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# **Bicarbonates pour l'acidose : BICAR-ICU**

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# Disclosures

## Consultants with honorarium

- Dräger
- Fisher-Paykel
- Xenios
- Baxter

# Background

## Severe Acidosis in ICU :

- Frequent (15-40%)
- Worse outcome
- Mortality up to 60%
- Sodium bicarbonate infusion to treat severe metabolic acidosis is controversial.

Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy. a prospective, multiple-center study



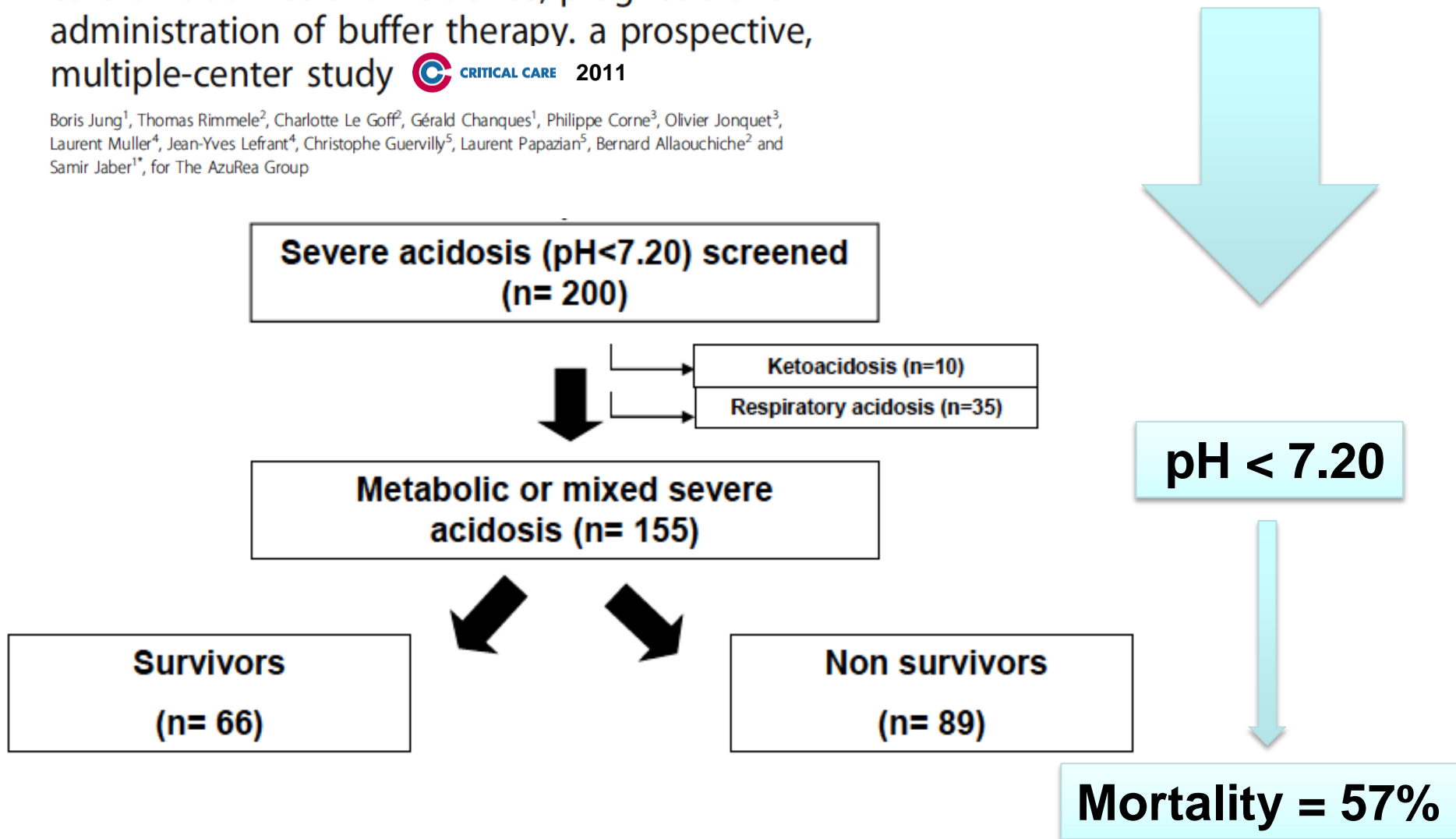
Boris Jung<sup>1</sup>, Thomas Rimmele<sup>2</sup>, Charlotte Le Goff<sup>2</sup>, Gérald Chanques<sup>1</sup>, Philippe Corne<sup>3</sup>, Olivier Jonquet<sup>3</sup>, Laurent Muller<sup>4</sup>, Jean-Yves Lefrant<sup>4</sup>, Christophe Guervilly<sup>5</sup>, Laurent Papazian<sup>5</sup>, Bernard Allaouchiche<sup>2</sup> and Samir Jaber<sup>1\*</sup>, for The AzuRea Group

Jung et al, Crit Care 2011

# Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy. a prospective, multiple-center study

