Tunisie 2025

Place des vasopresseurs non - adrénergiques dans le choc septique

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Liens d'intérêt

Membre du board VIATRIS

Lectures pour VIATRIS

Lectures pour AOP-ORPHAN

Lectures pour VYGON

1

Autres vasopresseurs?

A considérer uniquement en cas de **choc septique réfractaire**

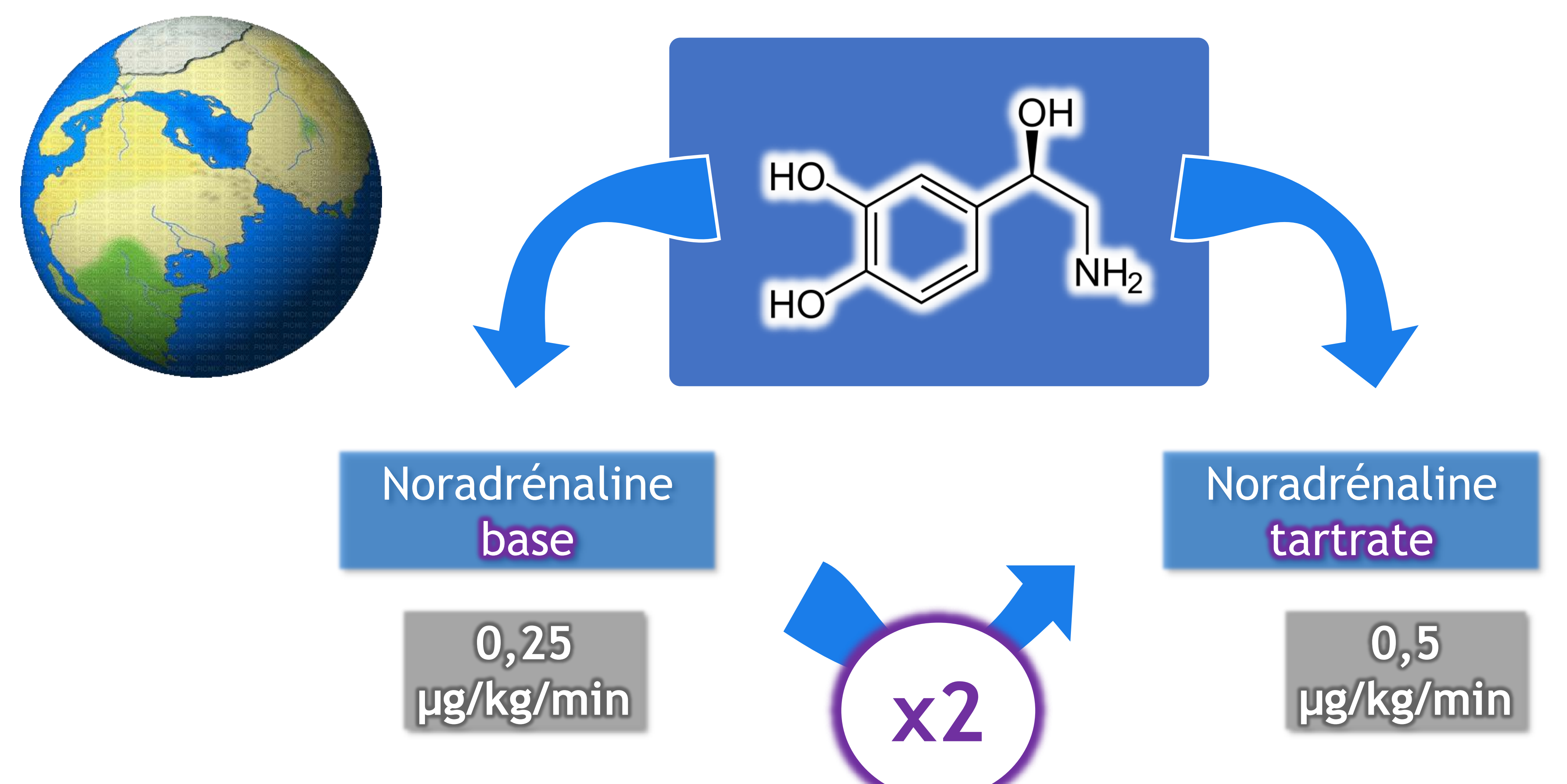
Définition choc septique réfractaire

Refractory septic shock is a life-threatening condition that is best defined by a state in which escalation of vasoactive therapy does not restore adequate tissue perfusion. At the bedside, this can be recognized by persistent hypotension and hypoperfusion in the absence of hypovolemia, while the patient is receiving more than 0.25 µg/kg min of norepinephrine

