 (79.1%)	1369 (86.3%)	447 (86.3%)	
PEA	50 (20.6%)	93 (20.9%)	217 (13.7%)	71 (13.7%)	
Low-flow duration (min)	15.5 $\pm$ 15.9	21.6 $\pm$ 13.5	27.6 $\pm$ 16.5	49.3 $\pm$ 30.9	< 0.001
Heart disease	76 (31.3%)	130 (29.2%)	464 (29.3%)	137 (26.5%)	0.51
Ischemic cardiopathy	39 (16.1%)	69 (15.5%)	243 (15.3%)	65 (12.6%)	0.41
Cancer	37 (15.2%)	55 (12.4%)	192 (12.1%)	34 (6.6%)	0.001
Renal disease	19 (7.8%)	38 (8.5%)	151 (9.5%)	33 (6.4%)	0.16
High blood pressure	103 (42.4%)	174 (39.1%)	689 (43.4%)	213 (41.1%)	0.39
Diabetes mellitus	32 (13.2%)	81 (18.2%)	392 (24.7%)	143 (27.6%)	< 0.001
Dyslipidemia	35 (14.4%)	72 (16.2%)	272 (17.2%)	94 (18.2%)	0.60
ECMO	11 (4.5%)	10 (2.3%)	97 (6.1%)	112 (21.6%)	< 0.001
Shock	4 (36.4%)	4 (40.0%)	21 (21.7%)	7 (6.2%)	
ARDS	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	
Refractory CA	7 (63.6%)	6 (60.0%)	75 (77.3%)	105 (93.8%)	
Coronary angioplasty	20 (8.2%)	40 (9.0%)	142 (9.0%)	54 (10.4%)	0.72
TTM	77 (32.6%)	202 (46.1%)	645 (41.5%)	171 (33.7%)	< 0.001
Post-resuscitation shock	118 (51.8%)	282 (66.7%)	1072 (70.9%)	370 (79.1%)	< 0.001
Presumed cause of CA					< 0.001
Cardiac	108 (44.4%)	209 (47.0%)	773 (48.7%)	321 (62.0%)	
Non-cardiac	135 (55.6%)	236 (53.0%)	813 (51.3%)	197 (38.0%)	
Outcomes					< 0.001
Alive	90 (37.1%)	57 (12.8%)	83 (5.2%)	12 (2.3%)	
Cardiocirculatory death	43 (17.7%)	100 (22.5%)	575 (36.3%)	286 (55.2%)	
Neurological death	72 (29.6%)	236 (53.0%)	750 (47.3%)	175 (33.8%)	
Other death	38 (15.6%)	52 (11.7%)	178 (11.2%)	45 (8.7%)	

CPR, cardiopulmonary resuscitation; PEA, pulseless electrical activity; CA, cardiac arrest; ECMO, extracorporeal membrane oxygenation; TTM, targeted temperature management

**Table S2.** Multinomial regression after multiple data imputation (n = 2,792), reference population: alive at hospital discharge (full model)