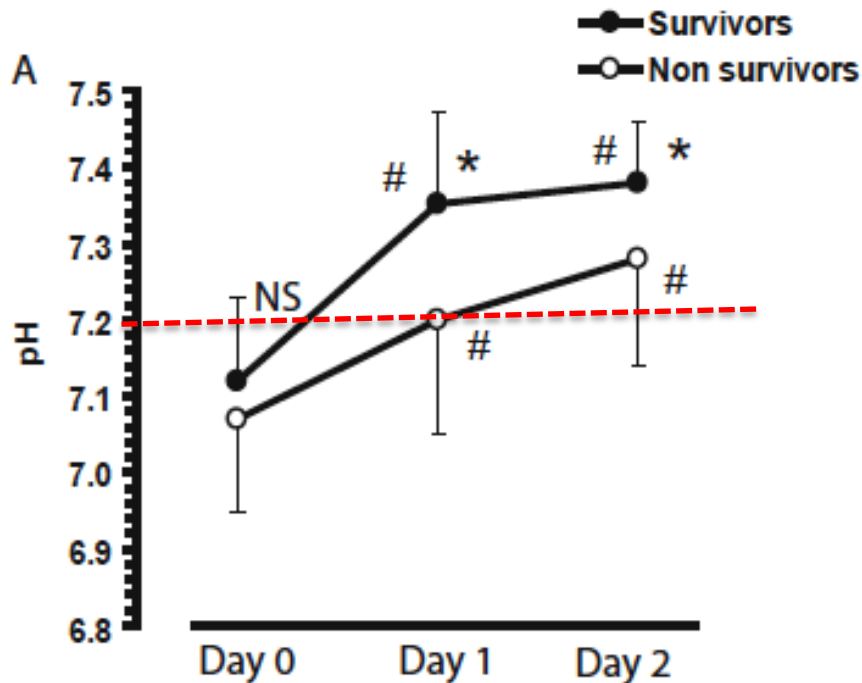
 **CRITICAL CARE** 2011

Boris Jung<sup>1</sup>, Thomas Rimmelé<sup>2</sup>, Charlotte Le Goff<sup>2</sup>, Gérald Chanques<sup>1</sup>, Philippe Corne<sup>3</sup>, Olivier Jonquet<sup>3</sup>, Laurent Muller<sup>4</sup>, Jean-Yves Lefrant<sup>4</sup>, Christophe Guervilly<sup>5</sup>, Laurent Papazian<sup>5</sup>, Bernard Allaouchiche<sup>2</sup> and Samir Jaber<sup>1\*</sup>, for The AzuRea Group



# Severe Acidemia is bad !

Persistent acidosis has been associated with poor prognosis





Sodium bicarbonate infusion to treat severe metabolic acidosis is controversial.



**Good ?**



**Neutral ?**



**Bad ?**

# Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

« The effect of bicarbonate administration on hemodynamics and vasopressor requirements at lower pH, ... is unknown.

**« No studies have examined the effect of bicarbonate administration on outcomes »»**

Dellinger et al; Intensive Care Med. 2013 Feb:165-228

Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017;43(3):304–77

# RCT ?



**NONE**

The lack of high-level evidence leaves ICU clinicians uncertain whether bicarbonate infusion is beneficial, ineffective, or indeed harmful



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# Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial

*Samir Jaber, Catherine Paugam, Emmanuel Futier, Jean-Yves Lefrant, Sigismond Lasocki, Thomas Lescot, Julien Pottecher, Alexandre Demoule, Martine Ferrandière, Karim Asehnoune, Jean Dellamonica, Lionel Velly, Paër-Sélim Abback, Audrey de Jong, Vincent Brunot, Fouad Belafia, Antoine Roquilly, Gérald Chanques, Laurent Muller, Jean-Michel Constantin, Helena Bertet, Kada Klouche, Nicolas Molinari, Boris Jung, for the BICAR-ICU Study Group\**

**LANCET 2018**

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# **AIM OF THE STUDY**

**To determine if Sodium Bicarbonate has an impact on the prognosis of severely acidotic patients in the ICU**

## **Hypothesis: Bicarbonate will decrease**

- D-28 mortality, or
- The number of patients presenting at least one organ failure at D7 as defined by a SOFA > 2

# SECONDARY ENDPOINTS

1. **SOFA Score:** D0, D1, D2, D5, D7
2. **AKIN Score:** D0, D1, D2, D5, D7
3. **RRT :** yes/no from D1 to D28
4. **MV (either invasive or NIV):** yes/no from D1 to D28
5. **Vasopressors:** yes/no from D1 to D28
6. **Fluid loading:** D0, D1, D2, D5
7. **Acid-base analysis (ABG):**
  1. D0 to D2: every 8h
  2. D3 to D5: every 24h
8. **Electrolytes disturbances (including calcemia)**
  1. D0 to D2: every 8h
  2. D3 to D5: every 24h
9. **Nosocomial infections:** up to D28 or ICU discharge
10. **ICU free-days:** up to D28 or ICU discharge
11. **Hospital free-days:** up to D28 or ICU discharge
12. **Survival at D28:** yes/no

# DESIGN OF THE STUDY

- RCT
- Multicenter (n=26)
- Stratified, two-arm unblinded parallel-arms study
- Stratification
- Intention To Treat analysis (n=400)

# INCLUSION CRITERIA

Within 48h following ICU admission  
(4 criteria must be present):

1.  $\text{pH} \leq 7.20$
2.  $\text{PaCO}_2 \leq 45 \text{ mmHg}$
3. Bicarbonatemia  $\leq 20 \text{ mmol/l}$
4.  $\text{SOFA}_{(\text{total})} \geq 4$  and/or lactatemia  $> 2 \text{ mmol/l}$

# NON INCLUSION CRITERIA

## 1. **Bicarbonate loss**

(profuse diarrhoea, ileostomy >1000ml/24h, proven tubular acidosis)

## 2. **Chronic Kidney failure needing RRT**

## 3. Stage IV Chronic Kidney Insufficiency (Clairance <30ml/min)

## 4. **Acidoketosis** / Acids poisoning

## 5. Withdrawal of care / death in the next 48h

## 6. Tutelage

## 7. No health insurance

## 8. Pregnancy

## 9. Consent refusal

N=400 patients - 2 Groups

**Group-0**  
**N=200**

Electronic  
Randomisation

**Group-Bicar**  
**N=200**

= 0 Bicar

3 stratifications  
(/center

= Bicar 4.2%

125-250 ml/30min



1. Sepsis upon inclusion:

☐ Yes

☐ No

2. Renal failure (AKIN):

☐ 0-1

☐ 2-3

3. Age:

☐ < 65 yrs

☐ ≥ 65 yrs



# ICU admission

H0-H48: screening

## 4 criteria needed

1.  $\text{pH} \leq 7.20$  and
2.  $\text{PaCO}_2 \leq 45 \text{ mmHg}$  and
3. Bicarbonatemia  $\leq 20 \text{ mmol/l}$  and
4.  $\text{SOFA} \geq 4$  and/or Lactates  $> 2 \text{ mmol/l}$