1 mg/h
70 kgs

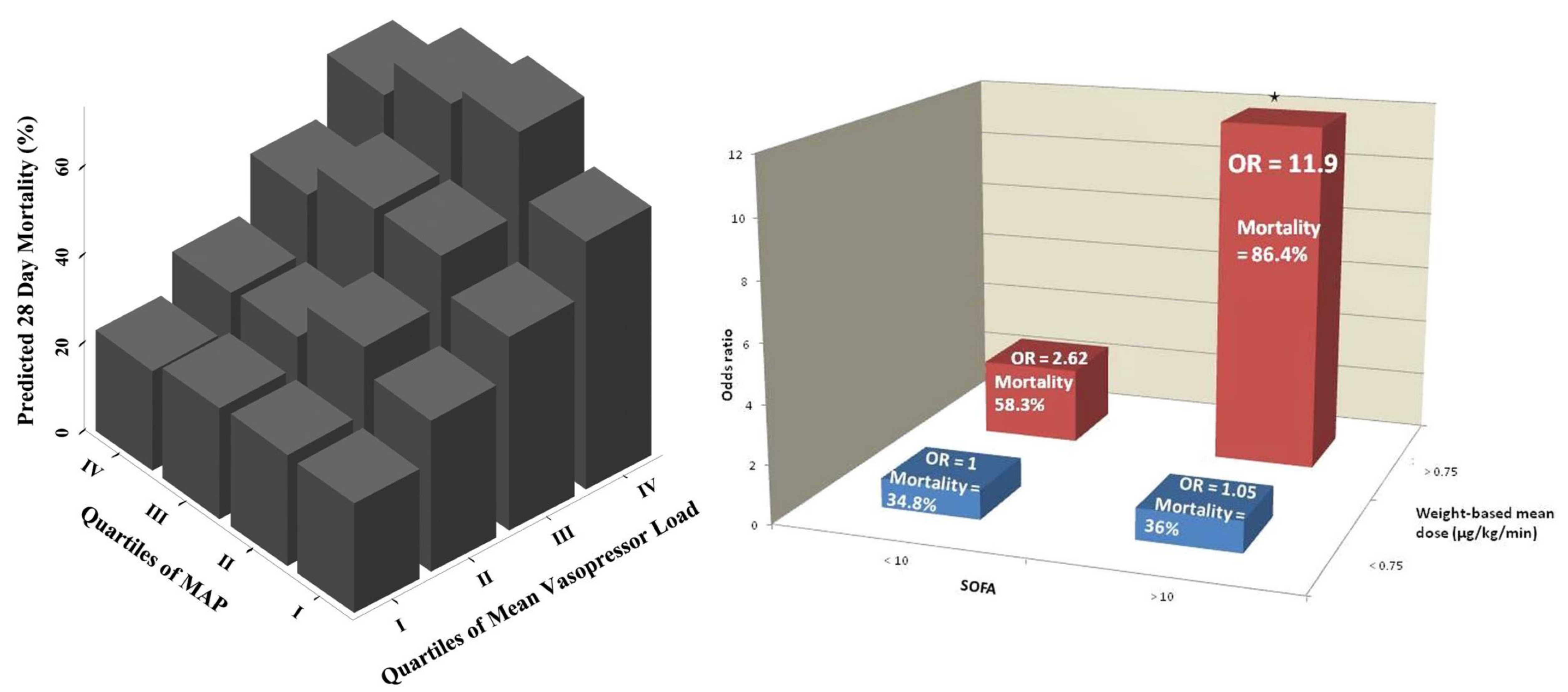
Bakker et al. *ICM* 2022;48:148-163

Définition du choc septique réfractaire



Leone et al. *ICM* 2022;48:638-640

NAD – *Stress catécholaminergique*

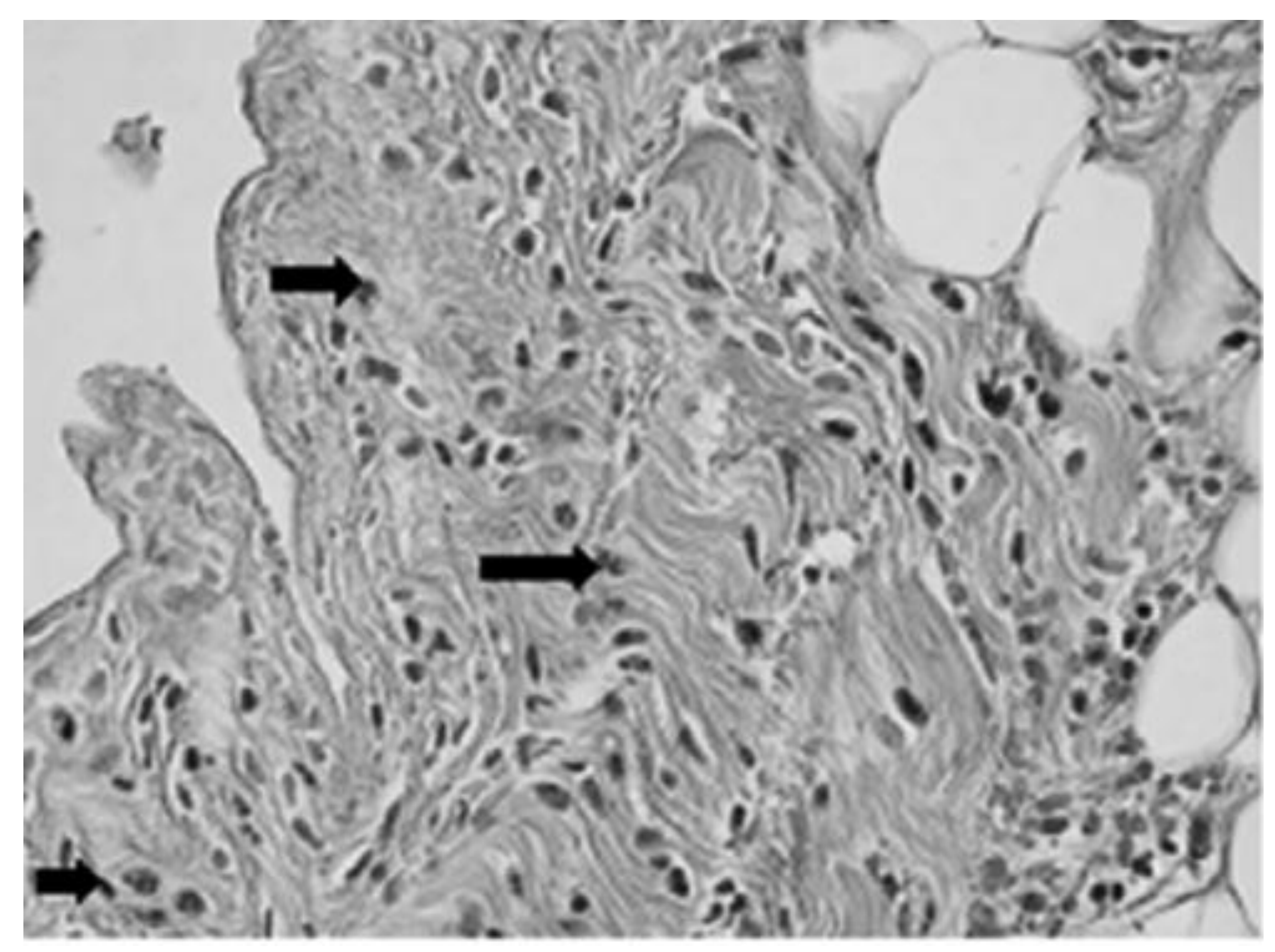


Dünser et al. *Crit Care* 2009;13(6):R181

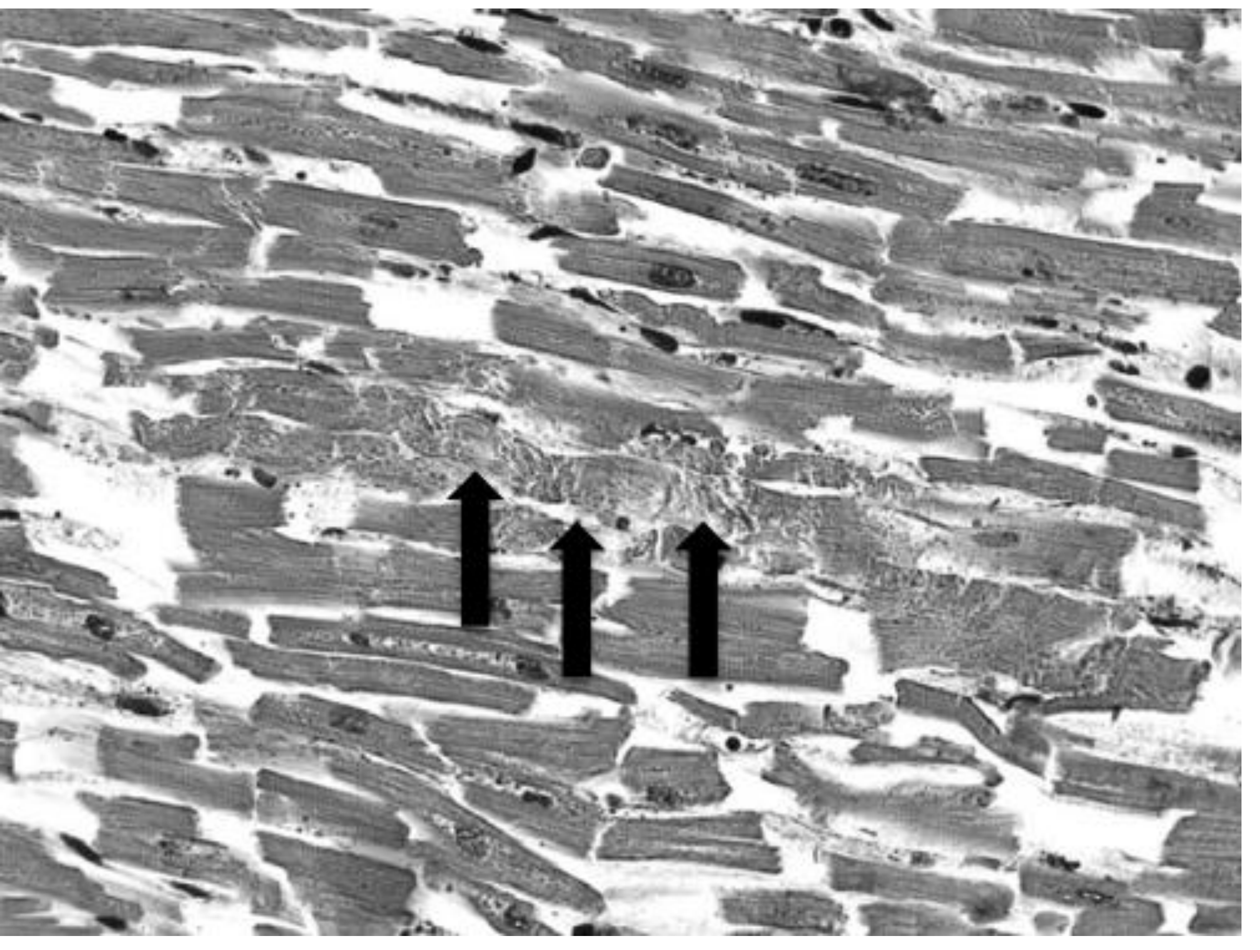
Auchet et al.*AIC* 2017;7(1):43

NAD – *Effets cardiaques*

Inflammation myocardique

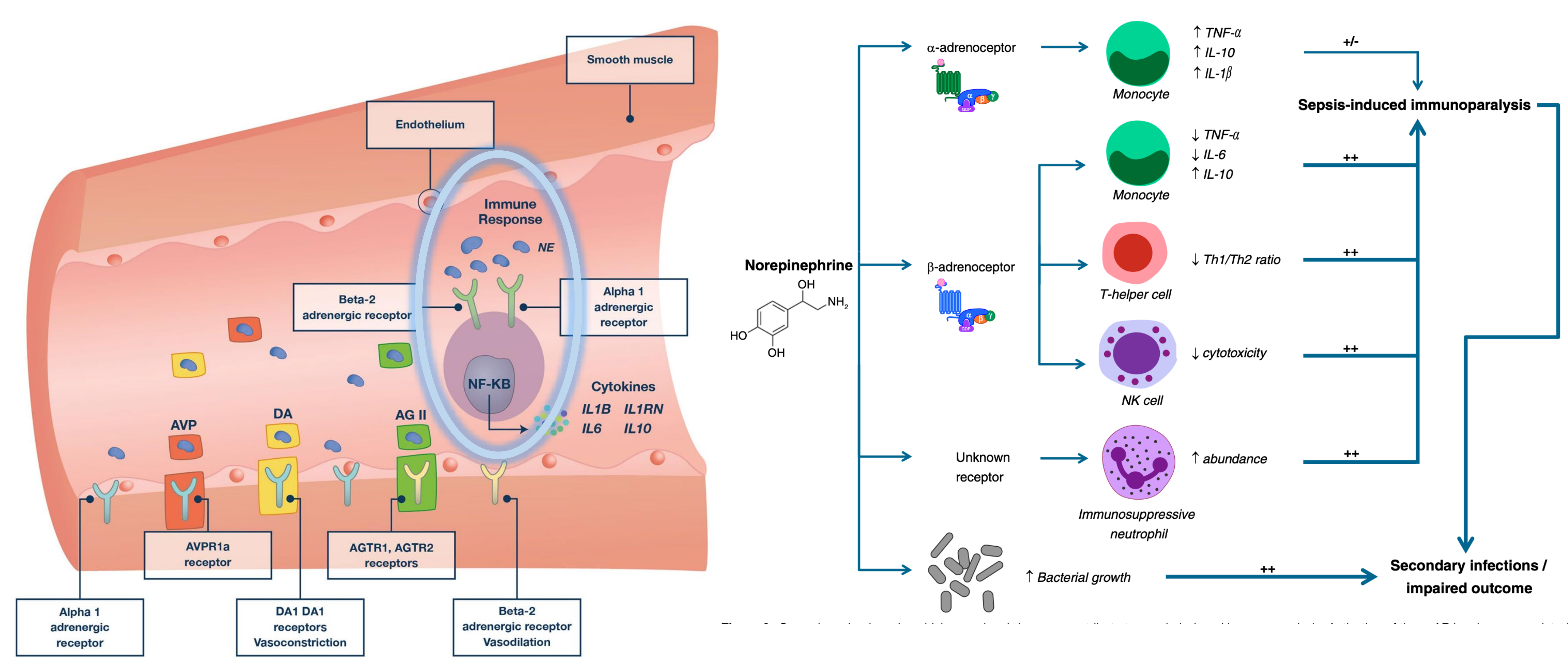


Nécrose myocardique



Schmittinger et al. *Shock* 2013;39:329-335

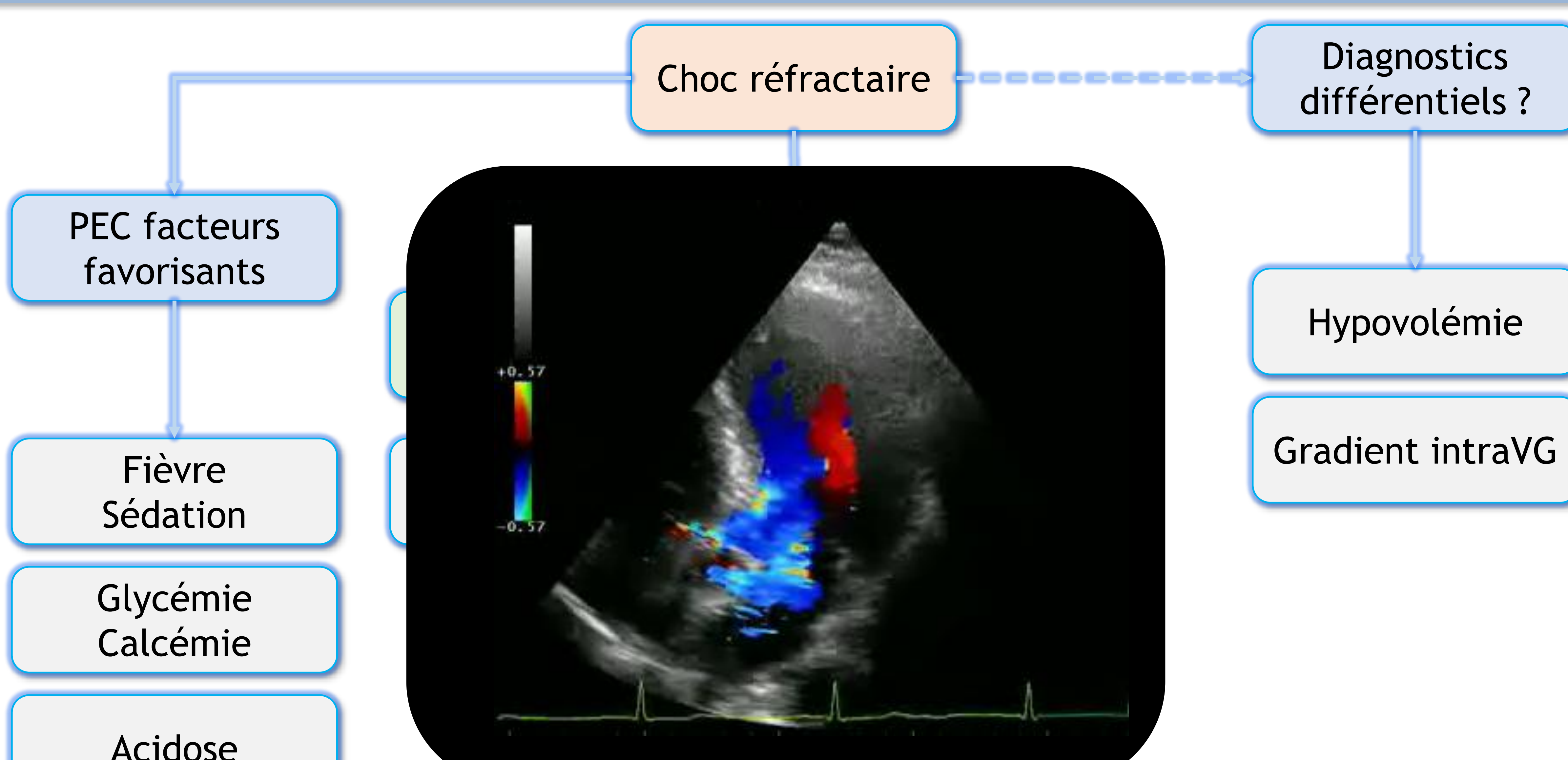
NAD – *Effets immunologiques*



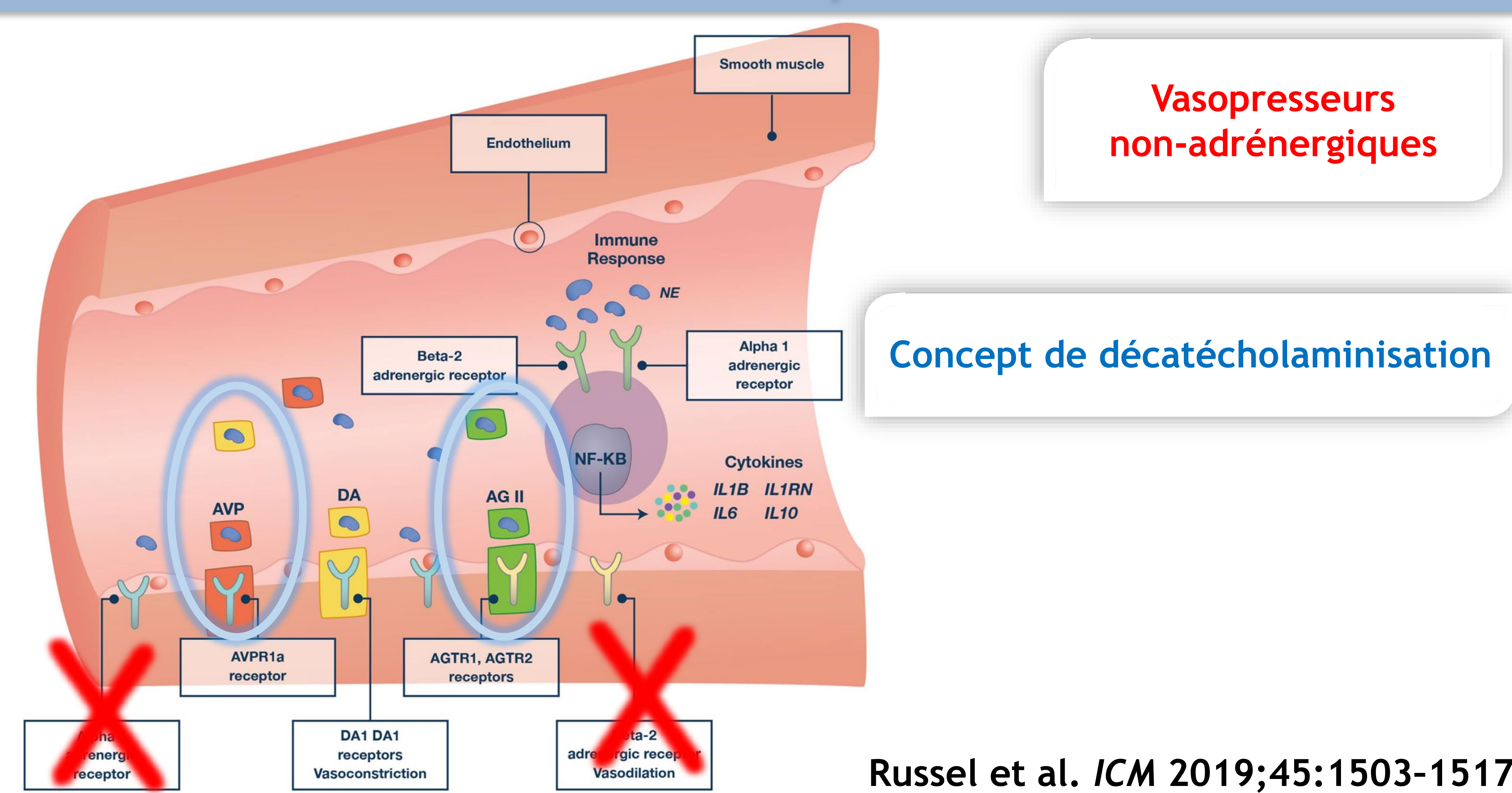
Russel et al. *ICM* 2019;45:1503-1517

Stolk et al. *AJRCCM* 2016;194:550-8

Quand considérer d'autres vasopresseurs ?



Autres vasopresseurs ?



Vasopresseurs
non-adrénergiques

Concept de décatécholaminisation

Russel et al. *ICM* 2019;45:1503-1517

Autres vasopresseurs?

2

Intensive Care Med (2021) 47:1181–1247
https://doi.org/10.1007/s00134-021-06506-y

GUIDELINES

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

Vasoactive Agent Management

Use norepinephrine as first-line vasopressor

For patients with septic shock on vasopressor

Target a MAP of 65mm Hg

Consider invasive monitoring of arterial blood pressure

If central access is not yet available

Consider initiating vasopressors peripherally*

If MAP is inadequate despite low-to-moderate-dose norepinephrine

Consider adding vasopressin

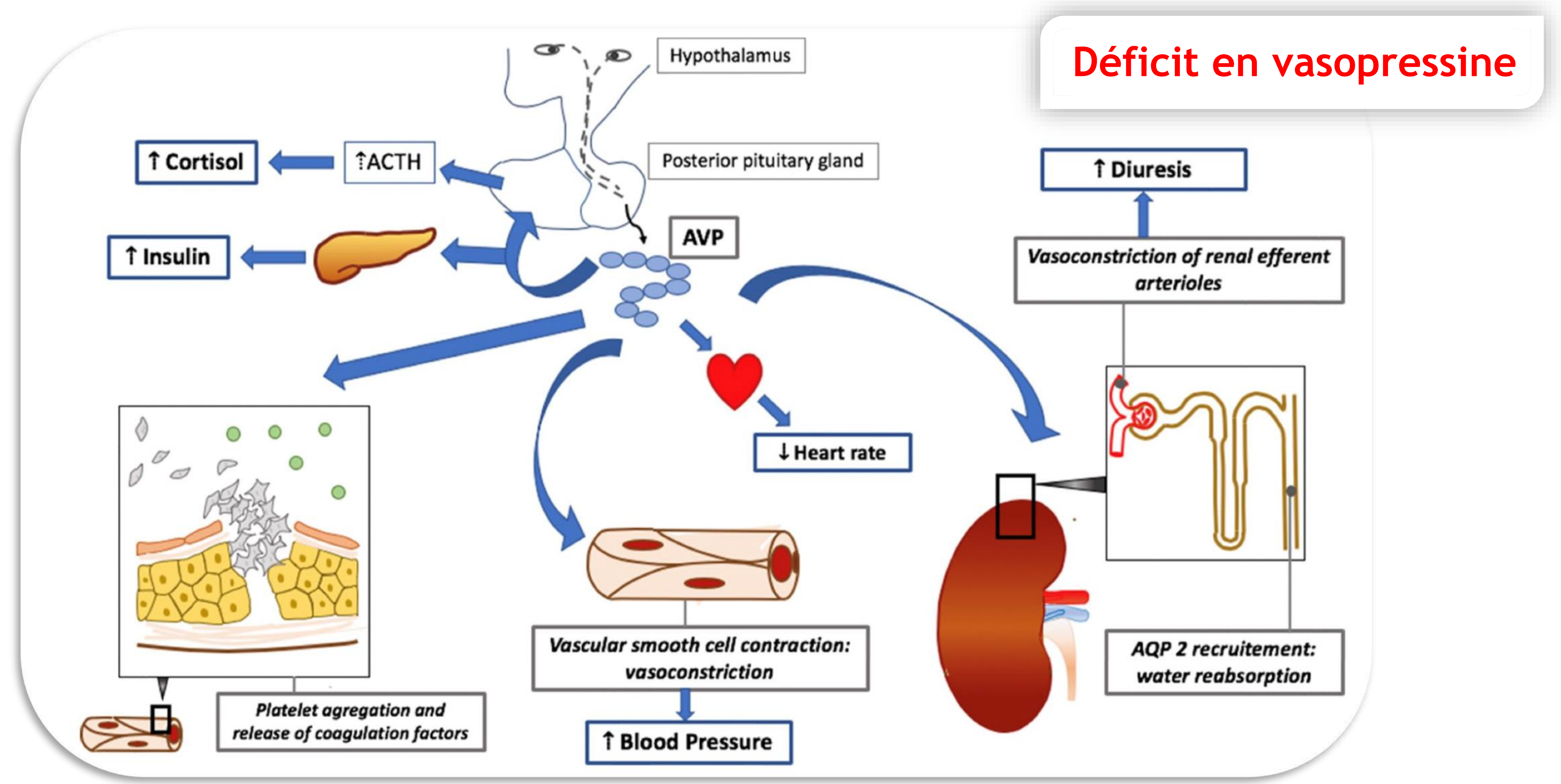
If cardiac dysfunction with persistent hypoperfusion is present despite adequate volume status and blood pressure