Reference outcome = alive	Cardiovascular death		Neurological death		Other death	
	aOR CI95%	p-value	aOR CI95%	p-value	aOR CI95%	p-value
Sex male	0.82 (0.58-1.16)	0.26	0.73 (0.53-1.02)	0.064	0.75 (0.51-1.11)	0.15
Age (per year)	1.04 (1.03-1.05)	<0.001	1.01 (1.00-1.03)	0.015	1.06 (1.04-1.07)	<0.001
Home location	1.57 (1.11-2.24)	0.011	1.25 (0.90-1.73)	0.19	1.96 (1.28-3.00)	0.002
Witnessed	1.69 (0.95-3.03)	0.076	1.51 (0.87-2.62)	0.15	2.24 (1.14-4.38)	0.019
Bystander CPR	0.97 (0.60-1.56)	0.90	0.77 (0.48-1.21)	0.25	0.99 (0.58-1.68)	0.97
No flow duration (per min)	1.08 (1.04-1.12)	<0.001	1.08 (1.04-1.11)	<0.001	1.08 (1.04-1.12)	<0.001
Asystole	Reference		Reference		Reference	
PEA	1.09 (0.72-1.64)	0.68	0.81 (0.55-1.21)	0.30	0.70 (0.43-1.16)	0.17
Epinephrine during CPR	Reference		Reference		Reference	
0 mg	Reference		Reference		Reference	
1 mg	3.45 (2.01-5.92)	<0.001	4.40 (2.79-6.94)	<0.001	2.69 (1.49-4.85)	0.001
2-5 mg	12.28 (7.52-20.06)	<0.001	8.88 (5.80-13.59)	<0.001	5.95 (3.49-10.13)	<0.001
>5 mg	23.71 (11.02-50.97)	<0.001	10.26 (4.94-21.31)	<0.001	7.45 (3.20-17.33)	<0.001
Low flow duration (per min)	1.04 (1.03-1.06)	<0.001	1.04 (1.02-1.05)	<0.001	1.04 (1.02-1.05)	<0.001
Heart disease	0.86 (0.58-1.28)	0.46	1.04 (0.71-1.51)	0.84	1.08 (0.70-1.67)	0.73
Cancer	0.99 (0.59-1.67)	0.98	1.10 (0.67-1.81)	0.69	1.74 (1.01-3.01)	0.047
Renal disease	1.27 (0.68-2.36)	0.45	1.23 (0.69-2.21)	0.49	1.44 (0.74-2.80)	0.29
High blood pressure	0.55 (0.38-0.79)	0.001	0.76 (0.54-1.08)	0.13	0.58 (0.38-0.87)	0.008
ECMO	0.57 (0.27-1.18)	0.13	0.35 (0.17-0.73)	0.005	0.88 (0.37-2.12)	0.78
Coronary angioplasty	0.51 (0.30-0.86)	0.012	0.51 (0.31-0.85)	0.010	0.42 (0.22-0.79)	0.008
TTM	0.25 (0.18-0.35)	<0.001	0.83 (0.61-1.14)	0.25	0.30 (0.20-0.45)	<0.001
Post resuscitation shock	2.13 (1.48-3.05)	<0.001	0.78 (0.56-1.08)	0.13	0.86 (0.58-1.28)	0.46
Presumed cardiac cause	2.44 (1.69-3.52)	<0.001	1.06 (0.74-1.50)	0.75	1.80 (1.20-2.71)	0.005

CPR, cardiopulmonary resuscitation; PEA, pulseless electrical activity; ECMO, extracorporeal membrane oxygenation; TTM, targeted temperature management

**Table S3.** Multinomial regression without multiple data imputation (n = 2,037), reference population: alive at hospital discharge

Reference outcome = alive	Cardiovascular death		Neurological death		Other death	
	aOR CI95%	p-value	aOR CI95%	p-value	aOR CI95%	p-value
Epinephrine during CPR						
0 mg	Reference		Reference		Reference	
1 mg	3.30 (1.74-6.26)	<0.001	3.75 (2.20-6.39)	<0.001	2.64 (1.33-5.23)	0.005
2-5 mg	11.99 (6.62-21.68)	<0.001	8.41 (5.08-13.91)	<0.001	5.87 (3.12-11.03)	<0.001
>5 mg	19.06 (7.92-45.87)	<0.001	9.16 (4.02-20.86)	<0.001	5.61 (2.11-14.89)	0.001

Adjustment variables: gender, age, location, witnessed OHCA, bystander CPR, no-flow duration, initial electrical rhythm, low-flow duration, medical history: heart disease, cancer, renal disease, high blood pressure; ECMO use, coronary angioplasty intervention, TTM, post resuscitation shock, presumed cardiac cause.

**Table S4.** Sensitivity analysis (+ years) after multiple data imputation (n = 2,792), reference population: alive at hospital discharge

Reference outcome = alive	Cardiovascular death		Neurological death		Other death	
	aOR CI95%	p-value	aOR CI95%	p-value	aOR CI95%	p-value
Epinephrine during CPR						
0 mg	Reference		Reference		Reference	
1 mg	3.49 (2.03-5.99)	<0.001	4.50 (2.85-7.10)	<0.001	2.73 (1.51-4.94)	0.001
2-5 mg	12.39 (7.58-20.26)	<0.001	9.02 (5.89-13.82)	<0.001	6.02 (3.53-10.25)	<0.001
>5 mg	23.76 (11.05-51.11)	<0.001	10.19 (4.91-21.17)	<0.001	7.41 (3.19-17.25)	<0.001
Years (per year)	0.99 (0.94-1.04)	0.65	0.97 (0.92-1.02)	0.18	0.97 (0.91-1.04)	0.41

Adjustment variables: gender, age, location, witnessed OHCA, bystander CPR, no-flow duration, initial electrical rhythm, low-flow duration, medical history: heart disease, cancer, renal disease, high blood pressure; ECMO use, coronary angioplasty intervention, TTM, post resuscitation shock, presumed cardiac cause, years.