## Randomisation

0

ABG  
H1 - H4

1 test minimum

$\text{pH} > 7.30$

Consider RRT

$\text{pH} \leq 7.30$

Sodium Bicarbonate 4.2% :  
125 to 250 ml / 30min

ABG  
H1 - H4  
post Bicar

1 test minimum

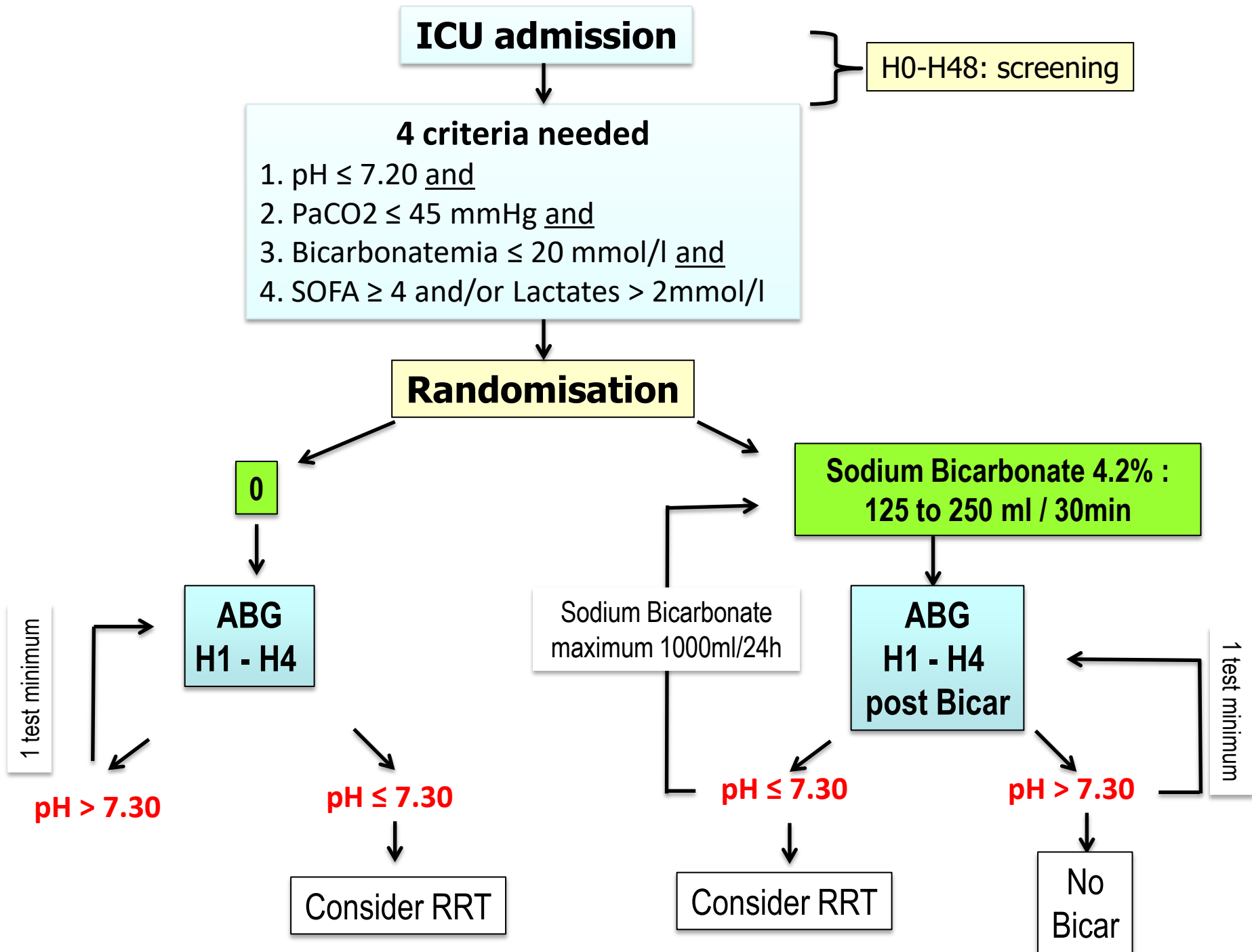
$\text{pH} > 7.30$

