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# Epinephrine and short-term survival in cardiogenic shock: an individual data meta-analysis of 2583 patients

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## Abstract

**Objective:** Catecholamines have been the mainstay of pharmacological treatment of cardiogenic shock (CS). Recently, use of epinephrine has been associated with detrimental outcomes. In the present study we aimed to evaluate the association between epinephrine use and short-term mortality in all-cause CS patients.

**Design:** We performed a meta-analysis of individual data with prespecified inclusion criteria: (1) patients in non-surgical CS treated with inotropes and/or vasopressors and (2) at least 15% of patients treated with epinephrine administered alone or in association with other inotropes/vasopressors. The primary outcome was short-term mortality.

**Measurements and results:** Fourteen published cohorts and two unpublished data sets were included. We studied 2583 patients. Across all cohorts of patients, the incidence of epinephrine use was 37% (17–76%) and short-term mortality rate was 49% (21–69%). A positive correlation was found between percentages of epinephrine use and short-term mortality in the CS cohort. The risk of death was higher in epinephrine-treated CS patients (OR [CI] = 3.3 [2.8–3.9]) compared to patients treated with other drug regimens. Adjusted mortality risk remained striking in epinephrine-treated patients ( $n = 1227$ ) (adjusted OR = 4.7 [3.4–6.4]). After propensity score matching, two sets of 338 matched patients were identified and epinephrine use remained associated with a strong detrimental impact on short-term mortality (OR = 4.2 [3.0–6.0]).

**Conclusions:** In this very large cohort, epinephrine use for hemodynamic management of CS patients is associated with a threefold increase of risk of death.

**Keywords:** Meta-analysis, Cardiogenic shock, Epinephrine, Prognosis

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Alexandre Mebazaa and Tahar Chouihed are co-last authors.

## Introduction

Cardiogenic shock (CS) is a state characterized by acute cardiac failure leading to low cardiac output, hypotension, and end-organ hypoperfusion [1]. CS is mostly related to acute coronary syndrome (ACS) and its mortality remains high despite improvements in ACS revascularization therapies [2]. The pharmacologic treatment

of CS may require the combination of vasopressor therapy to restore and maintain systemic blood pressure and/or inotropic support to improve cardiac output. Hence, agents such as epinephrine and norepinephrine have been recommended owing to their cardiac and/or vascular benefits via alpha- and beta-adrenergic receptor stimulation [3, 4].

However, the use of catecholamines in acute heart failure may be associated with higher short- and long-term mortality [5, 6]. Among catecholamines, retrospective analyses have linked the need for epinephrine to worse outcome in patients with myocardial infarction or treated with mechanical circulatory support [7, 8]. More recently, data from a prospective patient cohort [9] and two small randomized trials [10, 11] suggest that in cardiogenic shock, epinephrine might be associated with detrimental short-term outcome.

Accordingly, we performed a systematic review of all studies assessing cardiogenic shock treatment and short-term mortality using individual patient data. Across multiple cohorts with varying prevalence of epinephrine use and mortality, we sought to evaluate the association between epinephrine use and short-term outcome in CS. We hypothesized that epinephrine use was associated with a higher mortality compared to other inotrope(s) and/or vasopressor(s) regimen in cardiogenic shock patients.

## Methods

### Search strategy and selection of articles

We performed a systematic search of MEDLINE, Cochrane, and Web of Science databases using the following detailed search terms: Adrenaline, Epinephrine, Catecholamines, Vasopressors, Inotropes, and Cardiogenic shock, excluding articles in a language other than English, published prior to January 1, 1995, and case reports. The prespecified keyword combination used to run the literature search was “Adrenaline”[All Fields] OR “Epinephrine”[MeSH Terms] OR “Epinephrine”[All fields] OR “Catecholamines”[MeSH Terms] OR “Catecholamines”[All Fields] OR “Vasopressors”[All Fields] OR “Inotropes”[All Fields] AND (“Shock, Cardiogenic”[MeSH Terms] OR “cardiogenic shock”[Title]) AND (“1995/01/01”[PDAT]: “2017/11/01”[PDAT]) AND English[lang]) NOT “case reports”[Publication Type]. The last search was performed on November 11, 2017 (Fig. 1). Studies were included if they met the following prespecified inclusion criteria: (1) patients in cardiogenic shock treated with inotropes and/or vasopressors excluding postoperative CS and (2) at least 15% of patients of each study should have been treated with epinephrine used alone or in association with other inotropes/vasopressors. All findings

are reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD) [12]. The quality of the included studies was assessed using the Newcastle–Ottawa scale [13].