Consider adding dobutamine or switching to epinephrine

Strong recommendations Weak recommendations

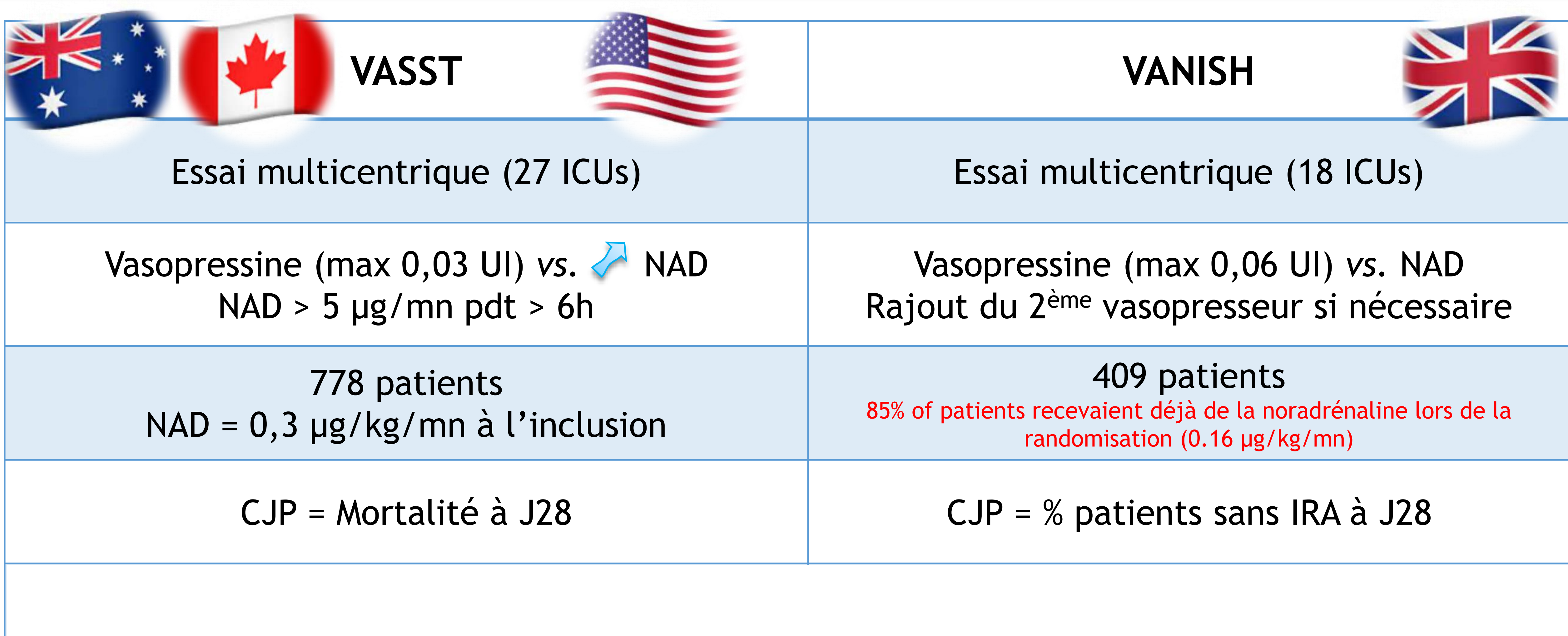
*When using vasopressors peripherally, they should be administered only for a short period of time and in a vein proximal to the antecubital fossa.

Vasopressine – *Rationnel*



Demiselle et al. *AIC* 2020;10:9

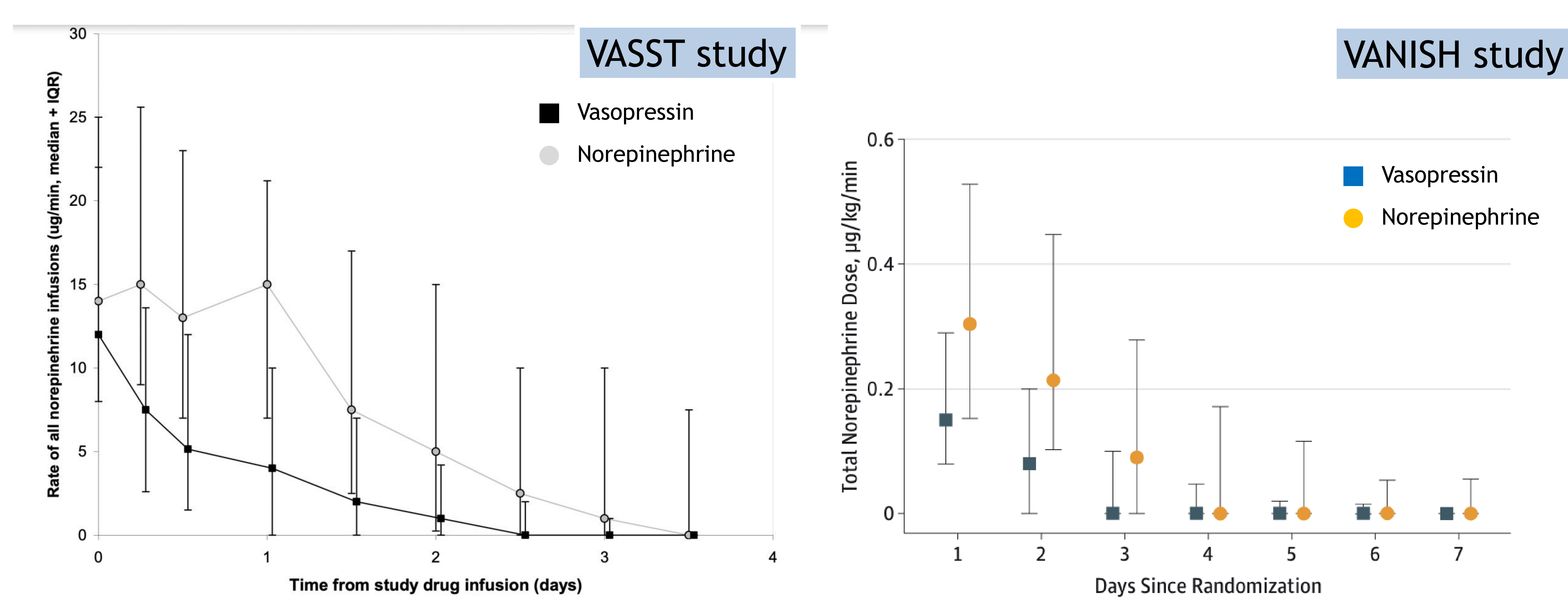
Vasopressine – *RCT*



VASST	VANISH
Essai multicentrique (27 ICUs)	Essai multicentrique (18 ICUs)
Vasopressine (max 0,03 UI) *vs.* ↗ NAD NAD > 5 µg/mn pdt > 6h	Vasopressine (max 0,06 UI) *vs.* NAD Rajout du 2ème vasopresseur si nécessaire
778 patients NAD = 0,3 µg/kg/mn à l'inclusion	409 patients 85% of patients recevaient déjà de la noradrénaline lors de la randomisation (0.16 µg/kg/mn)
CJP = Mortalité à J28	CJP = % patients sans IRA à J28

Vasopressine – *RCT*

Epargne en vasopresseurs
Sevrage plus rapide en vasopresseurs



Russell et al. *NEJM* 2008;358:877-887

Gordon et al. *JAMA* 2016;358:877-887

Vasopressine – *RCT*

VASST	VANISH
Essai multicentrique (27 ICUs)	Essai multicentrique (18 ICUs)
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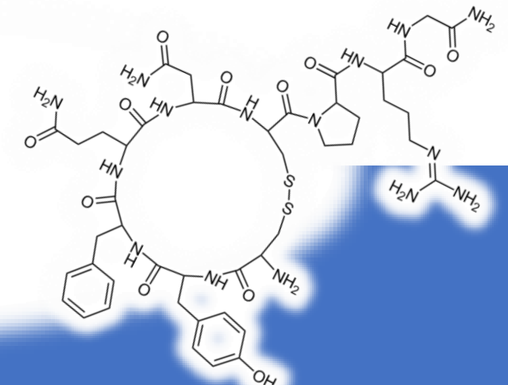
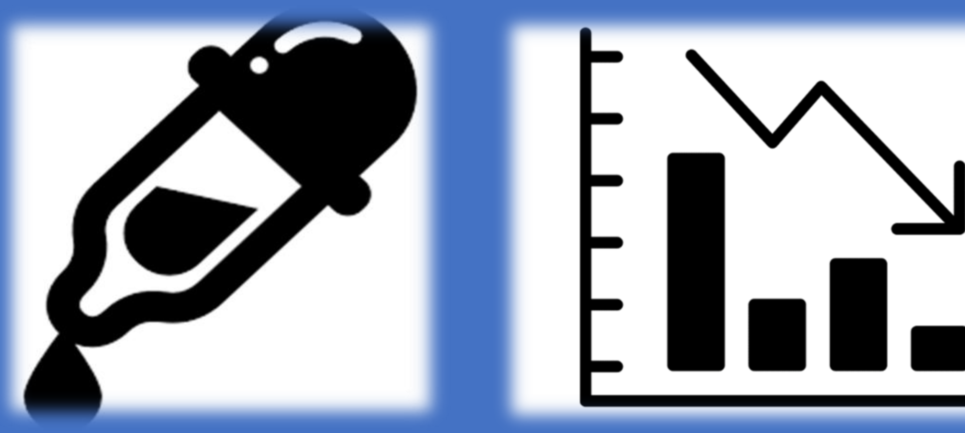
CJP = Mortalité à J28	CJP = % patients sans IRA à J28
35,4 *vs.* 39,3%, p=0,26 **Signal patients moins sévères**	**57 *vs.* 59,2% p=0,88** **Moins de recours EER**