No  
Bicar

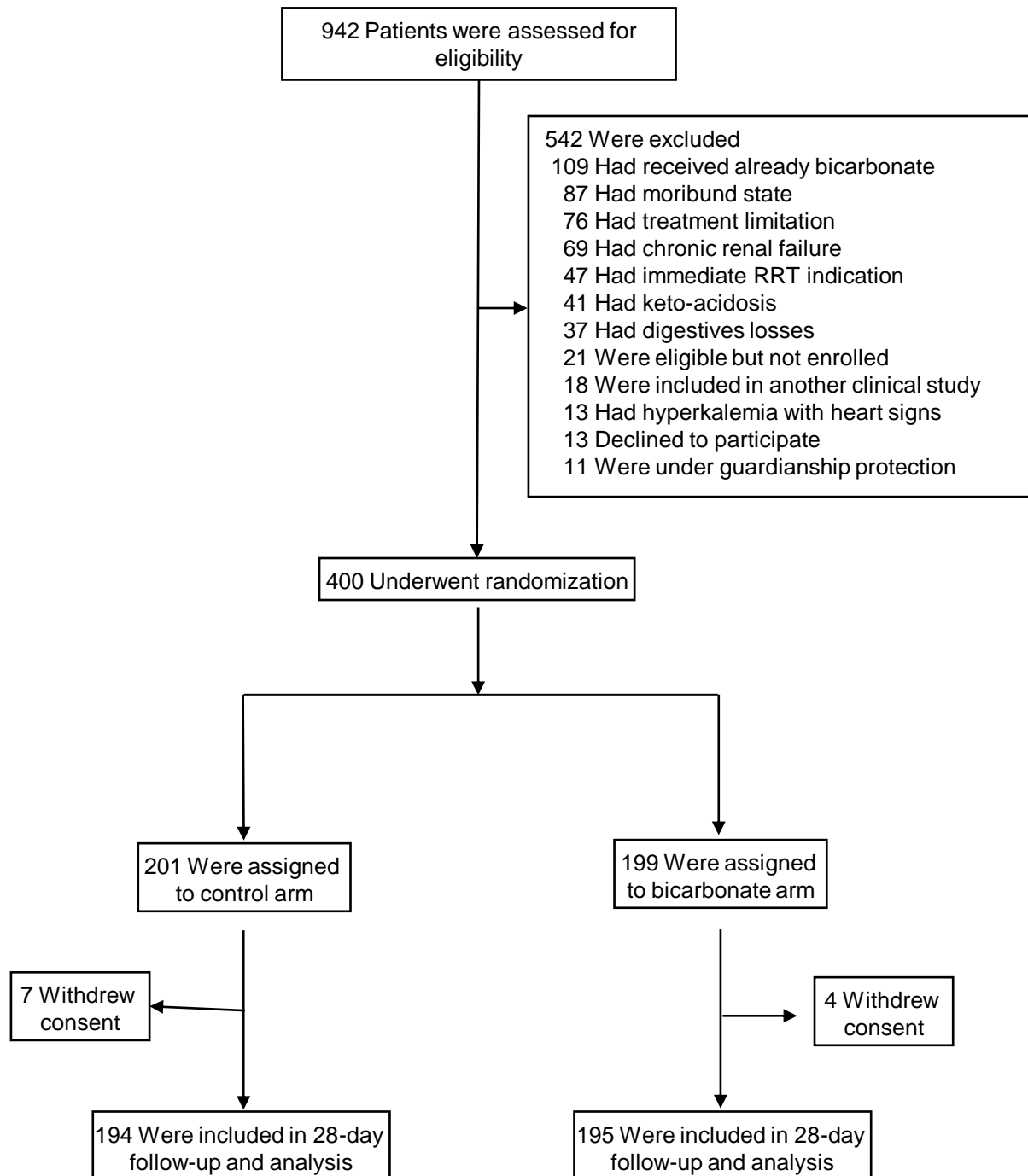
Consider RRT

$\text{pH} \leq 7.30$

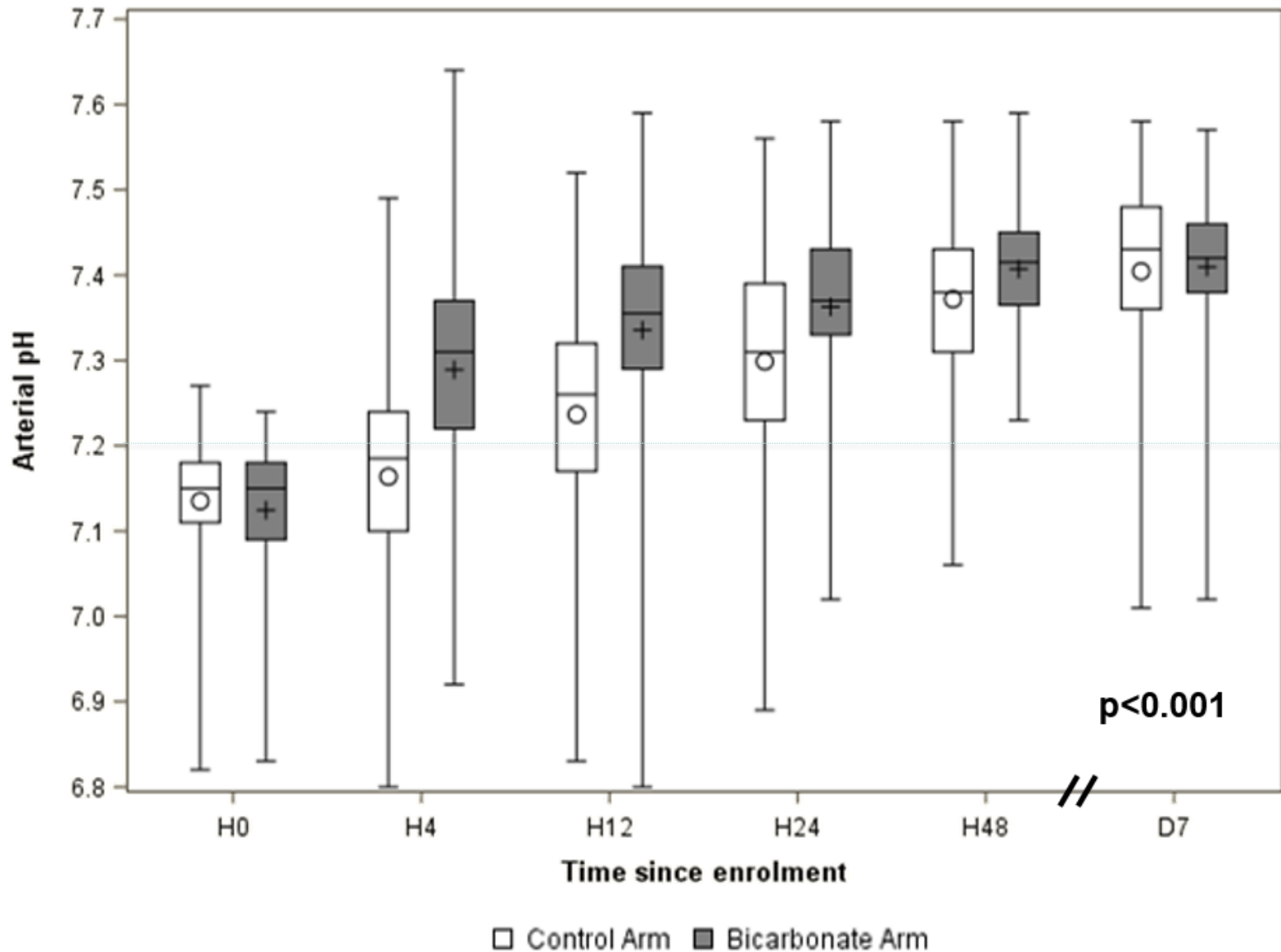
Sodium Bicarbonate  
maximum 1000ml/24h



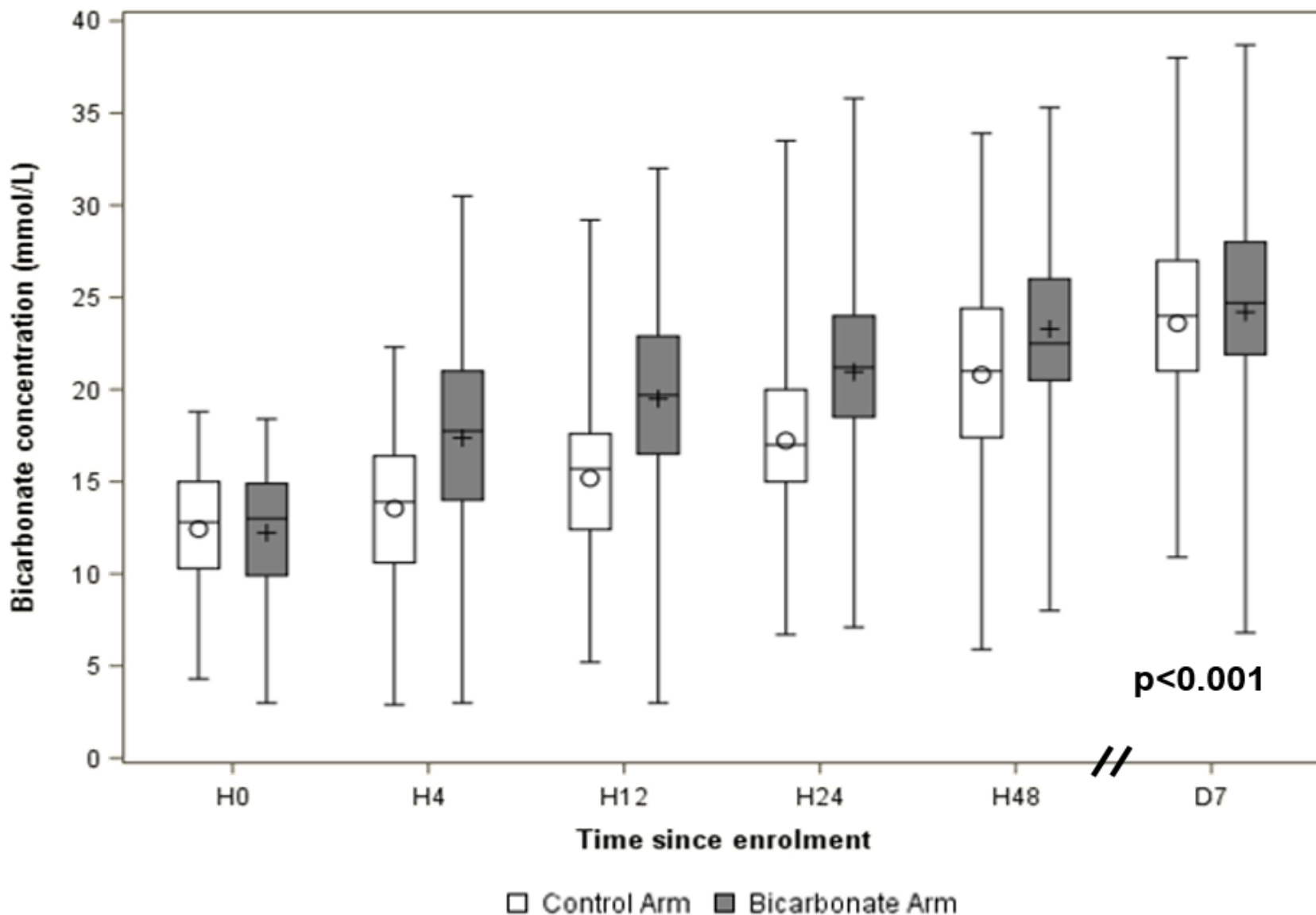




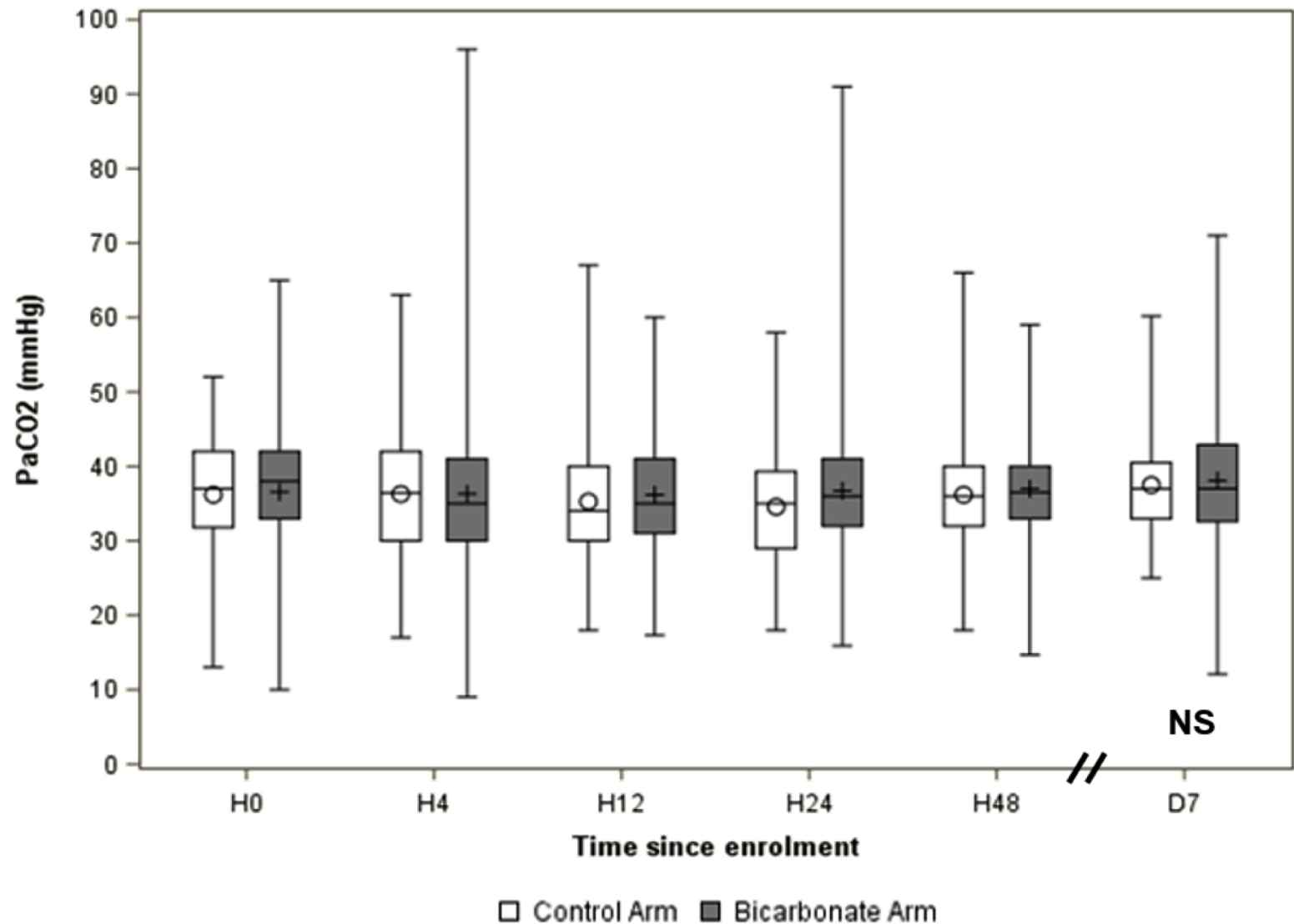
## Arterial pH level in patients in the control and in the bicarbonate arms at baseline and after enrolment (overall population)



Arterial bicarbonate level in patients in the control and in the bicarbonate arms at baseline and after enrolment (overall population).