### Data extraction

Two investigators (V.L. and T.C.) performed the initial screening of titles and abstracts. Full-text reports of potentially relevant articles were obtained and assessed by both investigators using a prespecified protocol (PROSPERO Registration Number CRD42017082370). Two investigators (E.G. and A.M.) adjudicated all disagreements. Corresponding author(s) of each eligible cohort were contacted with a request for anonymized individual data sets and prespecified covariates: age, sex, medical history, systolic and diastolic blood pressure (SBP/DBP), heart rate (HR), left ventricular ejection fraction (LVEF), Acute Physiology and Chronic Health Evaluation II (APACHE II), Sepsis-related Organ Failure Assessment (SOFA), cause of CS, mechanical support [defined as extracorporeal life support (ECLS) or Impella; and ECLS defined as extracorporeal membrane oxygenation (ECMO) or left ventricular assist device (LVAD)], lactate, estimated glomerular filtration rate (eGFR), BNP or NT-proBNP, and troponin. All studies were conducted in accordance with the Declaration of Helsinki with approval from the regional ethics committee or institutional review board.

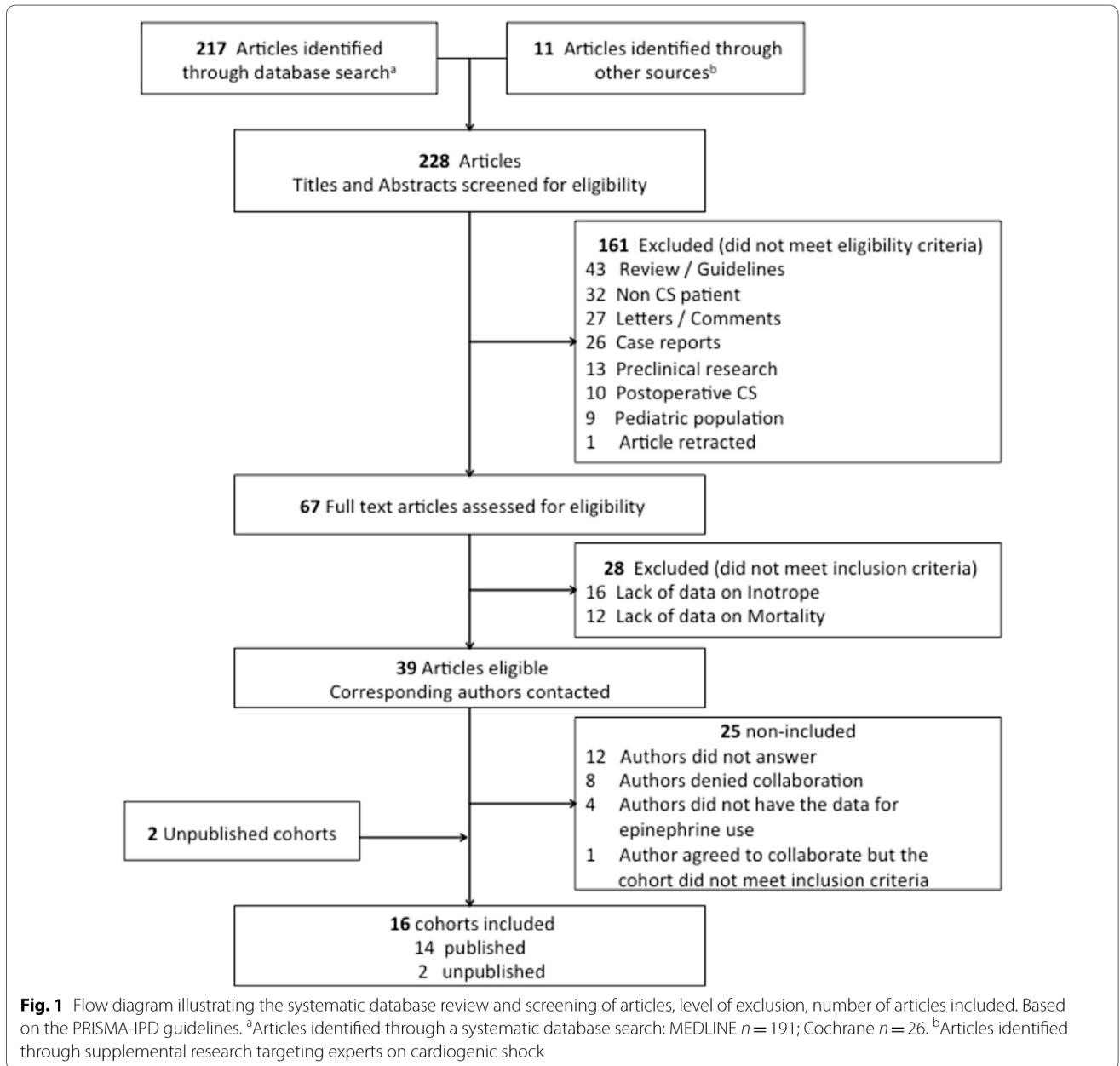
### Analysis population and primary outcome