Vasopressine – *En pratique*

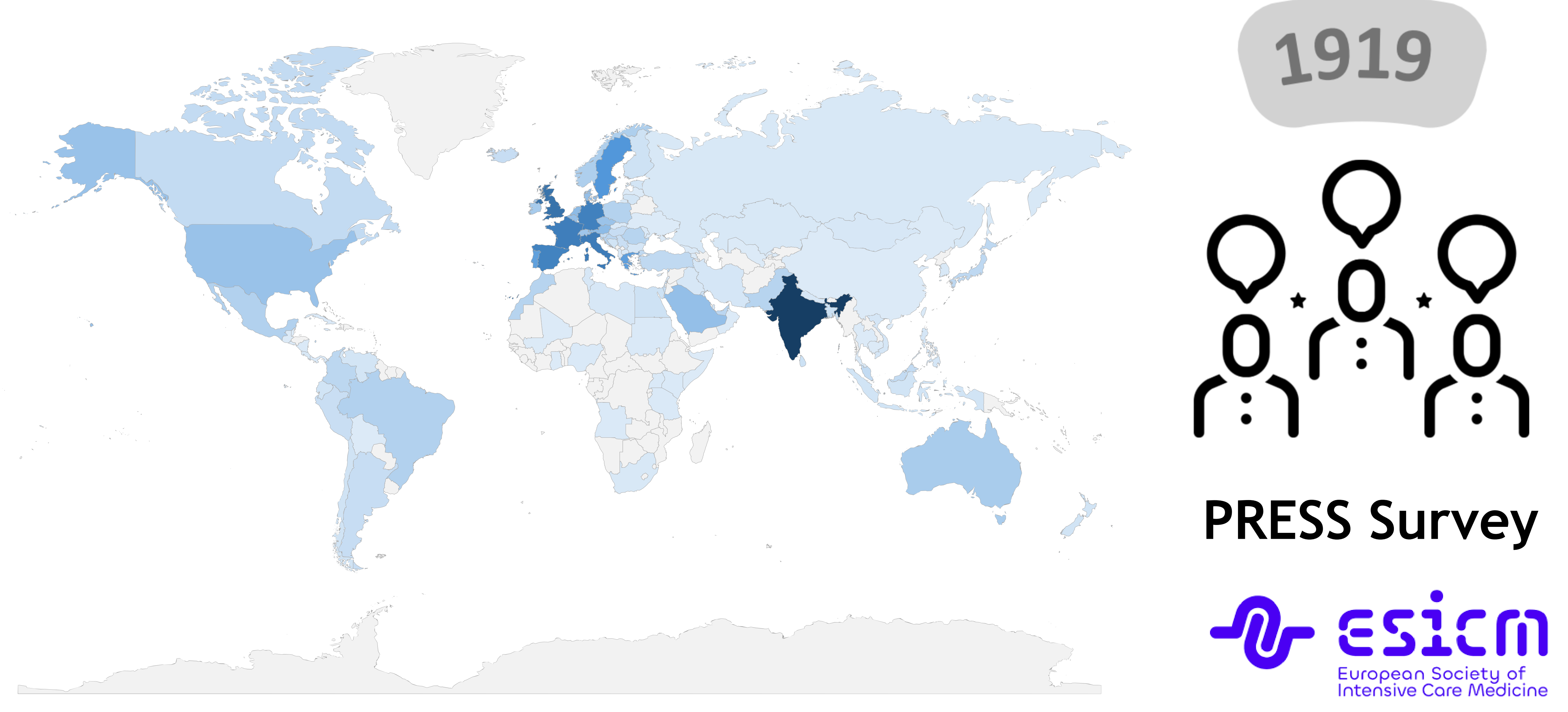
Vasopressine



Contre-indications: coronaropathies, ischémie mésentérique

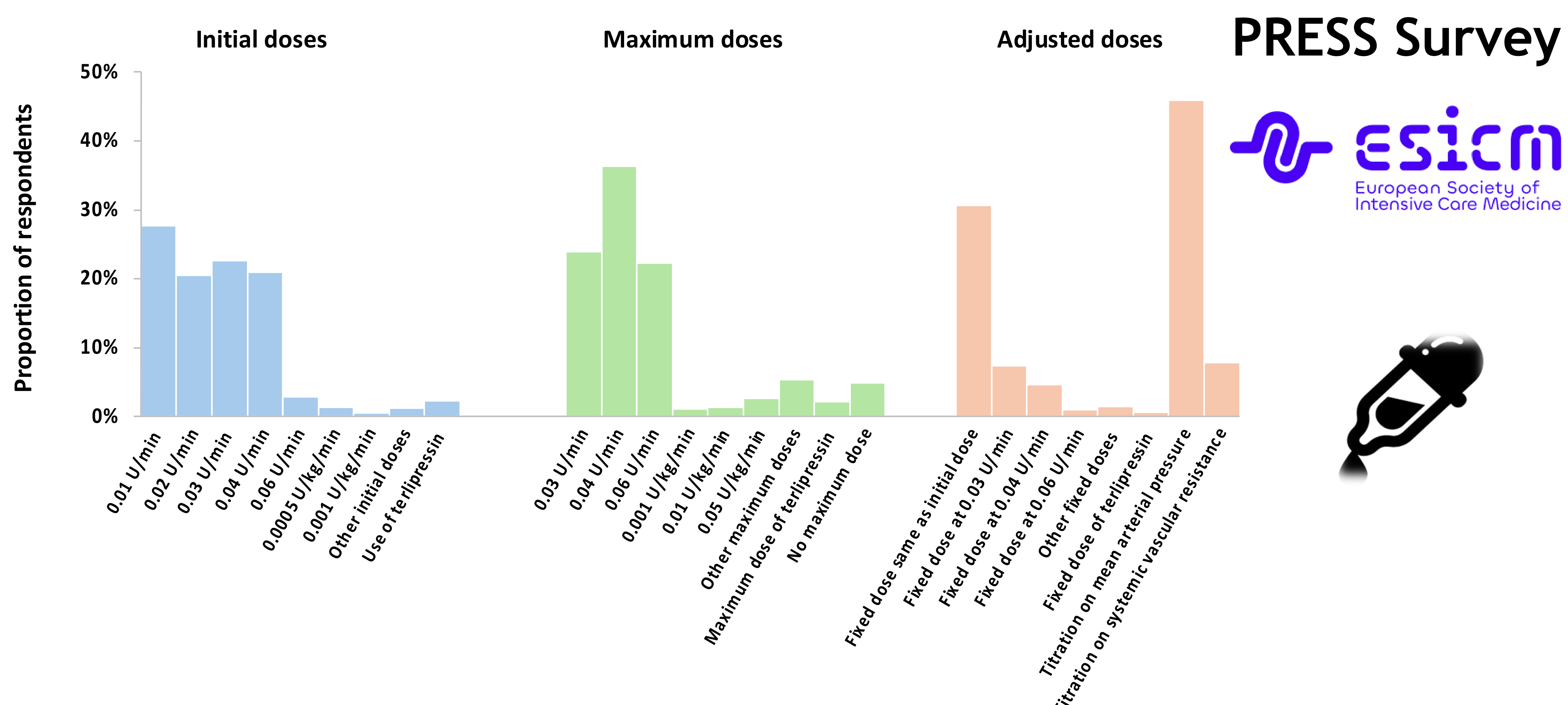


Vasopressine - *En pratique*



Jozwiak et al. Crit Care 2025 (accepted)

Vasopressine - *En pratique*



Vasopressine - *En pratique*

Effets secondaires
Variables biologiques
27%
33%
88%
PAM
RVS
31%
43%
Marqueurs hypoperfusion périphérique
46%
32%
Dose vasopresseur 1ère ligne
Diurèse

43% des répondants

Après diminution dose vasopresseur 1ère ligne sous un seuil prédéfini

89% des répondants

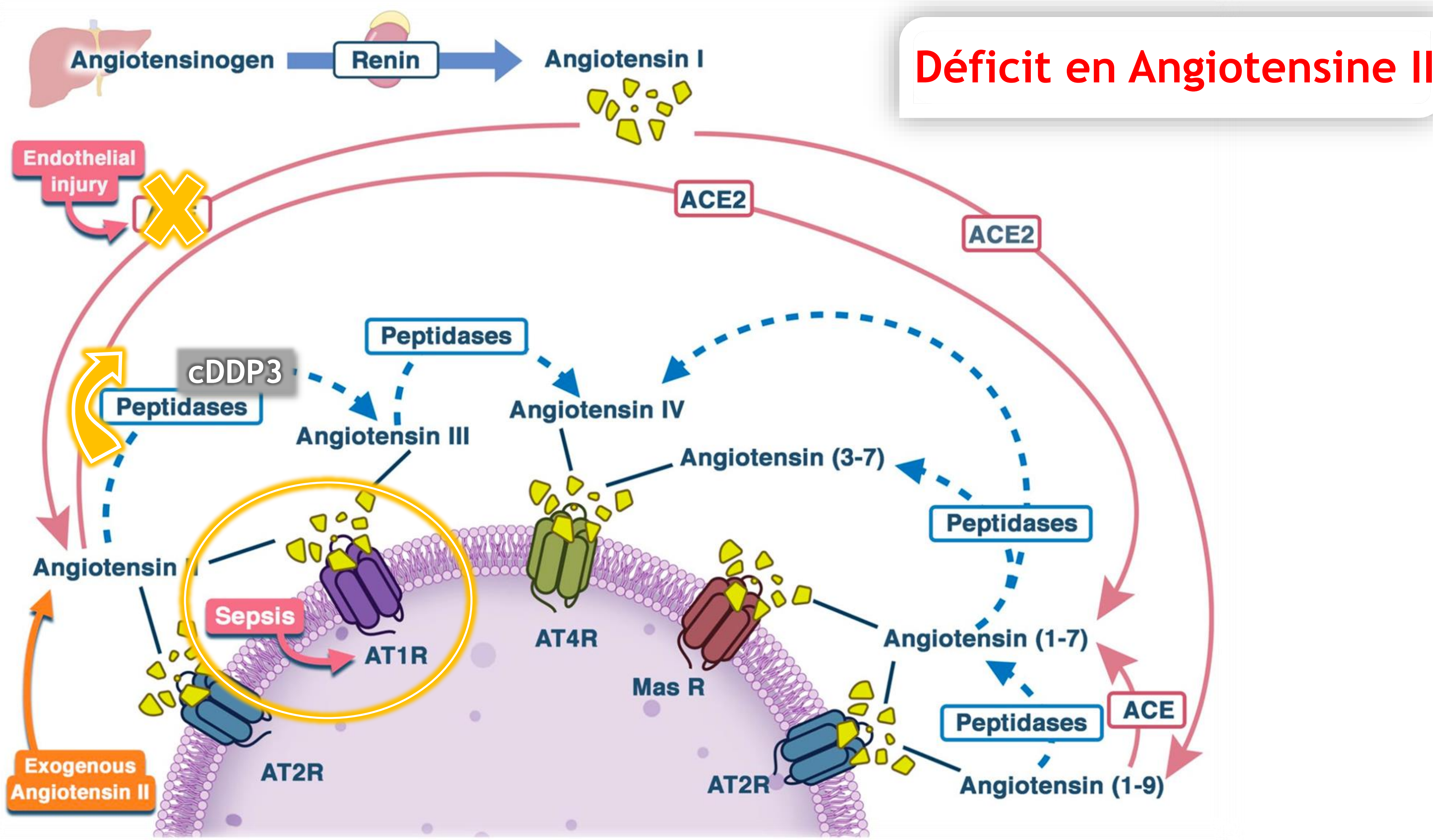
Diminution progressive dose

Jozwiak et al. Crit Care 2025 (accepted)