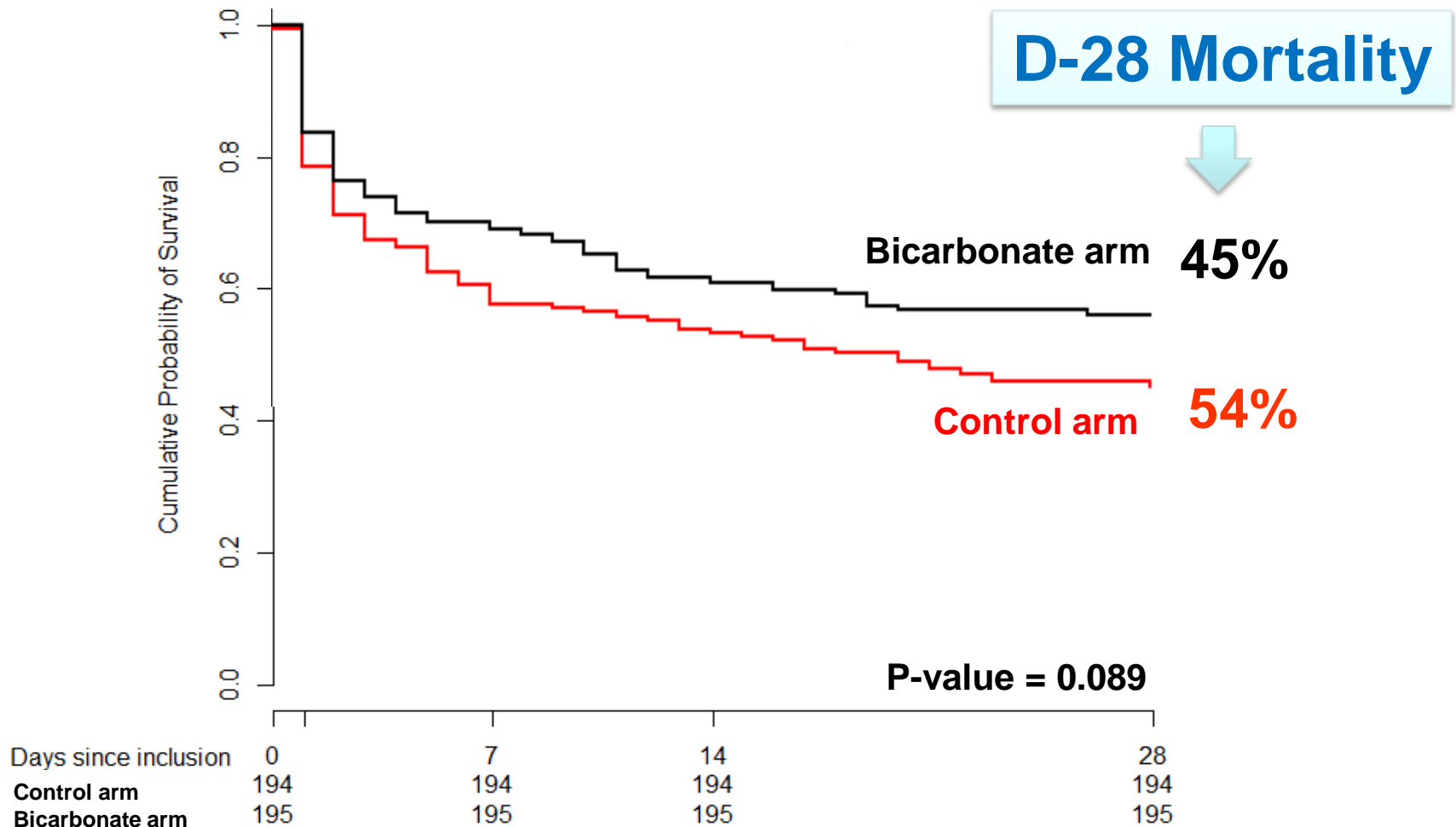
## PaCO<sub>2</sub> level in patients in the control and in the bicarbonate arms at baseline and after enrolment (overall population)