The analysis population comprised patients with all causes of CS treated with epinephrine versus others catecholamines. Patients who presented post cardiac arrest were included in the analysis. The prespecified primary outcome was short-term mortality whether at 28 or 30 days, during ICU or hospital stay. The number of patients available for analysis is shown in Table 1.

### Statistical analysis

Data were expressed as median and quartiles for continuous variables and numbers and percentages for nominal variables. The main outcome measure was short-term mortality. The analysis of the combined data was conducted using Metafor Package and the R statistical software [14].

One purpose of the present study was to conduct meta-regression to assess the relation between mortality rate and the rate of epinephrine use. A linear mixed-effect model was used to assess association. Random-effects models were used for the meta-analysis of the effect of epinephrine on mortality. Results were summarized as odds ratio (OR) with 95% confidence interval



(95% CI). Adjustment for main prognostic variables (age, gender, ischemic heart disease, eGFR, and LVEF at admission) was also considered. Moreover, given the observational nature of the data, treatment allocation was not randomly allocated in the study population. The risk of allocation bias due to the presence of confounders was handled using propensity score (PS) matching [15]. Using PS matching, we could estimate the causal effect of the exposure on the outcome more precisely assuming a set of identifiability and causal assumptions. The PS was estimated from the observed data using a logistic regression model including a set of variables selected

among available baseline variables (age, gender, LVEF, ACS as cause of CS, eGFR, HR, and low blood pressure). Each patient treated with epinephrine was matched to one untreated control with similar PS using the nearest-neighbor approach, with no replacement and a caliper size of 0.15. In this approach, each treated subject was matched to the nearest untreated subject within a specified maximum difference in the PS between two matched subjects (so-called caliper). Covariate balance between the two groups before and after PS matching was assessed using the mean standardized differences (MSD). An absolute MSD less than 10% was considered



**Table 1 Sample size, inclusion criteria, outcome and main patients' characteristics in all the studies included**

Observational studies	Inclusion period	Cause of cardiogenic shock	Single/multi-center	Number of patients (n)	Epinephrine-treated patients n (%)	Death n (%)	Mortality endpoint	ECLS (n)
Adler, 2012 [16]	2007–2008	Out of hospital cardiac arrest	Single	40	10 (25)	11 (28)	Day 30	No
Adler, unpublished		All-cause	Single	47	9 (19)	10 (21)	Day 30	No
AHEAD, 2011 [17]	2006–2009	All-cause	Multi	674	304 (45)	469 (69)	Day 30	No
ALARM, 2011 [5]	2006–2007	All-cause	Multi	520	86 (17)	215 (41)	Day 30	No
Basir, 2018 [35]	2016	Acute coronary syndrome	Single	45	8 (18)	31 (69)	In-hospital	No
CARDSHOCK, 2016 [9]	2010–2012	All-cause	Multi	219	46 (21)	80 (37)	Day 30	Yes (8)
Champion, 2014 [18]	2012–2014	All-cause	Single	192	130 (68)	93 (48)	In-hospital	Yes (15)
Chua, 2012 [19]	2008–2011	Out of hospital cardiac arrest	Single	105	80 (76)	46 (43)	In-hospital	No
EFICA, 2006 [20]	2001–2001	All-cause	Multi	158	75 (48)	87 (55)	Day 30	No
Gaudard, 2015 [21]	2008–2013	All-cause	Single	40	11 (28)	14 (35)	Day 28	Yes (17)
Popovic, 2014 [22]	2007–2011	Acute coronary syndrome	Single	86	47 (55)	37 (43)	In-ICU	No
Valente, 2012 [23]	2004–2009	All-cause	Single	152	34 (22)	71 (46)	In-ICU	Yes (3)
Randomized controlled trials—intervention other than inotrope(s) and/or vasopressor(s) effect								
IMPRESS in severe shock, 2017 [24]	2012–2015	Acute coronary syndrome	Multi	48	14 (29)	23 (47)	Day 30	Yes (2)
Simonis, 2012 [25]	2007–2009	All-cause	Single	89	25 (28)	31 (34)	Day 30	No
SMASH, 1999 [26]	1992–1996	Acute coronary syndrome	Multi	111	41 (37)	34 (30)	Day 30	Yes (9)
Randomized controlled trial—epinephrine versus norepinephrine								
OPTIMA CC, 2018 [11]	2011–2016	Acute coronary syndrome	Multi	57	27 (47)	21 (37)	Day 30	Yes (3)
Total				2583	947 (37)	1273 (49)		