Angiotensine 2 – *Rationnel*

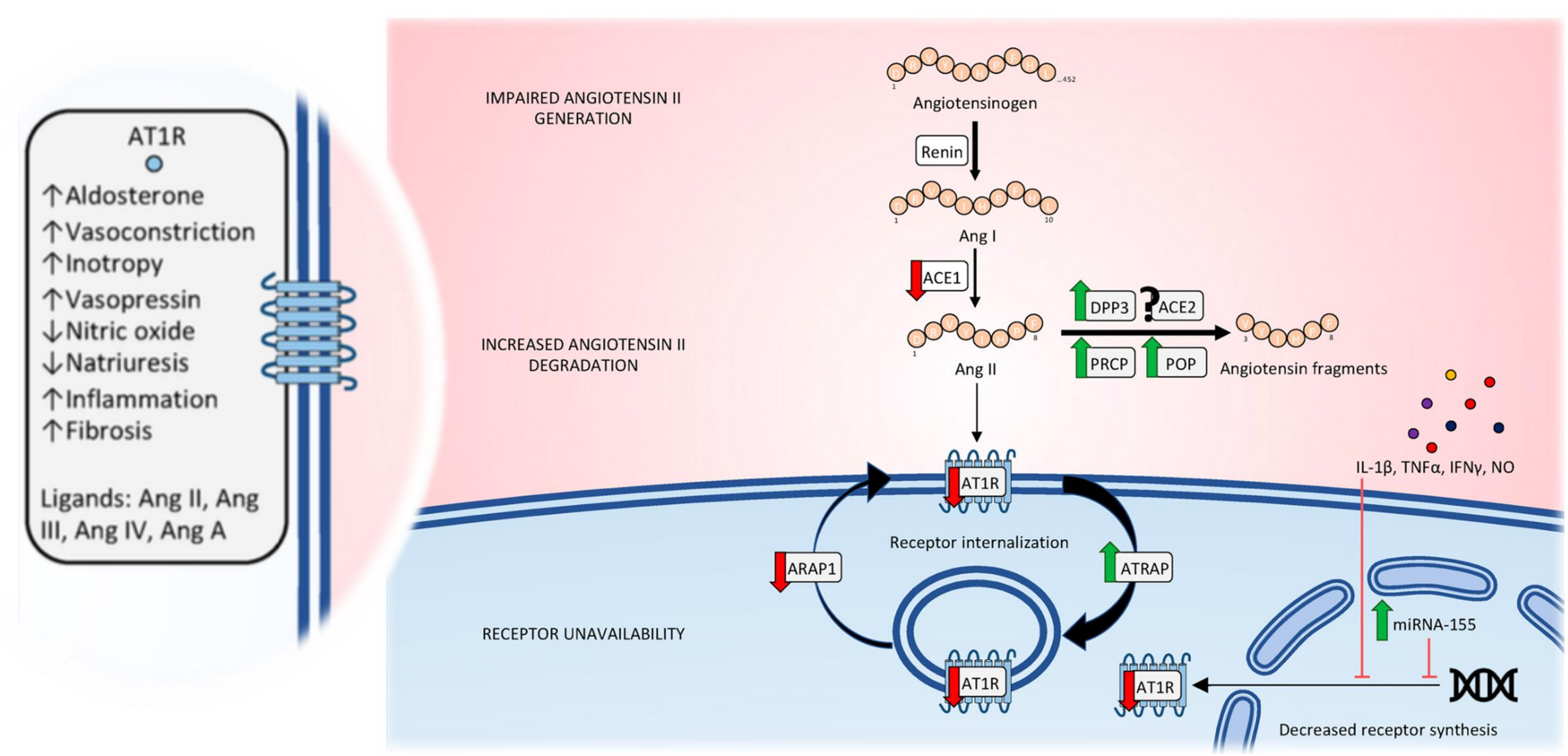
Voie canonique

Déficit en Angiotensine II



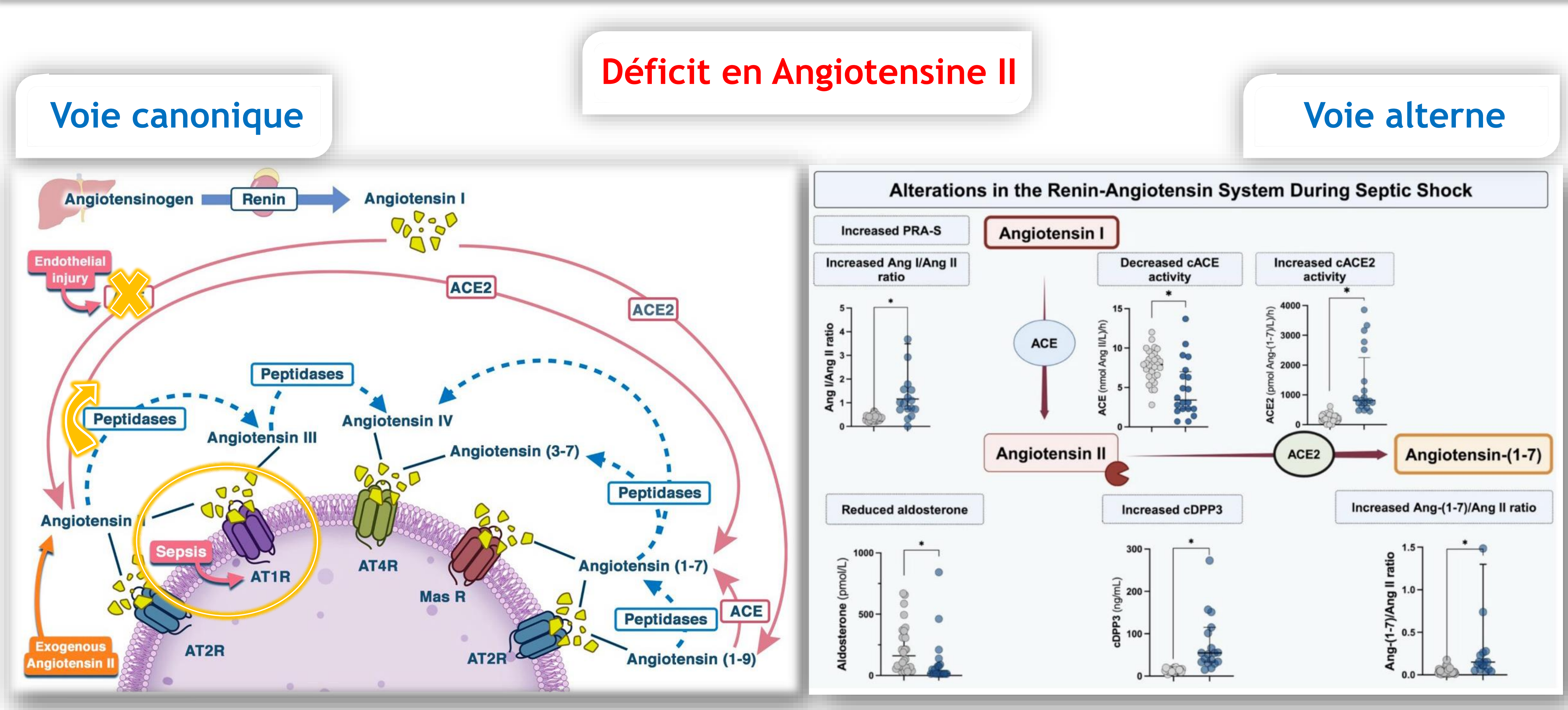
Bellomo et al. *ICM* 2024;50:279-282

Angiotensine 2 – *Rationnel*



Picod et al. *AIC* 2024;14:89

Angiotensine 2 – *Rationnel*



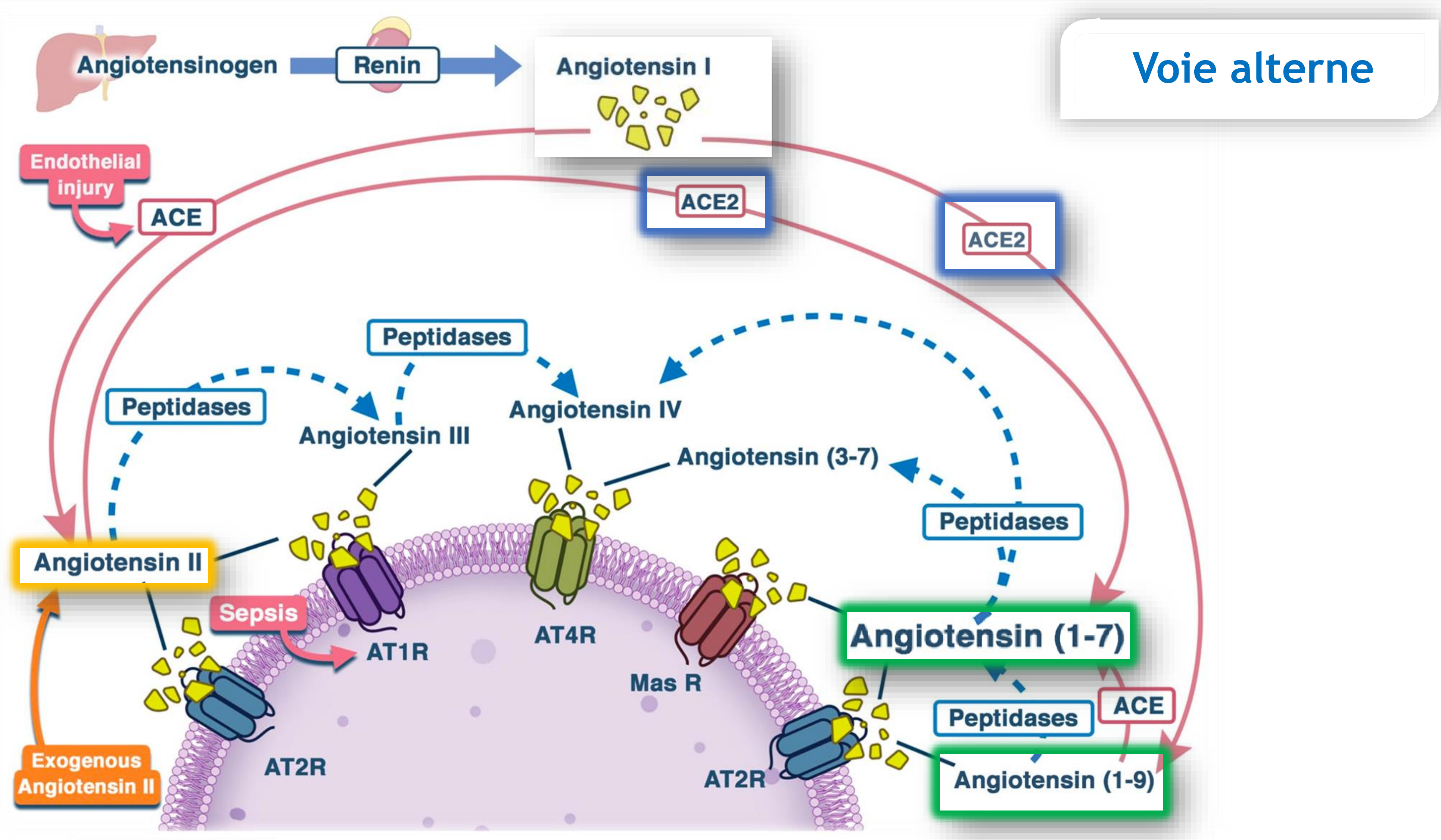
Bellomo et al. *ICM* 2024;50:279-282

Benaroua et al. *AIC* 2025;15:40

Angiotensine 2 – *Rationnel*

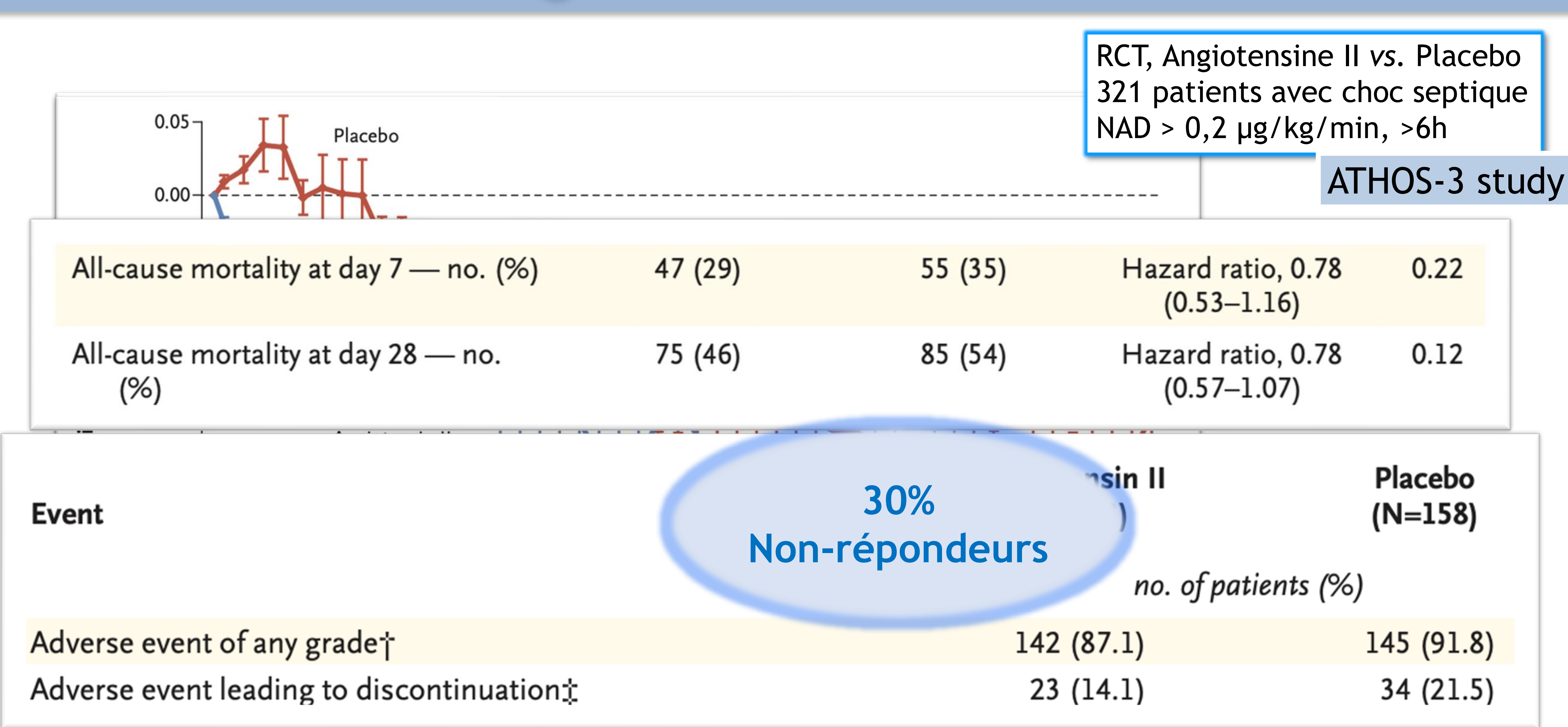
Voie canonique

Voie alterne



Bellomo et al. *ICM* 2024;50:279-282

Angiotensine 2 – *RCT*



All-cause mortality at day 7 — no. (%)	47 (29)	55 (35)	Hazard ratio, 0.78 (0.53–1.16)	0.22
All-cause mortality at day 28 — no. (%)	75 (46)	85 (54)	Hazard ratio, 0.78 (0.57–1.07)	0.12

Event	…nsin II	Placebo (N=158)
	no. of patients (%)	
Adverse event of any grade†	142 (87.1)	145 (91.8)
Adverse event leading to discontinuation‡	23 (14.1)	34 (21.5)

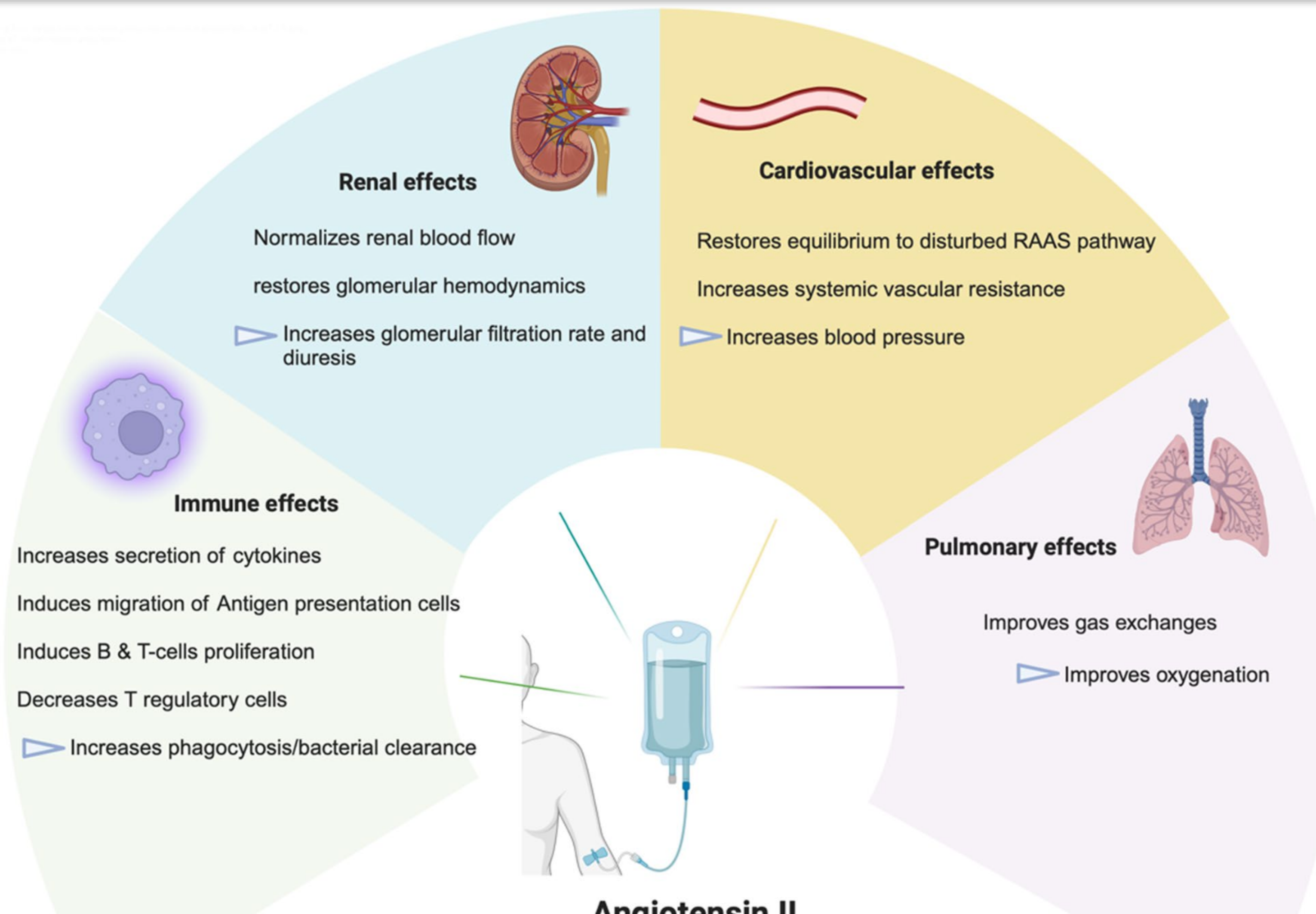
Khanna et al. *NEJM* 2017;377:419-30

Angiotensine 2 – *RCT*

Event	Angiotensin II (N=163)	Placebo (N=158)
	no. of patients (%)	
Adver		(91.8)
Adver		(21.5)
Cardiac disorder	27 (16.6)	32 (20.3)
Vascular disorder	17 (10.4)	15 (9.5)
Hypotension	5 (3.1)	3 (1.9)
Peripheral ischemia	5 (3.1)	3 (1.9)
Shock	3 (1.8)	3 (1.9)
Deep-vein thrombosis	3 (1.8)	0
Distributive shock	1 (0.6)	4 (2.5)
Tachycardia	2 (1.2)	0
Ventricular fibrillation	2 (1.2)	0
Supraventricular tachycardia	1 (0.6)	4 (2.5)
Bradycardia	1 (0.6)	2 (1.3)

Khanna et al. *NEJM* 2017;377:419-30

Angiotensine 2 – *Quels patients?*

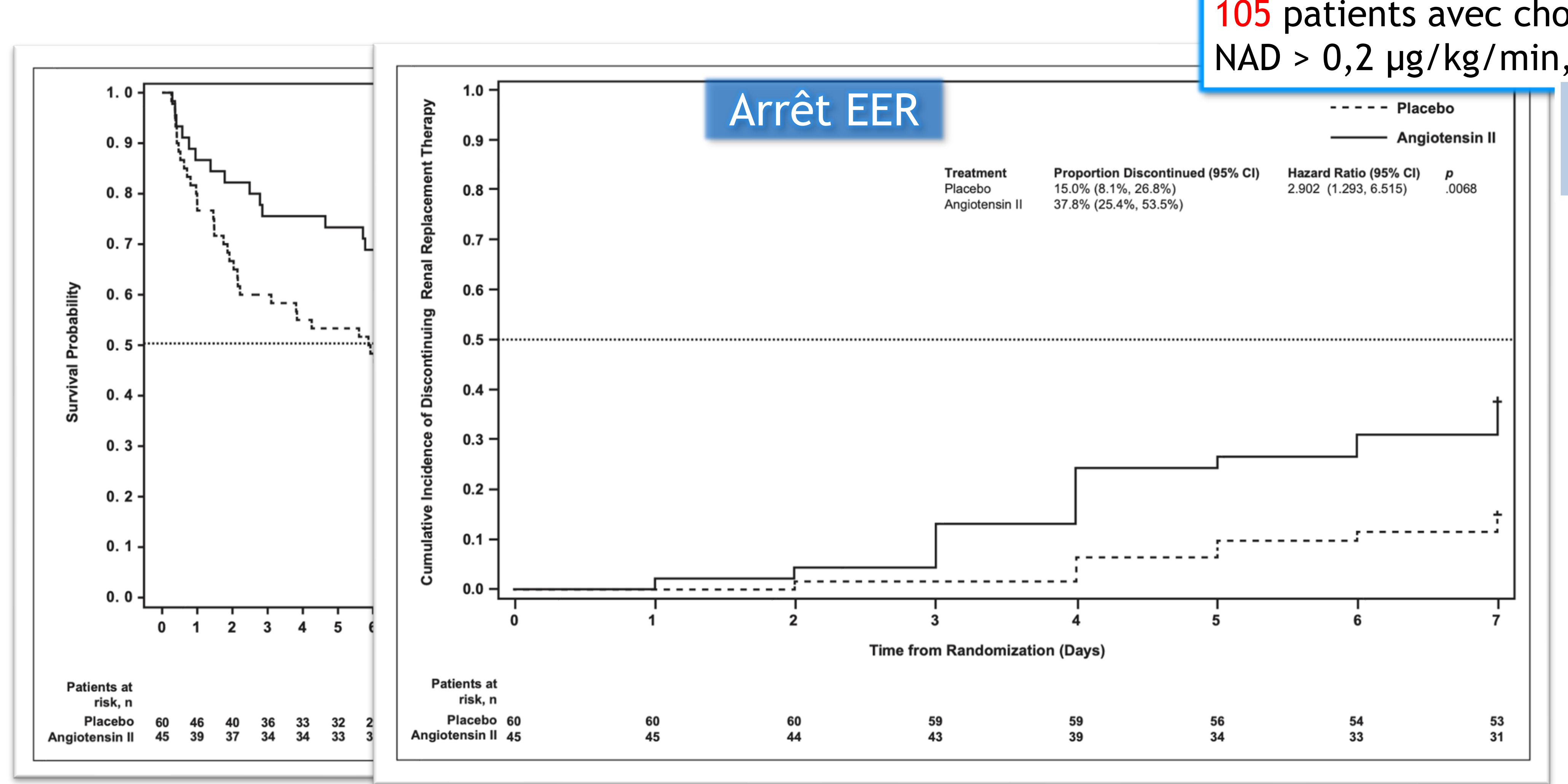


Legrand et al. *Crit Care*

Angiotensine 2 – *Quels patients?*

RCT, Angiotensine II *vs.* Placebo
105 patients avec choc septique + EER
NAD > 0,2 µg/kg/min, >6h