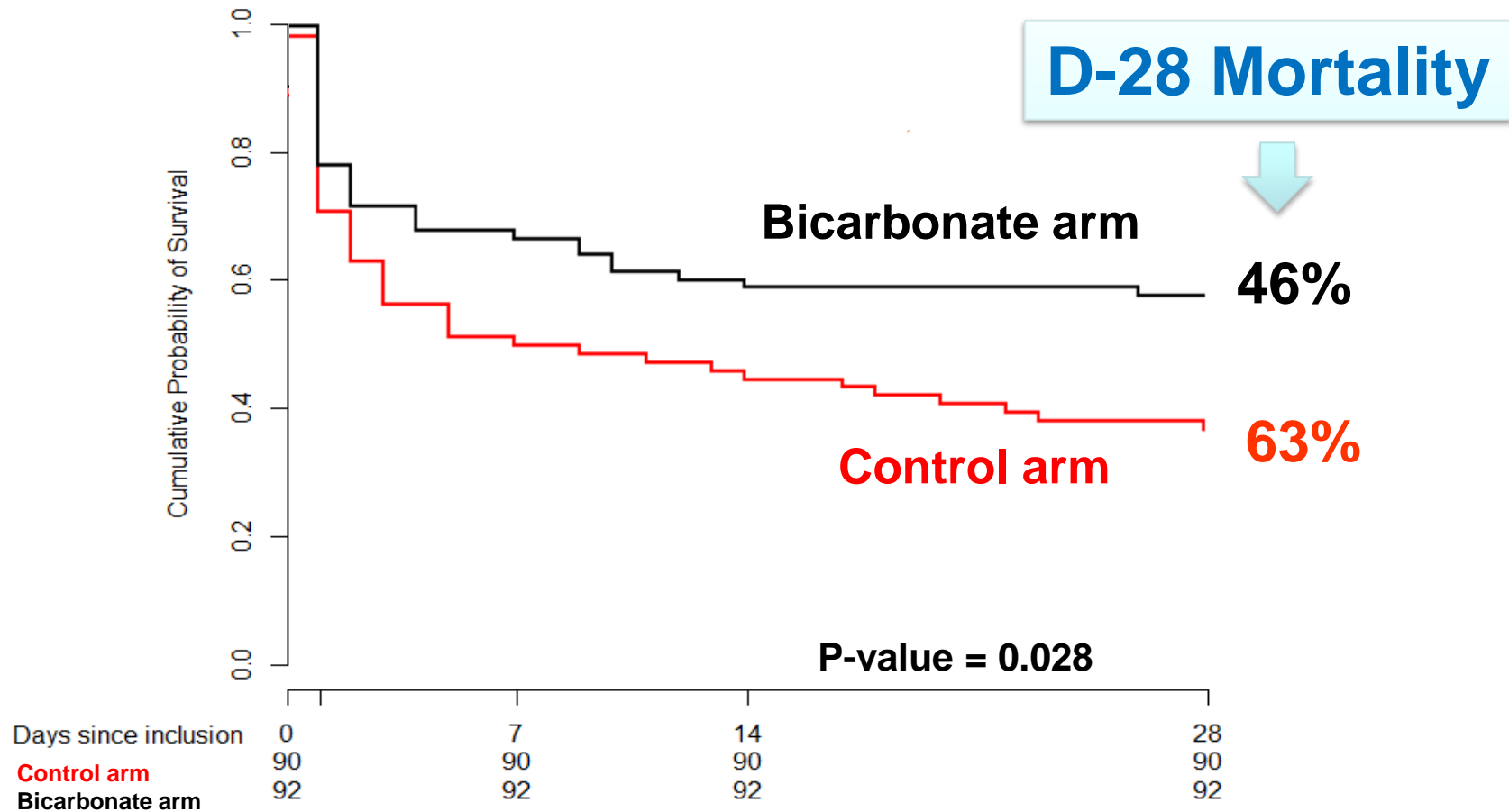
Outcome	Control Arm (N = 194)	Bicarbonate Arm (N = 195)	P value
<b>Primary outcome — no. (%)</b>			
<b>Overall population (n=389)</b>			
Composite outcome	138 (71)	128 (66)	0.244
<b>Day 28 mortality</b>	104 (54)	87 (45)	<b>0.076</b>
At least one organ failure at day 7	50 (46)	55 (43)	0.661

<b>Patients with AKIN 2-3 † (n=182)</b>			
Composite outcome	74/90 (82)	64/92 (70)	<b>0.046</b>
Day 28 mortality	57/90 (63)	42/92 (46)	<b>0.017</b>
At least one organ failure at day 7	74/90 (82)	61/92 (66)	<b>0.014</b>

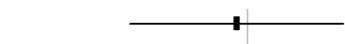
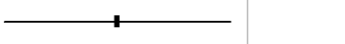
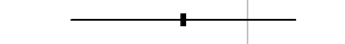
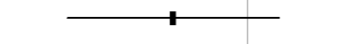
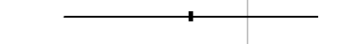
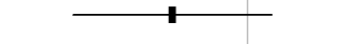

