Abstention or intervention for isolated hypotension in the first 3 days of life in extremely preterm infants: association with short-term outcomes in the EPIPAGE 2 cohort study – Supplementary material

Selection process and list of covariates included in the propensity score:

Variables potentially influencing antihypotensive treatment administration were selected from available variables if they preceded the treatment decision. The precise date of antihypotensive treatment within the first 3 days of life was not available, neither was the precise date of some events that occurred during the first 3 days.

All the following variables related to birth conditions were included in the propensity score since they necessarily preceded antihypotensive treatment:

Gestational age, sex, birth weight Z-score based on Olsen's curves,(1) multiple birth, antenatal corticosteroid treatment, main cause of prematurity, antenatal magnesium sulfate treatment, inborn status, mode of delivery, delayed cord clamping, 5-minute Apgar score, intubation in the delivery room.

The following early interventions or diagnosis were also included because they most plausibly preceded antihypotensive treatment:

surfactant therapy, suspected early-onset neonatal sepsis, metabolic acidosis (defined as a base excess <-7 in the first 12 hours of life).

Two variables with an important imbalance between treated and untreated groups were also included, although we did not have the information to be certain that they preceded antihypotensive treatment:

sedative or analgesic treatment before 72 hours of life and minMAP $\leq$ GA-5.

From a clinical point of view, sedative or analgesic treatments are known to cause hypotension(2, 3) and might therefore influence the treatment decision. The inverse relation, i.e. that antihypotensive treatments are associated with an increased use of sedative or analgesic treatments, has never been reported and is not supported by any physiological mechanism or clinical reasoning. Therefore we considered that sedative or analgesic treatments mainly preceded antihypotensive treatments. In addition, removing this variable that was strongly imbalanced between the untreated and treated group might have induced an important bias.

Similarly, severe hypotension, defined in our study as minMAP≤ GA-5, could not be attributable to antihypotensive treatment, since the effect and the goal of such a treatment is to increase(4), or at least maintain(4, 5), blood pressure. Therefore, we considered that minMAP≤ GA-5 mainly preceded antihypotensive treatment. In addition, removing this variable that was strongly imbalanced between the untreated and treated group might have induced an important bias.

Finally, we also included in the propensity score a proxy for centre's expertise, defined by summing the number of preterm babies who spent their first consecutive 48 hours in the centre, in order to limit bias due to the centre's expertise.

Methods: Management of missing data

For variables in which the frequency of missing data was below 3% in the selected population, we imputed the dominant value for categorical variables for the missing values; we treated missing data as a separate category for other variables.

Detailed methods for sensitivity analysis

Logistic regression model (model (1))

In the overall cohort, we used a logistic regression model to assess the relation between exposure (antihypotensive treatment) and the primary outcome after adjustments for all covariates associated with the primary outcome, namely: gestational age, cause of preterm birth, multiple births, birth-weight percentile, sex, surfactant therapy, suspected early-onset sepsis, analgesic or sedatives before day 3, minMAP < GA-5, metabolic acidosis (defined as a BE<-7 in the first 12 hours of life), inborn status, and NICU patient volume.

Inverse propensity score weighted model (model (2))

We also used a generalized estimating equation logistic regression model weighted by the propensity score, in which each infant was weighted by on his/her own propensity score dividing by (1- his/her own propensity score), to estimate the average treatment effect in the treated group.(2)

Multiple imputation

Multiple imputation was used as another sensitivity analysis. To account for missing data for covariates included in the propensisty score we conducted multiple imputation by Monte Carlo Markov chains as implemented in the SAS MI procedure, using all baseline variables of the propensity score model, as well as antihypotensive treatment and the outcome, as recommended.(3) Thirty independent imputed datasets were generated. A propensity score was estimated for each imputed dataset and was used to create two matched sets, as in the main analysis. Each matched imputed dataset was then analyzed and the resulting estimates were pooled according to Rubin's rule.(3)

The same procedure was applied for missing data concerning the reasons for antihypotensive infants administration (n=54, see Figure 1).