ECLS extracorporeal life support (combining extracorporeal membrane oxygenation (ECMO) and left ventricular assist devices (LVAD))

to support the assumption of balance between the groups. Subgroups analyses were also considered. In particular, the population was dichotomized according to median value of LVEF, natriuretic peptides, and troponin levels. To take into account intercenter variability regarding the measurement of those three continuous parameters, median values used for the dichotomization were assessed within each center. All statistical analyses were performed using R statistical software with the statistical package MatchIt for the matching process (R Foundation for Statistical Computing, Vienna, Austria; <http://www.jstatsoft.org/v42/i08/>).

## Results

### Systematic review

The initial search found 228 studies (Fig. 1), of which 67 were eligible for full text review and 39 studies were included. Authors consented to provide individual

participant data from 14 published cohorts and 2 unpublished data sets.

Characteristics of the 16 included cohorts are described in Table 1. Of note, 12 were observational cohorts [5,9,16–23] and 4 were randomized controlled trials, but only one compared epinephrine and norepinephrine on outcome [11, 24–26]. The quality of the nonrandomized included studies was assessed using the Newcastle–Ottawa scale (Supplemental Table 1). The main characteristics of the 25 non-included cohorts are depicted in Supplemental Table 2.

### Study population

Individual patient-level data were obtained for a total population of 2583 patients with CS (Table 2) of which 462 (18%) occurred after resuscitation of cardiac arrest. In our studied population of CS patients, the incidence of epinephrine use was 37%, ranging from 17% to 76% across all cohorts, and epinephrine was the third most

**Table 2 Total population characteristics, n = 2583**

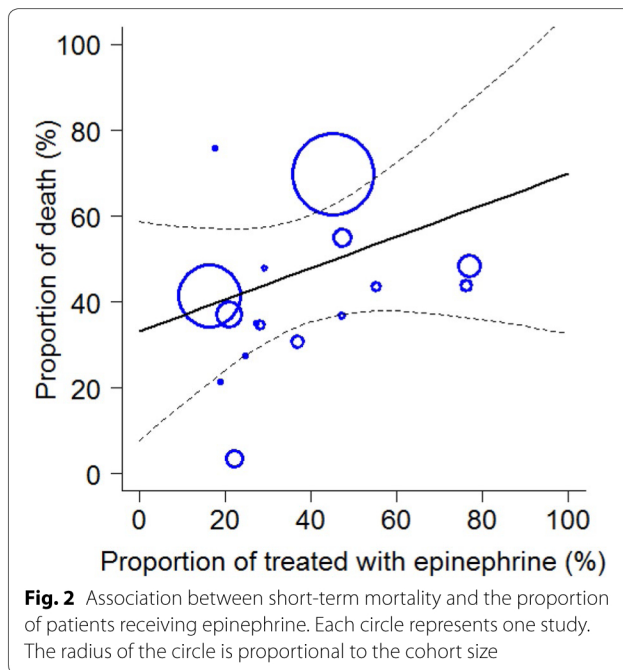
	% of missing data	All included patients (n = 2583)
<b>General characteristics</b>		
Age (years)		
< 45	2.2	172 (7%)
45–60		563 (22%)
60–70		675 (26%)
70–80		730 (29%)
> 80		416 (16%)
Male gender	2.1	1335 (52%)
Coronary artery disease	16	1101 (51%)
Chronic heart failure	32.1	582 (33%)
History of hypertension	66.2	458 (51%)
Diabetes mellitus	9.1	861 (36%)
Chronic kidney disease	14	523 (23%)
<b>Hemodynamic at admission</b>		
SBP (mmHg)	17.8	90 [80; 117]
MBP (mmHg)	71.6	65 [55; 77]
DBP (mmHg)	78.6	50 [41; 60]
Heart rate (bpm)	17.2	98 [78; 118]
LVEF (%)	32.7	30 [20; 40]
Cardiac arrest prior to admission	67.9	462 (53.8)
<b>Severity score</b>		
APACHE II	80.4	41 [27; 90.2]
SOFA score	91	10 [9; 12]
<b>Cause of cardiogenic shock</b>		
Acute coronary syndrome	9.3	1563 (66)
Post cardiac arrest	61.7	456 (45)
Cardiomyopathy	61.6	103 (10)
Myocarditis	65.1	7 (1)
Endocarditis	70.1	3 (0)
Takotsubo	65.1	5 (1)
<b>Biology at admission</b>		
Hemoglobin (g/dL)	68.2	12.7 [11.2; 14.5]
Hematocrit (%)	86.4	40 [35.5; 43]
eGFR (mL/min/1.73 m <sup>2</sup> )	19.4	64.8 [43.5; 94.8]
Creatinin (μmol/L)	29.3	124 [95; 173]
Lactate (mmol/L)	63.6	4.7 [2.5; 9.3]
Troponin (OR)	77.7	75 [4.5; 572]
Natriuretic peptide	79.9	BNP: 1150 [351; 2419] NT-proBNP: 3604 [1069; 10,117]
<b>Treatment of cardiogenic shock</b>		
PCI	63.0	516 (54%)
CABG	67.3	36 (4%)
IABP	9.9	676 (29%)
ECLS	70.8	55 (7%)
Impella	70.0	81 (11%)
Epinephrine	0.0	947 (37%)