**Table S5.** Sensitivity analysis (+ years) without multiple data imputation (n = 2,037), reference population: alive at hospital discharge

Reference outcome = alive	Cardiovascular death		Neurological death		Other death	
	aOR CI95%	p-value	aOR CI95%	p-value	aOR CI95%	p-value
Epinephrine during CPR						
0 mg	Reference		Reference		Reference	
1 mg	3.34 (1.76-6.35)	<0.001	3.81 (2.24-6.50)	<0.001	2.68 (1.35-5.31)	0.005
2-5 mg	12.08 (6.67-21.86)	<0.001	8.48 (5.12-14.04)	<0.001	5.90 (3.14-11.10)	<0.001
>5 mg	19.11 (7.93-46.06)	<0.001	9.06 (3.98-20.65)	<0.001	5.55 (2.09-14.76)	0.001
Years (per year)	0.99 (0.93-1.06)	0.75	0.97 (0.91-1.03)	0.34	0.98 (0.91-1.05)	0.51

Adjustment variables: gender, age, location, witnessed OHCA, bystander CPR, no-flow duration, initial electrical rhythm, low-flow duration, medical history: heart disease, cancer, renal disease, high blood pressure; ECMO use, coronary angioplasty intervention, TTM, post resuscitation shock, presumed cardiac cause, years.

**Table S6.** Sensitivity analysis, epinephrine as continuous variable, reference population: alive at hospital discharge

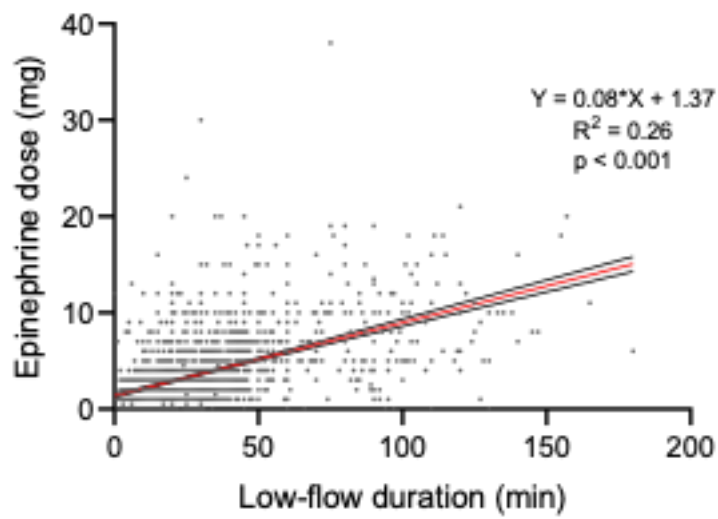
Reference outcome = alive	Cardiocirculatory death		Neurological death		Other death	
	aOR CI95%	p-value	aOR CI95%	p-value	aOR CI95%	p-value
Epinephrine during CPR, per mg	1.46 (1.33-1.61)	<0.001	1.33 (1.21-1.46)	<0.001	1.41 (1.27-1.57)	0.001

Adjustment variables: gender, age, location, witnessed OHCA, bystander CPR, no-flow duration, initial electrical rhythm, low-flow duration, medical history: heart disease, cancer, renal disease, high blood pressure; ECMO use, coronary angioplasty intervention, TTM, post resuscitation shock, presumed cardiac cause, years.

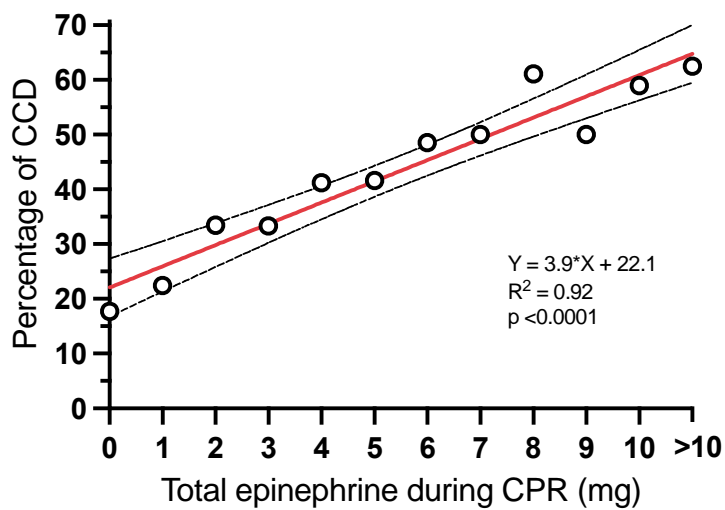
**Table S7.** Sensitivity analysis according to low-flow duration (tertiles), reference population: alive at hospital discharge