Symptomatic treated group

Another sensitivity analysis included the infants who received antihypotensive treatment for any reason other than isolated hypotension. We compared three groups of infants with early hypotension for the primary and secondary outcomes using a p-trend test: (a) infants who were not treated: the untreated group; (b) infants who received antihypotensive therapies only for isolated hypotension: the treated group; (c) infants who received antihypotensive therapies for additional clinical and/or echocardiographic and/or laboratory signs: the symptomatic treated group. We expected to observe worse outcomes in the third group, compared to the treated and untreated groups. This analysis was conducted to ensure that the untreated infants (with permissive hypotension) were not under-diagnosed for signs of hemodynamic compromise, which would have resulted in comparable or worse outcomes for the untreated compared with the symptomatic treated group.

Negative control

We also performed a negative control analysis using late-onset infections as a negative control outcome (i.e. an outcome without plausible causal association with the exposure) to detect uncontrolled confounding.(4)

References

1. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. *Pediatrics*. 2010;**125**:e214-24

2. Austin PC, Stuart EA. The performance of inverse probability of treatment weighting and full matching on the propensity score in the presence of model misspecification when estimating the effect of treatment on survival outcomes. *Stat Methods Med Res*. 2015;

3. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med*. 1991;**10**:585-98

4. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology*. 2010;**21**:383-8

Supplementary Table 1. Baseline characteristics in the overall and matched cohorts

	No. of Events (%)					
	Overall Cohort[a]			Matched cohort		
	Untreated (N=325)	Treated (N=131)	Standardized difference, %	Untreated (N=119)	Treated (N=119)	Standardized difference, %
GA (weeks), mean (sd)	26.6 (1.2)	26.7 (1.1)	1.1	26.5 (1.2)	26.5 (1.2)	0
24	21 (5.5)	5 (3.3)		5 (4.2)	5 (4.2)	
25	61 (15.9)	23 (15.0)		19 (16.0)	19 (16.0)	
26	75 (19.6)	37 (24.1)		33 (27.7)	33 (27.7)	
27	78 (27.4)	33 (28.9)		30 (25.2)	30 (25.2)	
28	90 (31.6)	33 (28.9)		32 (26.9)	32 (26.9)	
Multiple births	97 (29.6)	55 (41.6)	25.3	46 (38.7)	48 (40.3)	3.4
Birthweight <10th centile	53 (16.4)	13 (9.8)	19.6	13 (10.9)	13 (10.9)	0
Antenatal corticosteroids	270 (83.5)	107 (82.4)	2.9	99 (83.2)	100 (84.0)	2.3
Cause of preterm birth						
Preterm labor	154 (47.1)	69 (51.8)	9.5	71 (59.7)	66 (55.5)	8.5
Preterm premature rupture of membranes	88 (26.5)	23 (17.0)	23.2	23 (19.3)	23 (19.3)	0
Hypertensive disorders or Placental abruption	64 (20.3)	22 (18.6)	4.4	16 (13.4))	19 (16.0)	7.1
Isolated fetal growth restriction	11 (3.7)	3 (2.4)	7.5	2 (1.7)	3 (2.5)	5.9
Other/Not defined	8 (2.4)	14 (10.2)	32.3	7 (5.9)	8 (6.7)	3.5
Antenatal magnesium sulfate	24 (7.6)	8 (6.1)	6.0	6 (5.0)	8 (6.7)	7.1
Caesarean delivery	195 (61.0)	76 (60.0)	2.1	69 (58.0)	70 (58.8)	1.7
Delayed cord clamping						
No	304 (93.5)	117 (89.1)	15.8	109 (91.6)	109 (91.6)	0
Yes	9 (2.8)	3 (2.4)	2.5	4 (3.4)	3 (2.5)	5.0
No information	12 (3.7)	11 (8.5)	20.3	6 (5.0)	7 (5.9)	3.7
Male	169 (52.1)	72 (54.7)	5.1	67 (56.3)	64 (53.8)	5.1
5 min Apgar Score <7						
No	223 (69.4)	83 (64.1)	11.3	79 (66.4)	78 (65.5))	1.8
Yes	75 (22.7)	28 (21.1)	3.9	28 (23.5)	25 (21.0)	6.1
No information	27 (7.9)	20 (14.8)	22	12 (10.1)	16 (13.4)	10.4
Intubation in delivery room	280 (85.3)	115 (86.9)	4.7	103 (86.6)	105 (88.2)	5.1
Metabolic acidosis						
No	207 (63.5)	91 (70.2)	14.2	83 (69.7)	82 (68.9)	1.8
Yes	84 (26.1)	28 (20.5)	13.4	28 (23.5)	26 (21.8)	4.0
No information	34 (10.4)	12 (9.4)	3.5	8 (6.7)	11 (9.2)	9.3