Analyse *post-hoc*
ATHOS-3 study



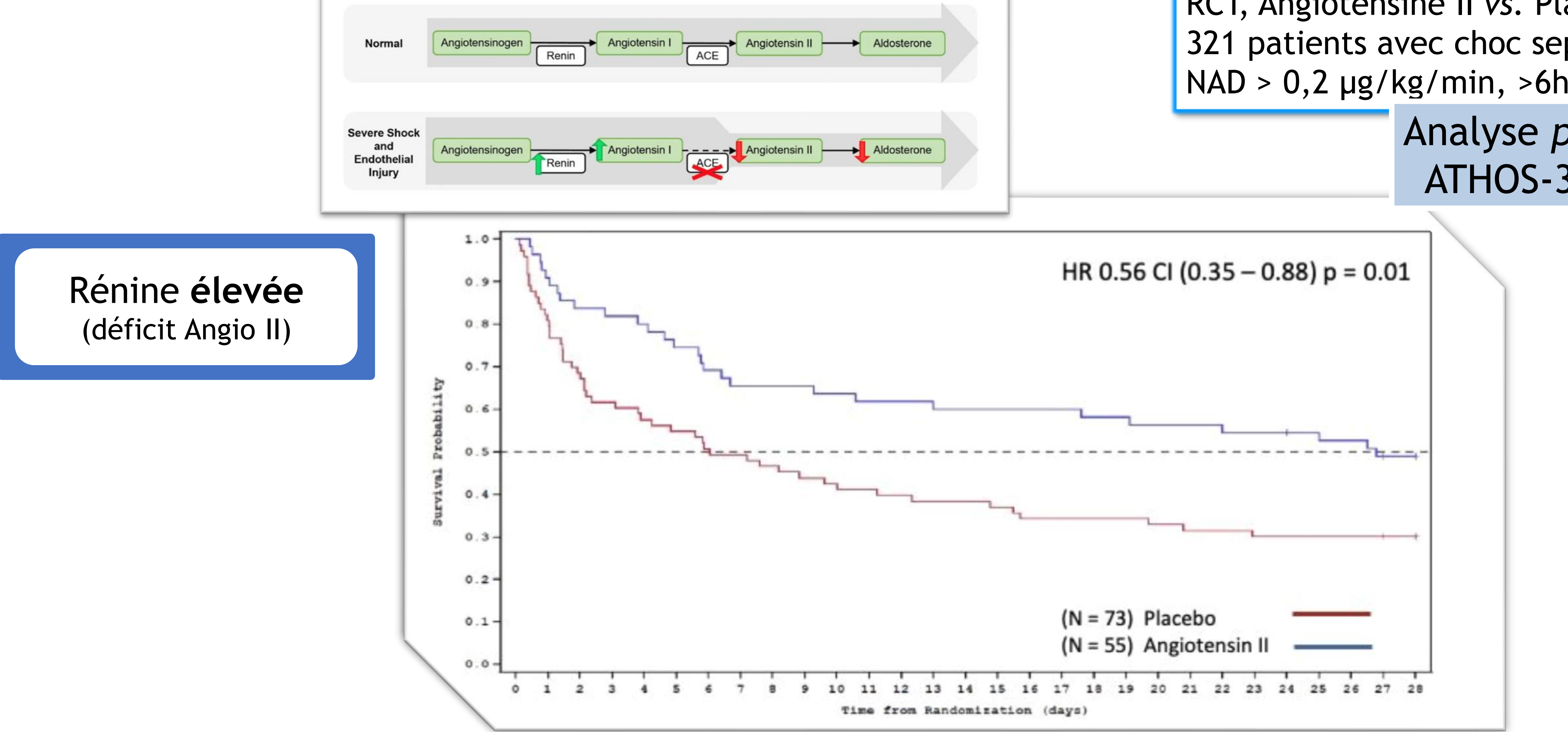
Tumlin et al. *CCM* 2018;46(6):949-957

Angiotensine 2 – *Quels patients?*

RCT, Angiotensine II *vs.* Placebo
321 patients avec choc septique
NAD > 0,2 µg/kg/min, >6h

Analyse *post-hoc*
ATHOS-3 study

Rénine **élevée**
(déficit Angio II)