# A. Time to Death in Overall Patients



## B Time to Death in Patients with pre-specified Acute Kidney Injury

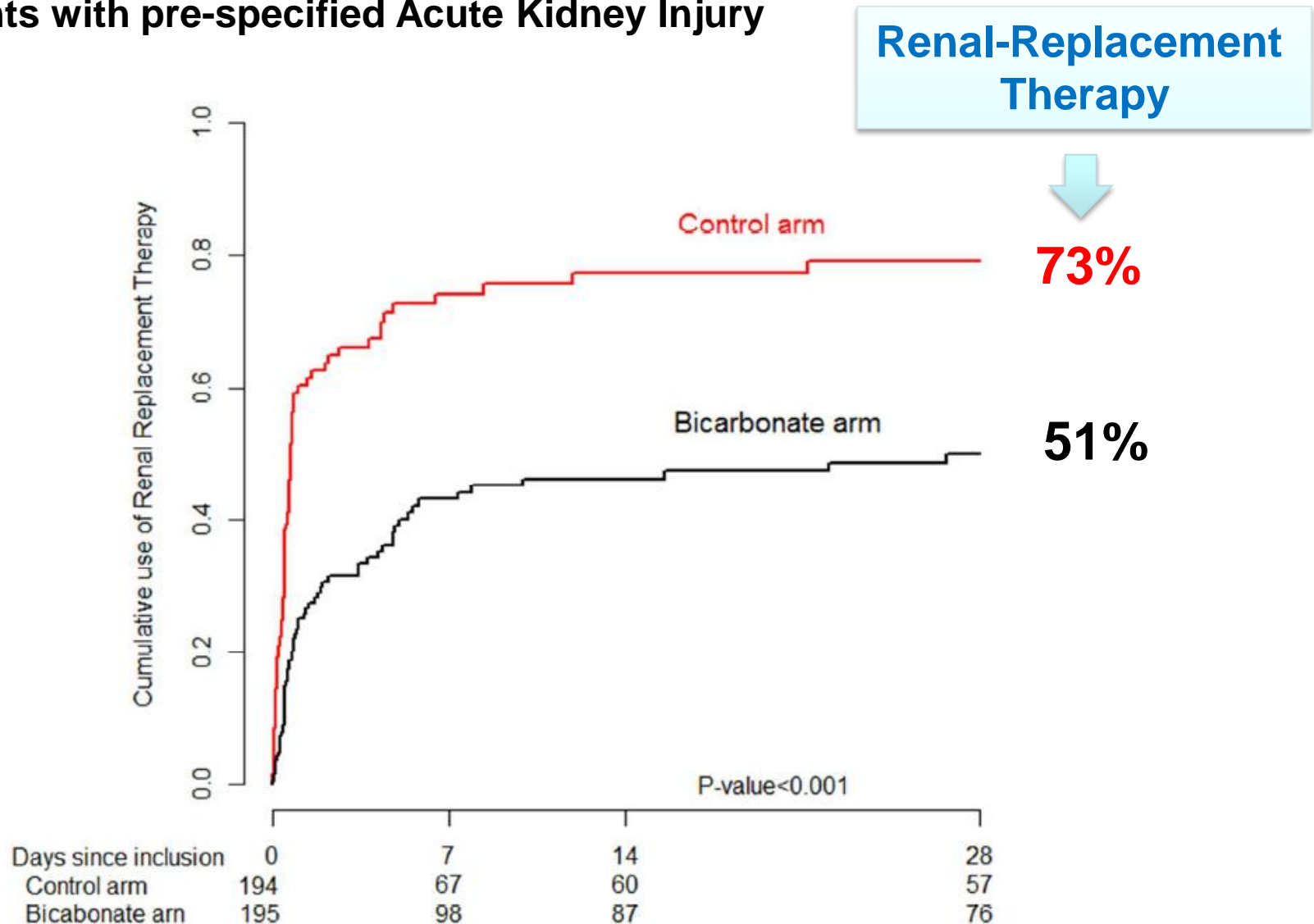


## C. Relative Risk of 28 day mortality among all the Patients and in the three prespecified strata

		Control arm	Bicarbonate arm		Absolute difference in % (95%CI)	P-value	P-value for heterogeneity
AKIN	0-1	47/104 (45)	45/103 (44)		-1,5 (-16.0;13.0)	0.828	0.023
	2-3	57/90 (63)	42/92 (46)		-17.7 (-33.0;-2.3)	0.017	
AGE	<65	42/94 (45)	32/89 (36)		-8.7 (-24.0;6.5)	0.229	0.003
	>=65	62/100 (62)	55/106 (52)		-10.1 (-24.5;4.3)	0.143	
SEPSIS	NO	39/79 (49)	30/72 (42)		-7.7 (-24.9;9.5)	0.343	0.212
	YES	65/115 (57)	57/123 (46)		-10.2 (-23.7;3.3)	0.116	
All patients		104/194 (54)	87/195 (45)		-9,0 (-19.4;1.4)	0.076	



**Figure 3. Cumulative use of renal-replacement therapy from enrolment until day 28 in the control and bicarbonate arms in Patients with pre-specified Acute Kidney Injury**



# Effectiveness of sodium bicarbonate infusion on mortality in septic patients with metabolic acidosis

*Intensive Care Medicine* (nov 2018)

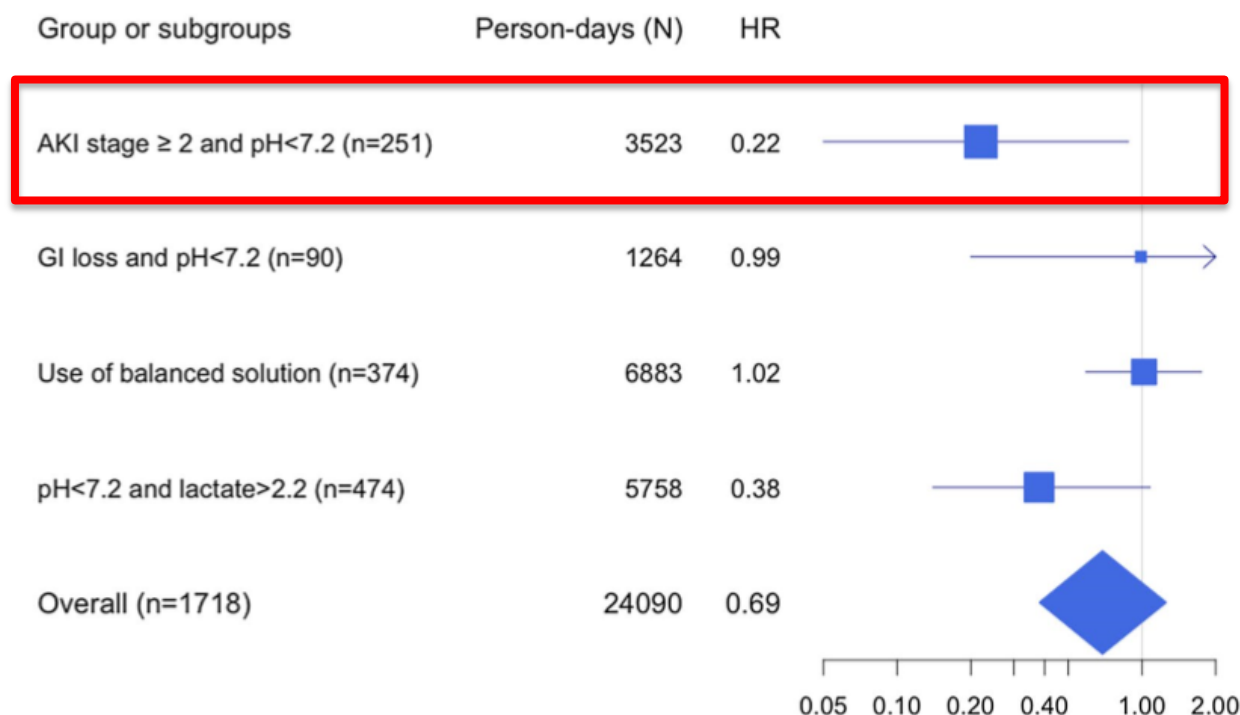
Zhongheng Zhang<sup>1\*</sup>, Carlie Zhu<sup>2</sup>, Lei Mo<sup>3</sup> and Yucai Hong<sup>1</sup>



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AND THE EUROPEAN SOCIETY OF PAEDIATRIC & NEONATAL INTENSIVE CARE



1. No significant mortality effect in the overall population (n=1718) of Sodium Bicarbonate
2. Sodium Bicarbonate infusion was associated with improved survival outcome in septic patients with AKI  $\geq 2$  and pH < 7.2.



**Fig. 2** Forest plot showing the effect of sodium bicarbonate treatment on mortality in overall sepsis population with metabolic acidosis and subgroups. The hazard ratios were estimated using the marginal structural Cox model. Person-days were the days of ICU length of stay. The x-axis tick marks follow a logarithmic scale. *AKI* acute kidney injury, *GI* gastrointestinal, *HR* hazard ratio

# Take Home Message (from Bicar-ICU)

1. Bicarbonate did not significantly decrease day-28 mortality or the presence of at least one organ failure at day-7 in the overall population with severe metabolic acidosis ( $\text{pH} \leq 7.20$ )
2. Bicarbonate infusion decreased the need for renal-replacement therapy (52 vs 35%,  $p < 0.01$ )
3. In the a priori stratum of patients with acute kidney injury, infusion of bicarbonate resulted in fewer deaths by day-28 (63 vs 46%,  $p = 0.017$ )

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# Thank you

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\*The BICAR-ICU study investigators are listed in the appendix

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