Supplementary Table 1. Baseline characteristics in the overall and matched cohorts[a] (continued)

Surfactant						
No	32 (10.7)	7 (5.9)	17.5	10 (8.4)	7 (5.9)	9.8
1 dose	199 (61.1)	80 (61.5)	0.8	67 (56.3)	75 (63.0)	13.7
≥2 doses	94 (28.2)	44 (32.7)	9.6	42 (35.3)	37 (31.1)	8.9
Suspected early onset sepsis	254 (76.9)	112 (86.8)	20.1	98 (82.4)	100 (84.0)	4.5
Sedative or analgesic treatment before day 3	113 (34.2)	68 (51.9)	36.3	52 (43.7)	59 (49.6)	11.8
MinMAP ≤ GA - 5mmHg	85 (27.2)	61 (46.9)	41.5	53 (22.3)	53 (22.3)	0
Inborn	287 (88.7)	108 (82.1)	18.8	102 (85.7)	100 (84.0)	4.7
Patient volume of neonatal unit, mean (sd)	36 (17)	34 (13)	14.3	35 (14)	34 (13)	2.8

a: % are weighted to take into account differences in the sampling process between gestational age groups

Abbreviation: GA, gestational age; minMAP, minimal mean arterial blood pressure

Denominators vary according to the number of missing data items for each variable.

Supplementary Table 2. Antihypotensive treatments and patent ductus arteriosus management in treated and untreated infants

	No. of Events/Total (%)			
	Overall Cohort[a]		Matched Cohort	
	Untreated	Treated	Untreated	Treated
Antihypotensive treatment before day 3 of life,				
Fluid bolus	-	101/130 (77.9)	-	90/118 (76.3)
Inotropic drugs	-	44/129 (33.9)	-	39/117 (33.3)
Corticosteroids	-	36/130 (27.0)	-	30/118 (25.4)
Treatment combinations Fluid bolus +inotropes Fluid bolus +corticosteroids Inotropes + corticosteroids Fluid bolus + inotropes + corticosteroids	-	 19/128 (15.4) 13/128 (9.8) 3/128 (2.2) 8/128 (5.8)	-	 17/116 (14.7) 9/116 (7.8) 3/116 (2.6) 6/116 (5.2)
Antihypotensive treatment after day 3 of life	80/317 (23.6)	44/127 (33.9)	25/115 (21.7)	41/115 (35.7)
PDA treatment				
No	148/322 (47.7)	49/126 (40.7)	47/118 (39.8)	46/115 (40.0)
Before day 3	77/322 (23.1)	28/126 (21.7)	33/118 (28.0)	25/115 (21.7)
On day 3 or after	97/322 (29.2)	49/126 (37.7)	38/118 (32.2)	44/115 (38.5)

a: % are weighted to take into account differences in the sampling process between gestational age groups.

Denominators vary according to the number of missing data items

Abbreviations: PDA, patent ductus arteriosus

Supplementary Table 3. Causes of death in the propensity score matched cohort among treated and untreated infants

	N/total (%)	
Cause of death	**Untreated**	**Treated**
Neurological complication	17/27 (63%)	5/20 (25%)
Including		
Treatment withholding or withdrawal	15/17	2/5
No treatment withholding or withdrawal	2/15	3/5
MOF with sepsis	6/27 (22%)	7/20 (35%)
MOF without sepsis	1/27 (4%)	5/20 (25%)
Respiratory failure	2/27 (7%)	3/20 (15%)
Unknown	1/27 (4%)	-
Treatment withholding or withdrawal among all previous categories	18/27 (67%)	3/20 (15%)
Total	27	20
Median time to death [IQR], days from birth	11 [5-20]	12 [4-20]