Bellomo et al. *AJRCCM* 2020;202(9):1253-61

Angiotensine 2 – *En pratique*

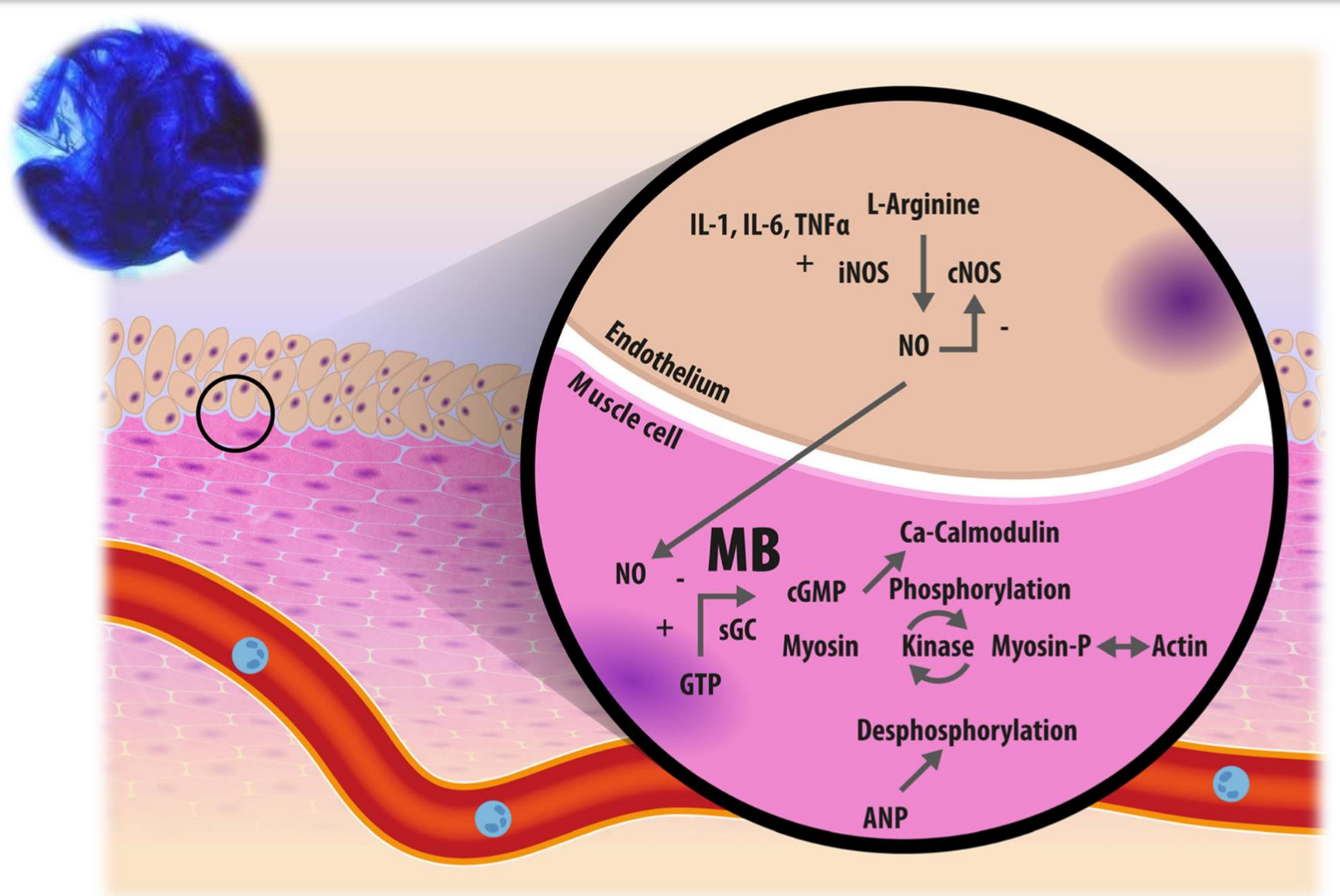
Angiotensine 2

Thérapeutique intéressante mais niveau de preuve insuffisant

Phénotype des patients encore à mieux identifier

Posologie optimale et tolérance encore à déterminer

Bleu de méthylène



Puntillo et al. *Adv Ther* 2020;37:3692-3706

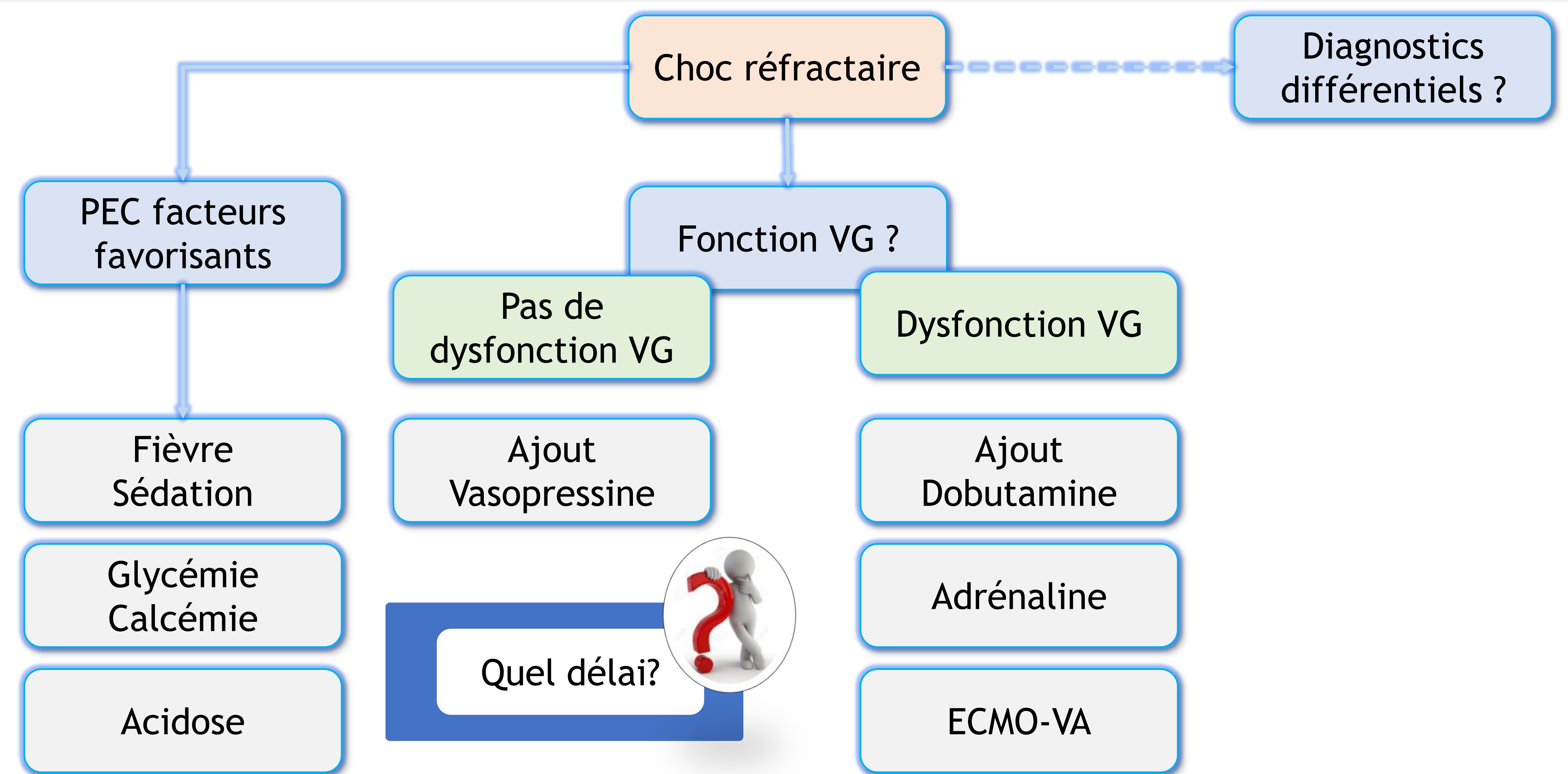
Bleu de méthylène – *En pratique*

Bleu de méthylène

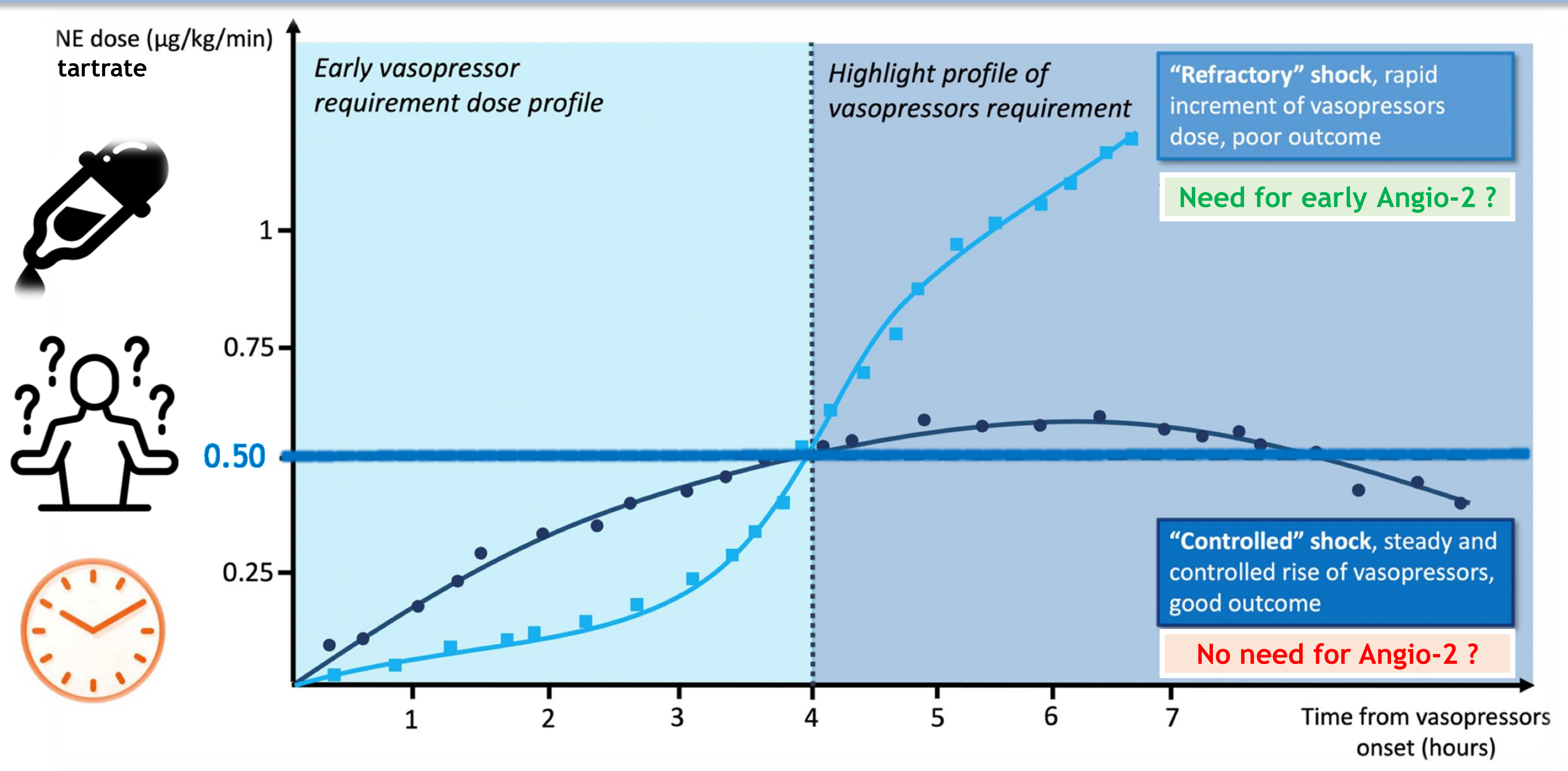
PROS	CONS
Different mechanism of action than adrenergic agents (blocks sGC activity)	Neutral effect or increased mortality in clinical trials of non-selective NO inhibitors in septic shock
Effectively increases vascular tone and arterial pressure	Other agents can also achieve this
Enables other vasopressor (norepinephrine) doses to be reduced	Lack of evidence that this is truly a beneficial effect
Easy application with a continuous infusion	No clear understanding of dosage and timing of administration in relation to norepinephrine administration
Maintains cardiac contractility	Lack of increase in cardiac output and oxygen delivery
Low-cost	Catecholamines are quite cheap too
Widely available	No clear safety profile

Arias-Ortiz et al. *Crit Care* 2024; 28:46

Comment faire face?

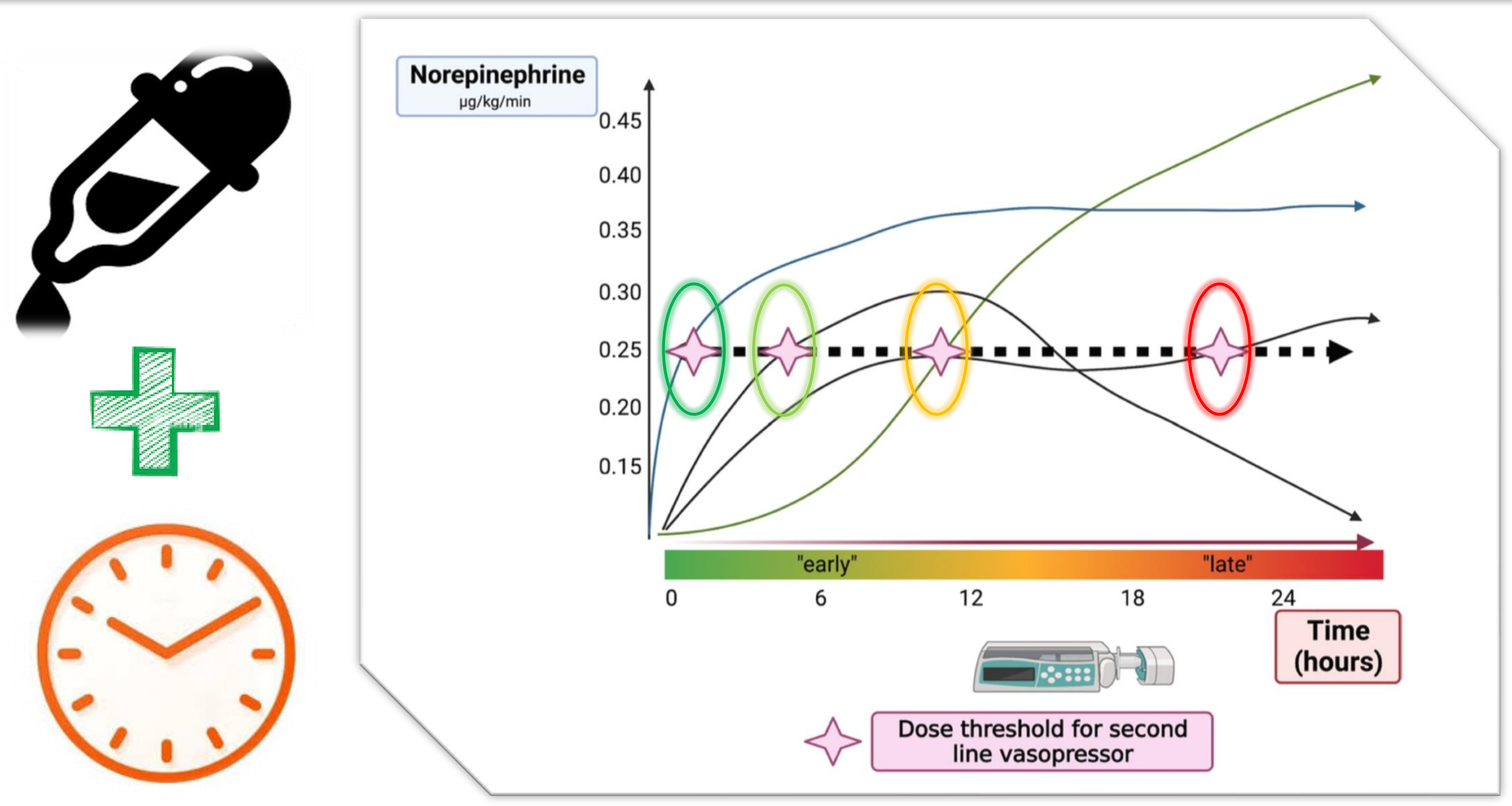


Dans quel délai ?



Gerci et al. *Crit Care* 2022;

Dans quel délai ?



Garcia et al. *Crit Care* 2023;27(1):210

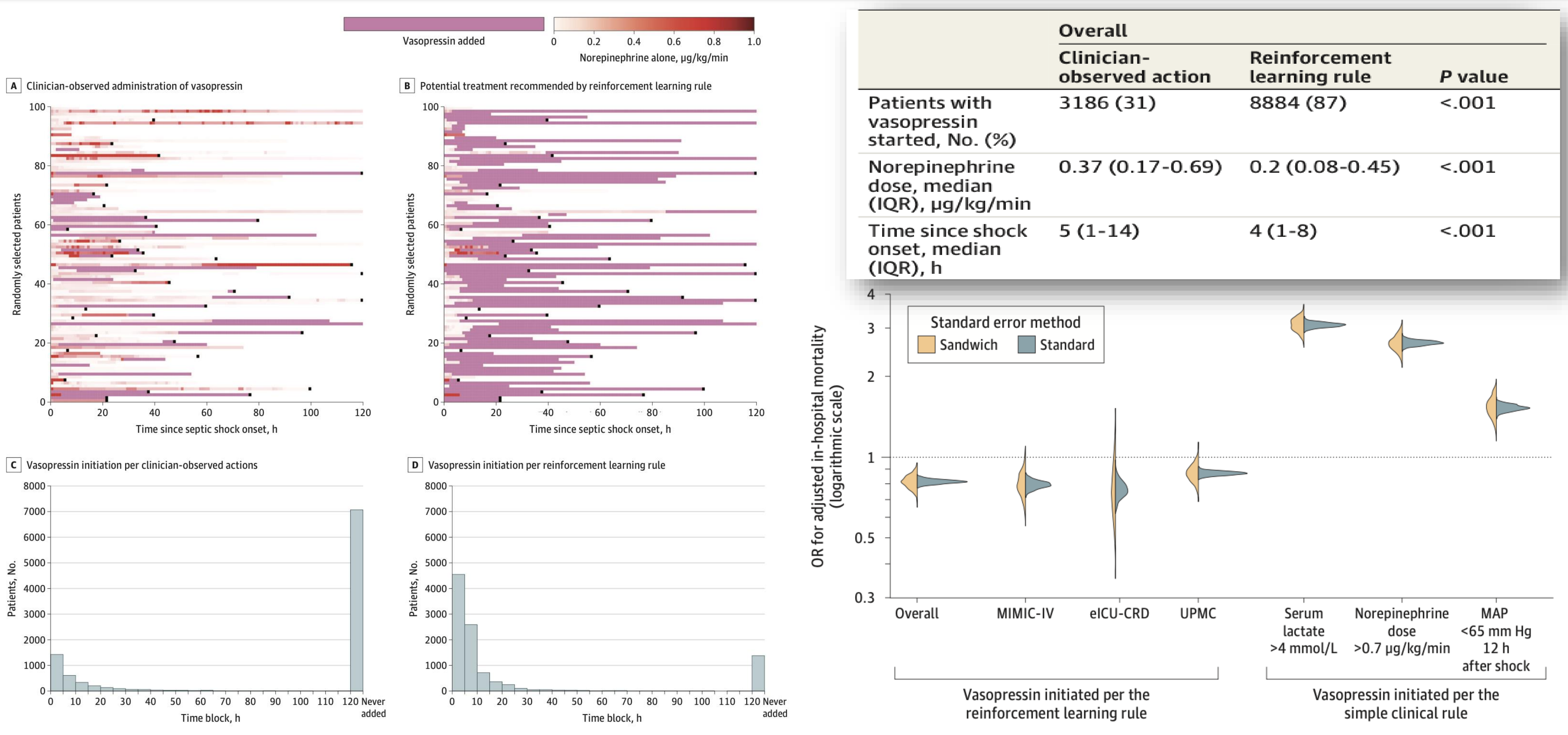
Dans quel délai ?

3

Autres vasopresseurs

Intérêt probable d'une administration **précoce** en termes de **charge catécholaminergique**

Dans quel délai ? – *Vasopressine*

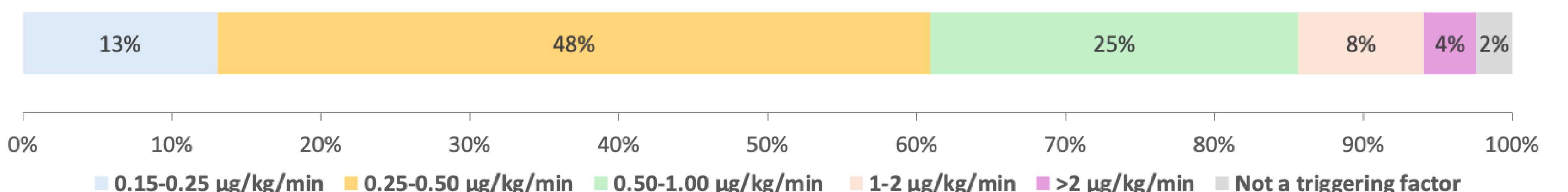


	Overall		
	Clinician-observed action	Reinforcement learning rule	*P* value
Patients with vasopressin started, No. (%)	3186 (31)	8884 (87)	<.001
Norepinephrine dose, median (IQR), µg/kg/min	0.37 (0.17-0.69)	0.2 (0.08-0.45)	<.001
Time since shock onset, median (IQR), h	5 (1-14)	4 (1-8)	<.001

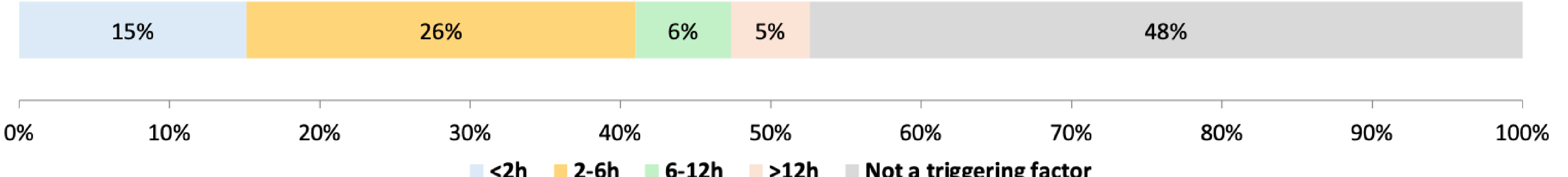
Kalimouttou et al. *JAMA* 2025;333(19):1688-1698