**Table 2 continued**

	% of missing data	All included patients (n = 2583)
Norepinephrine	13.8	1220 (54%)
Dopamine	21.4	557 (27%)
Dobutamine	9.3	1110 (47%)
Levosimendan	16.8	233 (11%)

Detailed data for every study are given in Supplemental Table 3

SBP systolic blood pressure, MBP mean blood pressure, DBP diastolic blood pressure, LVEF left ventricular ejection fraction, eGFR estimated glomerular filtration rate, PCI primary coronary intervention, CABG coronary artery bypass graft, IABP intra-aortic balloon pump, ICU intensive care unit



used catecholamine after norepinephrine (54%) and dobutamine (47%) (Supplemental Table 3). Short-term mortality rate was 49%, ranging from 21% to 69%. Figure 2 shows a correlation between the percentage of epinephrine use and short-term death by cohort.

### Epinephrine use and risk of short-term death

Across all cohorts ( $n=16$ ), risk of short-term death was significantly higher in epinephrine-treated patients (OR [CI]=3.3 [2.8–3.9]) compared to patients treated with other drug regimens for CS (Fig. 3). Of note, among the 16 cohorts, the majority had positive risk of death associated with the use of epinephrine whether statistically significant ( $n=6$ ) or as a trend ( $n=7$ ).

Risk of short-term death with the use of epinephrine was also adjusted for age, gender, ischemic heart disease, eGFR and LVEF at admission in a subset of 1227 patients. The adjusted mortality risk remained striking

in epinephrine-treated patients (adjusted OR=4.7 [3.4–6.4]) (Fig. 4).