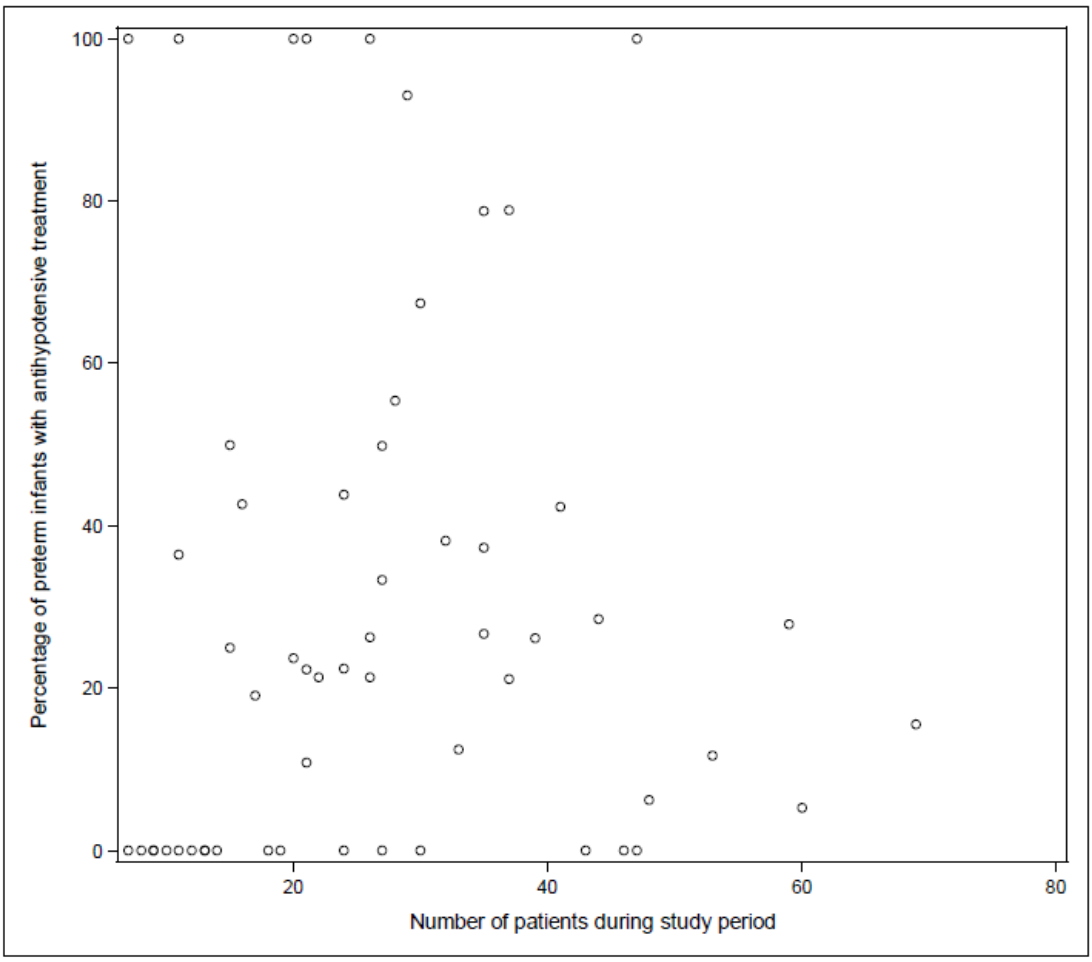
Abbreviation: MOF, multiple organ failure

Supplementary Table 4. Subgroup analysis for survival without major morbidity at discharge among infants with minMAP ≤ or > GA-5 in the propensity score matched cohort[a]

	No. of Events/Total (%)					
	MinMAP ≤ GA-5			MinMAP > GA-5		
	Untreated	**Treated**	**OR (95%CI)**	**Untreated**	**Treated**	**OR (95%CI)**
Survival without major morbidity at discharge	15/43 (34.9)	27/43 (62.8)	3.15 (1.28-7.74)	39/63 (61.9)	39/63 (61.9)	1.00 (0.51-1.96)