Vasopressine - *En pratique*

PRESS Survey

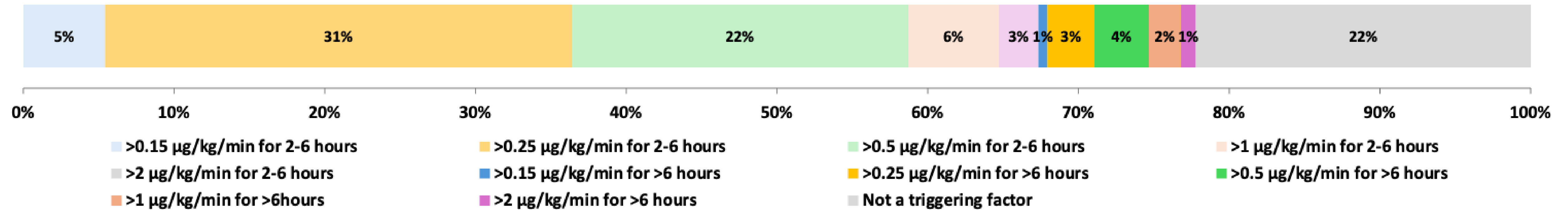


Duration of norepinephrine administration



Vasopressine – *En pratique*

PRESS Survey

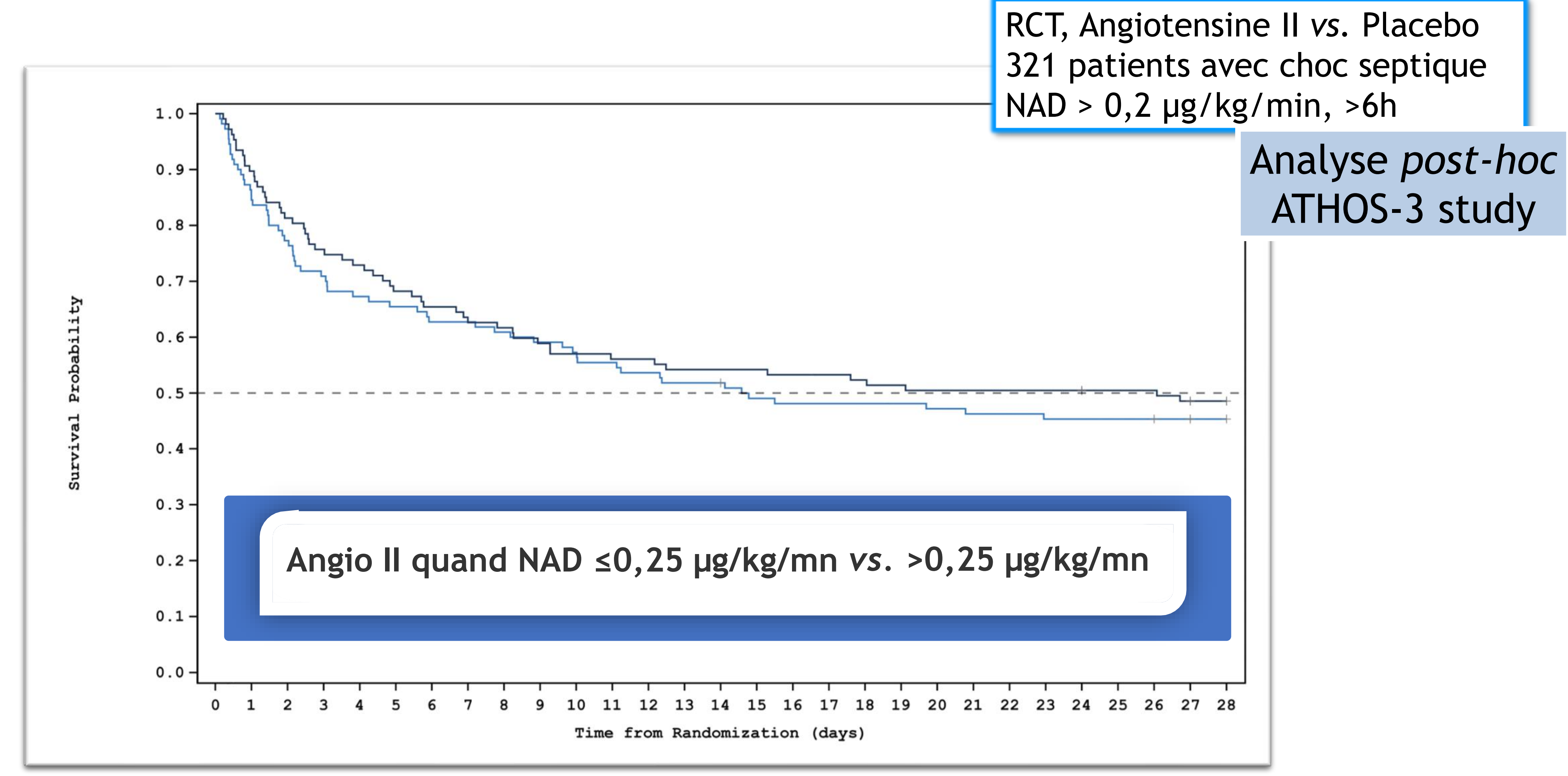


Jozwiak et al. Crit Care 2025 (accepted)

Dans quel délai ? – *Angiotensine 2*

RCT, Angiotensine II *vs.* Placebo
321 patients avec choc septique
NAD > 0,2 µg/kg/min, >6h

Analyse *post-hoc*
ATHOS-3 study



Wieruszewski et al. *Crit Care* 2023;27:175

Dans quel délai ?

RECOMMANDER
LES BONNES PRATIQUES

RECOMMANDATION

Prise en charge du sepsis du nouveau-né, de l'enfant et de l'adulte : recommandations pour un parcours de soins intégré

Validé par le Collège le 29 janvier 2025

Recommandation 22

Chez un patient avec sepsis, de l'intervention d'un professionnel de médecine d'urgence au terme de la prise en charge aiguë, nous recommandons de suivre les recommandations de la *Surviving Sepsis Campaign* en vigueur (recommandation forte, niveau modéré de certitude).

Recommandation 27

Chez un patient avec sepsis, de l'intervention d'un professionnel de médecine d'urgence au terme de la prise en charge aiguë, après l'admission en réanimation, si la pression artérielle moyenne est inférieure à 65 mmHg après initiation de noradrénaline, quelle que soit la dose, nous recommandons d'administrer de la vasopressine à une dose de 0,02 à 0,04 UI/min, en comparaison à l'augmentation des doses de noradrénaline (recommandation forte, faible niveau de preuve).

Dans quel délai ?

Severe hypovolemia

Cardiac dysfunction

Arterial stenosis

Capillary leak

Organ & tissues oedema

Low systemic vascular resistances

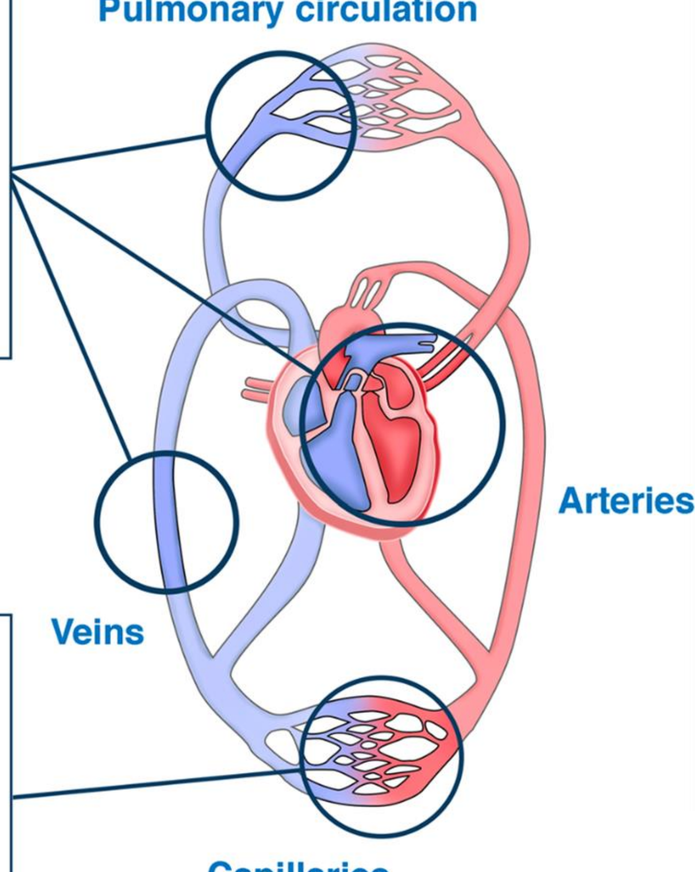
Vasopressors indications

Cardiac output

- \+ Increase venous return
- \+ Inotropic effects (e.g. B_1^+ agonists, norepinephrine)
- \+ Increase coronary perfusion pressure (diastolic pressure)
- \- Increase cardiac afterload (excessive vasoconstriction)
- \- Increase pulmonary circulation vascular resistance
- \- Coronary vasoconstriction

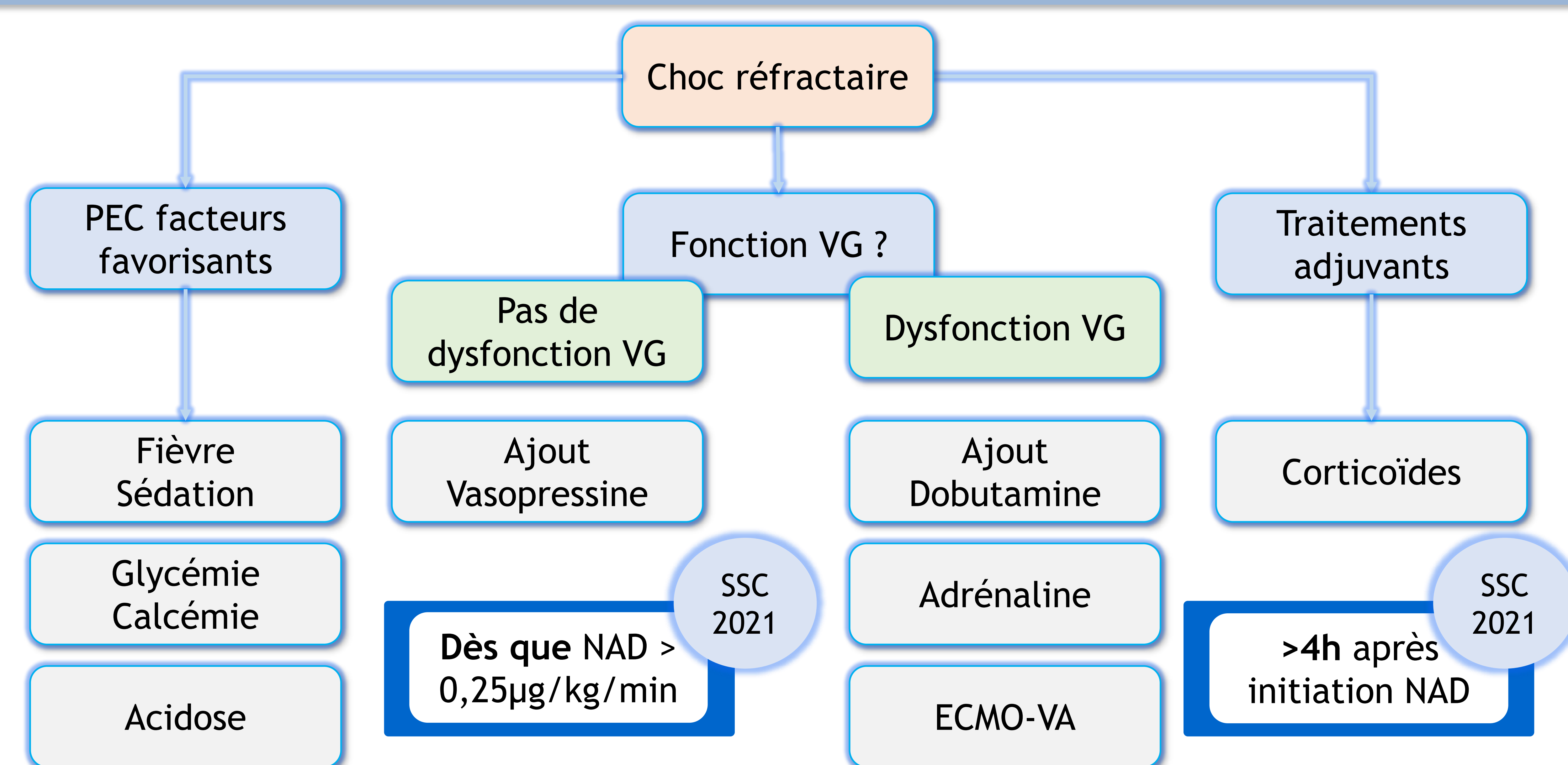
Microcirculatory and organs perfusion

- \+ Increase perfusion pressure
- \+ Increase blood flow
- \+ Decrease capillary permeability (i.e. norepinephrine)
- \- Increase critical closure pressure (excessive vasoconstriction)
- \- Decrease regional blood flow (excessive vasoconstriction, hypovolemia)

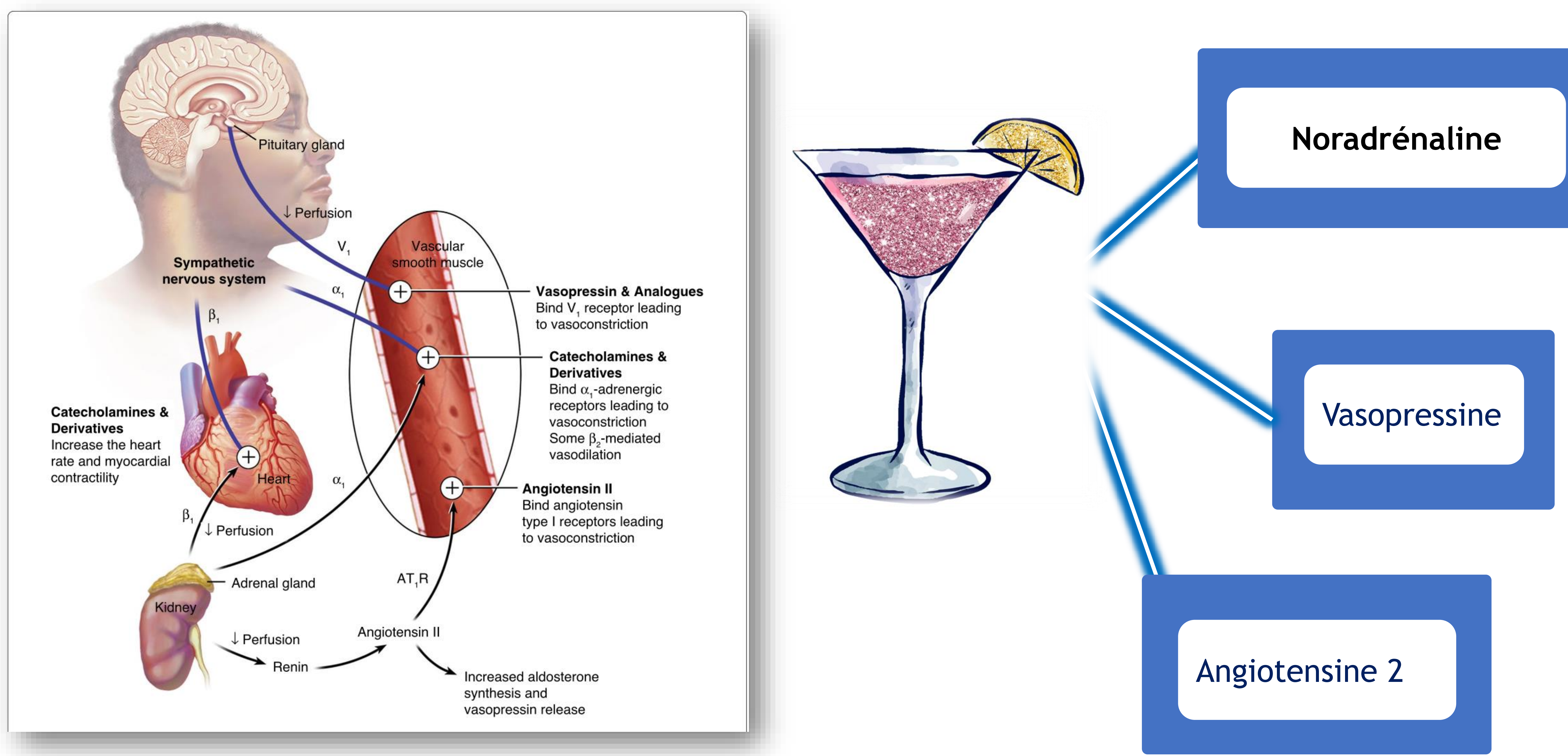


Legrand et al. *ICM* 2022;48:736-739

Comment faire face?



Le traitement vasopresseur du futur ?



Wieruszewski et Khanna *Crit Care* 2022;26:76

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