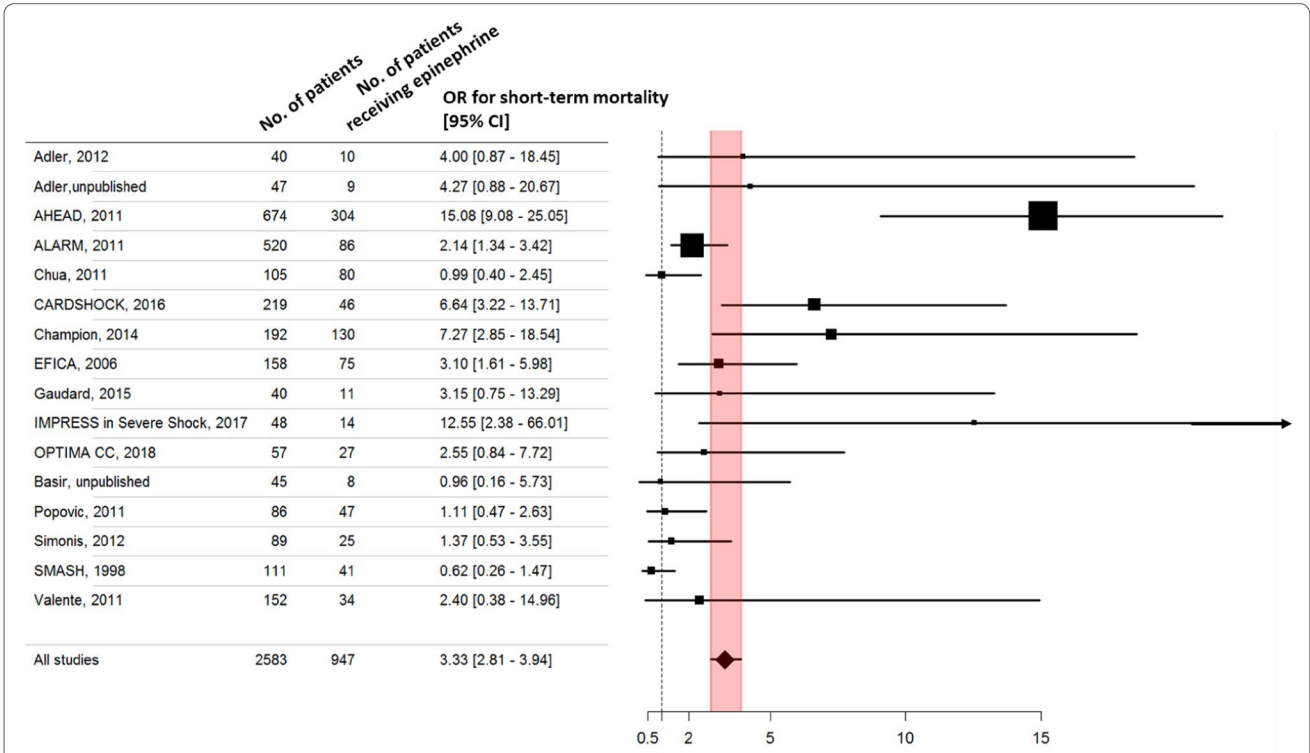
Furthermore, after propensity score matching, two sets of 338 matched patients balanced for all considered characteristics were identified (Supplemental Table 4) and epinephrine use was associated with a strong detrimental impact on short-term mortality (OR=4.2 [3.0–6.0]).

Sensitivity analysis showed persistent detrimental association between epinephrine use and short-term mortality. After exclusion of the largest cohort (AHEAD), the OR was 2.3 [1.9–2.8], with a robust estimation of the standard error (model with cluster effect). Figure 5 confirms that epinephrine use was significantly associated in all subgroups (including patients with acute coronary syndrome) except those who benefited from ECLS (189/671 (28%) without ECLS versus 58/124 (48%) with ECLS,  $p<0.0001$ ).

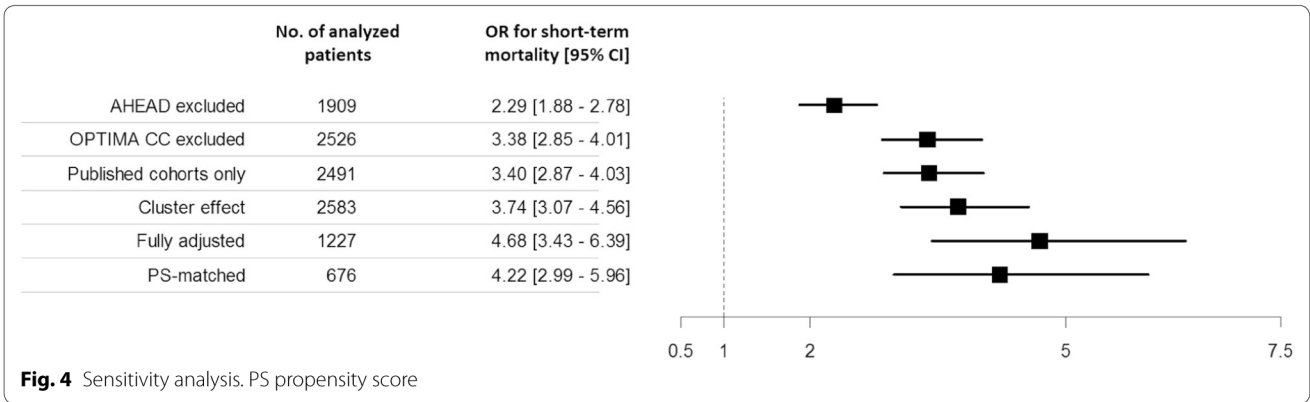
### Discussion

Using a large cohort of collaborative meta-analysis of all-cause cardiogenic shock patients, we demonstrated that epinephrine use is associated with a striking excess in mortality compared to other drug regimens. The association remains robust even after adjustment and propensity score matching and was consistent in the majority of the studied cohorts.