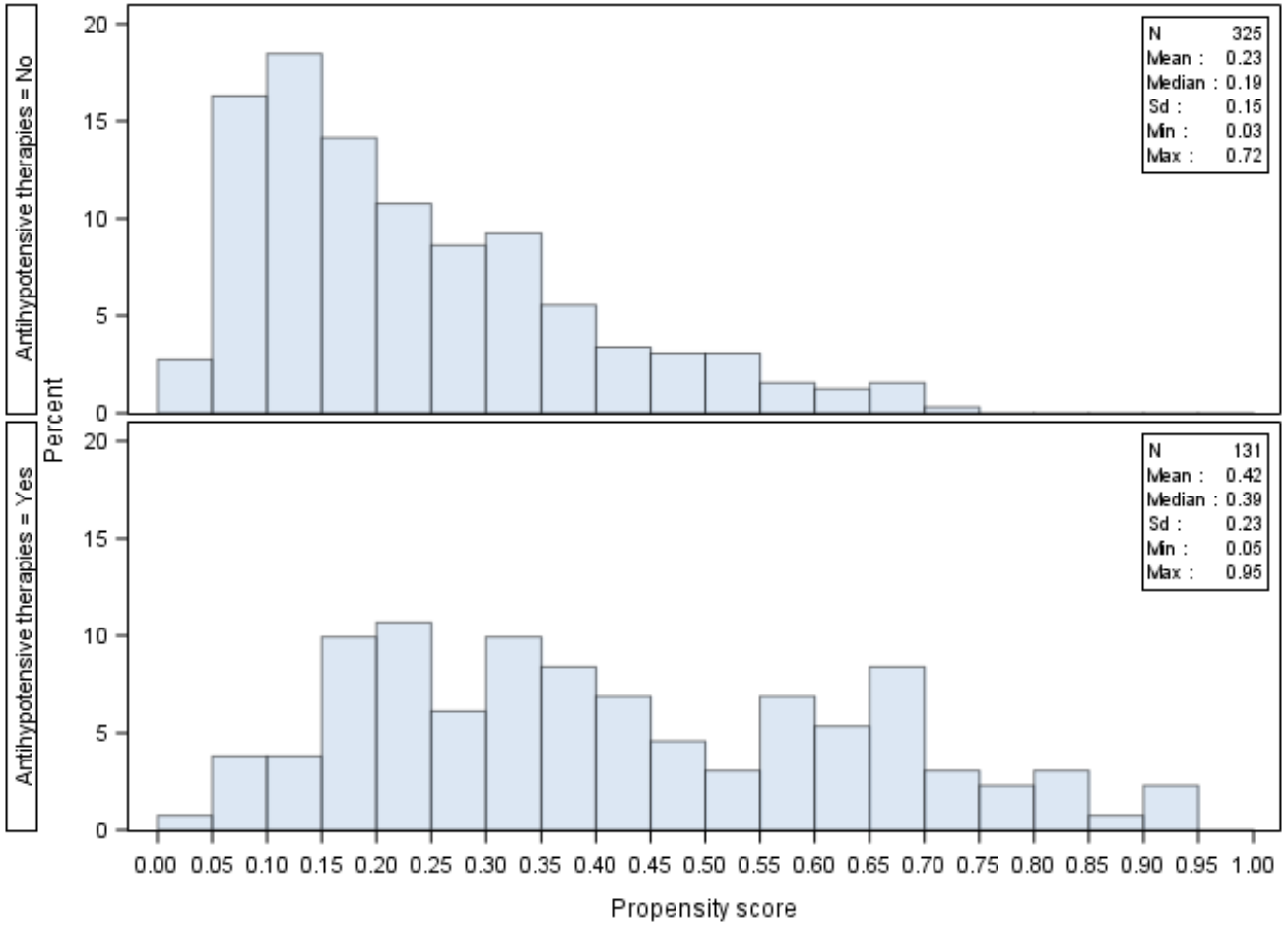
[a] Analyses were performed using a new propensity score within each subgroup.

Supplementary Figure S1. Relationship between unit patient volume and antihypotensive treatment



Each unit that admitted more than 5 extremely preterm infants during the study period is represented by a circle (n=57 units). The x-axis is the patient volume and the y-axis is the proportion of preterm infants with at least one episode of isolated hypotension who received antihypotensive treatment.

Supplementary Figure S2. Distribution of propensity scores in the whole untreated and treated populations



Values in each bin are greater than the lower limit and equal to or less than the upper limit

In the Matched cohort, the mean (SD) propensity score values were 0.34 (0.21) and 0.35 (0.21) in the untreated and treated groups, respectively.