	Cardiovascular death		Neurological death		Other death	
	aOR 95%CI	p-value	aOR 95%CI	p-value	aOR 95%CI	p-value
<b>Low-flow duration ≤ 19 min (n = 868)</b>						
Epinephrine during CPR	Reference		Reference		Reference	
0 mg	2.53 (1.27-5.06)	0.009	4.08 (2.34-7.12)	<0.001	2.14 (0.99-4.63)	0.053
1 mg	12.96 (6.96-24.15)	<0.001	8.26 (4.82-14.15)	<0.001	5.13 (2.56-10.26)	<0.001
2-5 mg	12.06 (3.76-38.69)	<0.001	5.42 (1.73-16.93)	0.004	5.64 (1.41-22.64)	0.015
> 5 mg						
<b>Low-flow duration 20 min to 30 min (n = 1,023)</b>						
Epinephrine during CPR	Reference		Reference		Reference	
0 mg	4.13 (1.46-11.71)	0.008	4.48 (1.81-11.08)	0.001	4.23 (1.36-13.11)	0.013
1 mg	12.06 (4.67-31.13)	<0.001	8.58 (3.78-19.47)	<0.001	6.53 (2.34-18.23)	<0.001
2-5 mg	44.58 (8.33-238.62)	<0.001	22.36 (4.48-111.50)	<0.001	14.89 (2.44-90.85)	0.003
> 5 mg						
<b>Low-flow duration &gt; 30 min (n = 901)</b>						
Epinephrine during CPR	Reference		Reference		Reference	
0 mg	4.63 (0.40-53.30)	0.219	4.99 (0.44-56.65)	0.195	3.83 (0.18-81.17)	0.388
1 mg	12.86 (1.52-108.85)	0.019	7.76 (0.91-66.41)	0.062	9.74 (0.63-149.99)	0.103
2-5 mg	52.76 (5.81-479.46)	<0.001	17.67 (1.92-162.62)	0.011	21.87 (1.33-358.93)	0.031
> 5 mg						

Adjustment variables: gender, age, location, witnessed OHCA, bystander CPR, no-flow duration, initial electrical rhythm, low-flow duration, medical history: heart disease, cancer, renal disease, high blood pressure; ECMO use, coronary angioplasty intervention, TTM, post resuscitation shock, presumed cardiac cause.

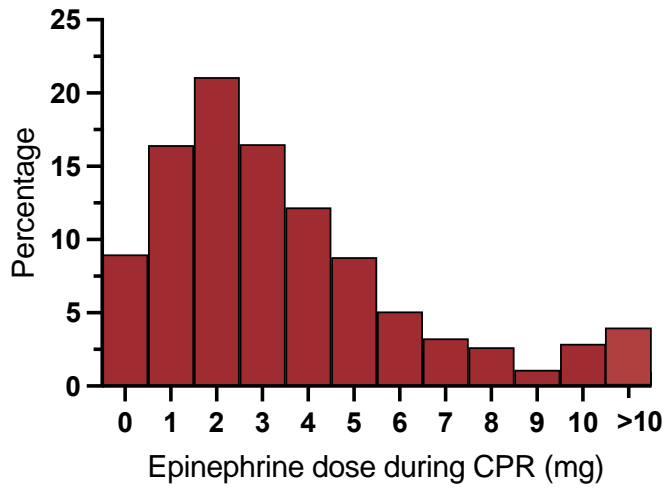


**Figure S1.** Linear regression of the low-flow duration (minutes) in relation to epinephrine dose used during CPR (mg).