Our meta-analysis of individual data shows that epinephrine is frequently used in CS regardless of the mechanisms of CS, including those not related to cardiac arrest. Our study further shows that the use of epinephrine in CS was associated with several-fold increase in short-term risk of death in crude, adjusted, or propensity score analysis. This excess of mortality is present in all subgroups, except among those who benefited from ECLS. Mechanisms of lack of detrimental association between epinephrine use and ECLS in CS remains elusive. They might be (1) related to early withdrawal of epinephrine in patients under ECLS and/or (2) less “detrimental” effect of epinephrine in hearts with reduced myocardial wall stress, and enhanced coronary perfusion [27]. We observed a low rate of ECLS (7%) that might be



**Fig. 3** Forest plot of the meta-analysis of short-term mortality



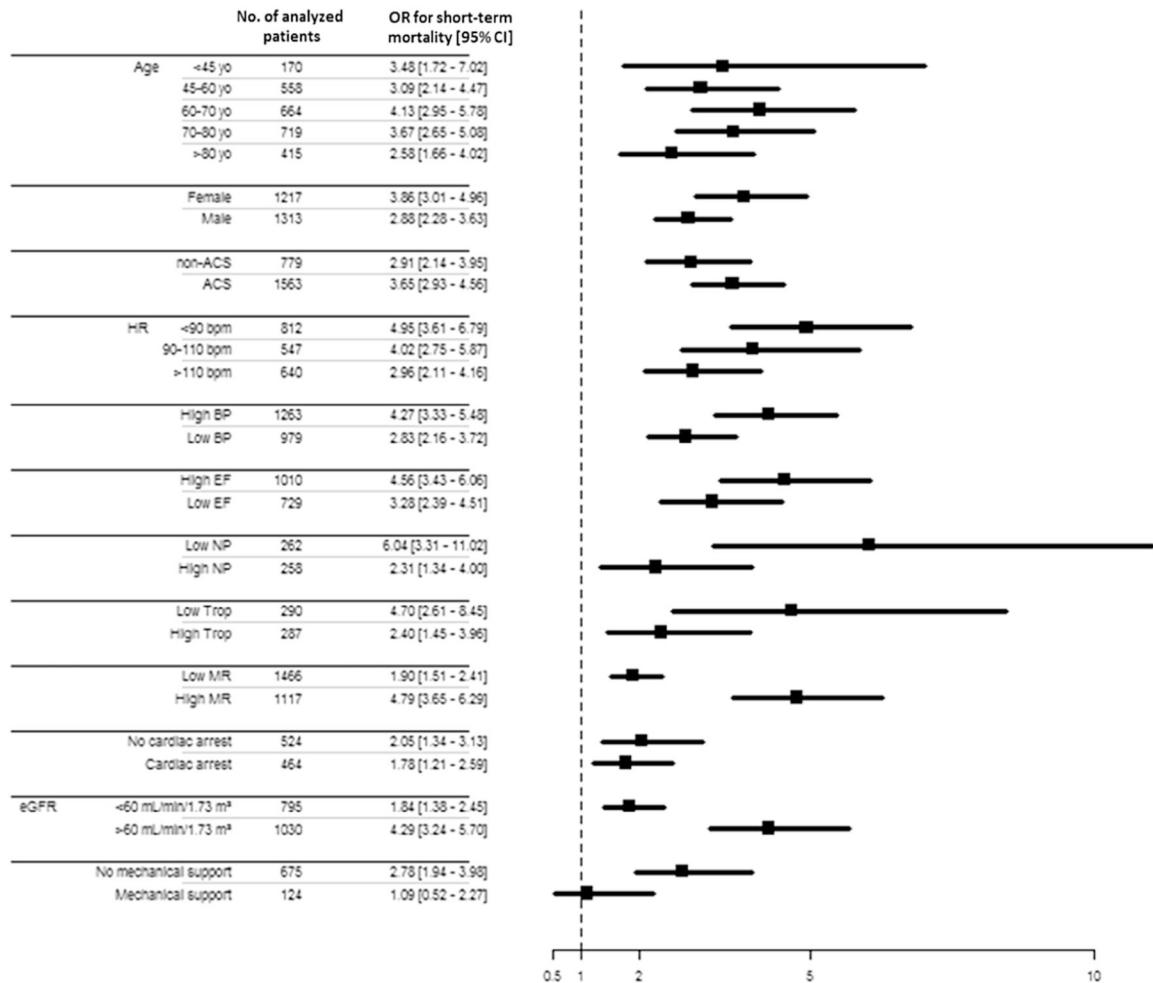
**Fig. 4** Sensitivity analysis. PS propensity score

explained by the recent increase in interest and use of mechanical support in cardiogenic shock management.

The mechanism of possible epinephrine toxicity remains unclear. Detrimental effects of epinephrine might be related to worsening of cardiac condition, despite hemodynamic benefits [2, 9, 28]. Epinephrine increases oxygen consumption and alters calcium homeostasis more than other catecholamine [29]. Hence, in CS where cardiac condition is already severely altered, epinephrine might markedly aggravate cardiac metabolism leading to death. Epinephrine may similarly affect

metabolism in other organs as recently shown in the OPTIMA CC and Cardshock studies [9, 11]. This may be due to epinephrine-induced alteration in microcirculation, specifically in the renal bed. These findings suggest that epinephrine's detrimental effect may be related to multiorgan toxicity [30–32].

Our meta-analysis indicates that in CS, the risk/benefit ratio favors the administration of inotropes and/or vasopressors other than epinephrine. Hence, the use of norepinephrine alone or combined with an inotrope, including dobutamine or levosimendan, may be



**Fig. 5** Forest plot of the meta-analysis of short-term mortality, with subgroup analysis. ACS acute coronary syndrome, HR heart rate, BP blood pressure (low BP, MAP < 65 mmHg or SBP < 90 mmHg), EF ejection fraction, NP natriuretic peptide, Trop troponin, MR mortality rate. Low/high cutoff was defined as the median value within each cohort

recommended as recently suggested [3, 4, 9, 11, 33, 34]. Concerning cardiogenic shock following cardiac arrest, in patients already on continuous epinephrine, our data suggest that replacing epinephrine with other inotropes and/or vasopressors may be desirable.

Our study has several limitations. First, our analysis included mostly observational studies because of the paucity of randomized trials on the safety effect of epinephrine. In addition to a potential publication bias, we were also dependent on the cooperation of original investigators, not all of whom responded to our request for collaboration. However, our meta-analysis confirmed the result of the recently published OPTIMA CC [11], the only randomized trial comparing epinephrine to norepinephrine. The results of the present meta-analysis are only exploratory. Prospective trials assessing the safety of epinephrine compared to other treatment regimen

in cardiogenic shock are urgently needed. Second, we were confronted with many available issues. This was expected as collaborating authors did not use the same data set in their studies, hindering the adjustment of our analysis for the full cohort. However, adjustment analysis, taking into account the severity of hemodynamic instability, and propensity score matching both confirmed the main result of the meta-analysis. Third, the impact of the quality of the studies on the risk of bias was not assessed in the present meta-analysis as only one of the 16 included cohorts originally aimed to assess the effect of epinephrine on mortality. Fourth, we were not able to collect data on dose or duration of epinephrine therapy or on its combination with other therapies (inotrope, vasopressor, or others). We were not able to assess whether there is a dose-dependent detrimental effect of epinephrine on outcome. However, our study shows that



epinephrine was consistently associated with worse outcome in almost every study, regardless of illness severity and heterogeneity in CS management. More importantly, our analysis showed that mortality of each study was positively associated with the proportion of CS patients treated with epinephrine. Finally, the primary endpoint (short-term mortality) may appear restrictive and inadequate for the 462 patients resuscitated from cardiac arrest. It would have been interesting to associate neurological recovery. The cerebral performance categories scores (CPC scores) were not available in the database and should be evaluated in further studies.

## Conclusion

Using a large collaborative meta-analysis, our study shows that epinephrine is associated with a threefold increase in risk of mortality in CS. This result highlights the need to perform controlled trials of different drug therapies in CS and supports the need to reconsider the use of epinephrine in future guidelines.

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## Compliance with ethical standards

### Conflict of interest

AM received lecture fees from Novartis, Orion and Abbott, research grants from Roche and consultant fees from Servier and Sanofi. Other coauthors have no conflicts to declare.

### Authors' comment

One of the two unpublished data set-the one of Basir-was published after data extraction, and is referred as [35].

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