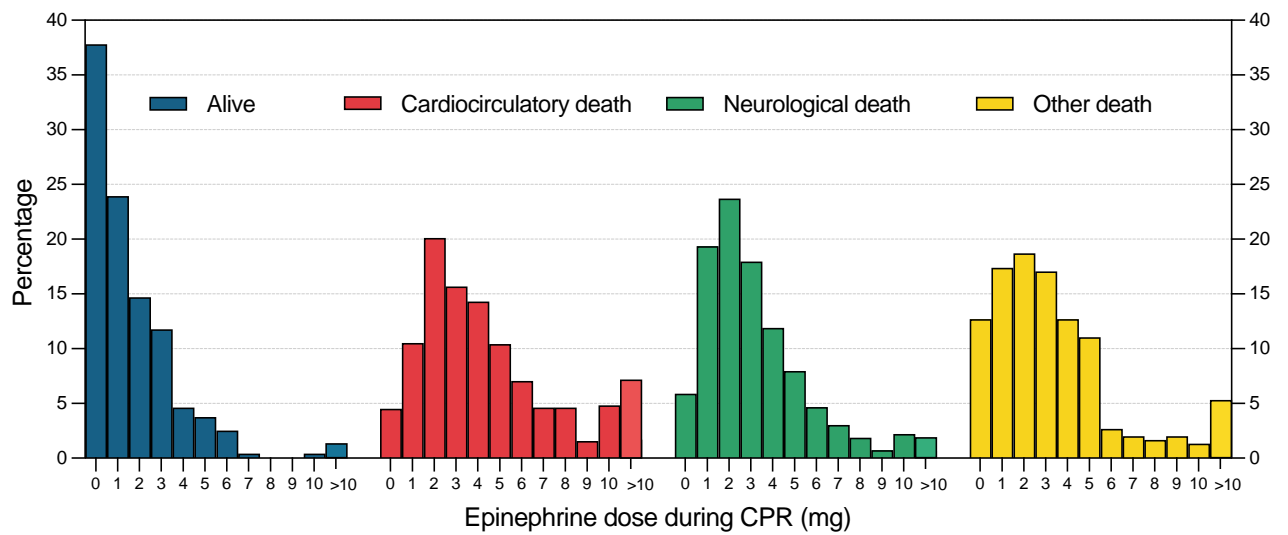


**Figure S2.** Linear regression of the proportion of deaths from cardiovascular causes (CCD, cardiovascular death) in relation to epinephrine dose used during CPR.

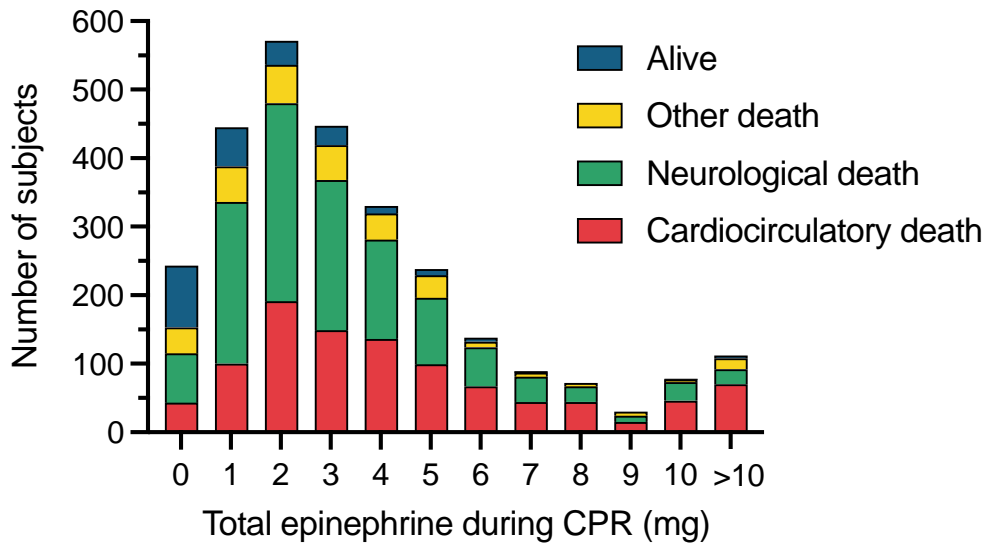




**Figure S3.** Total epinephrine dose used during CPR in the complete population of the study.



**Figure S4.** Percentage proportion of epinephrine use during CPR by outcome.



**Figure S5.** Number of subjects by epinephrine dose used during CPR and outcome.