Les IEC / ARA2 à travers 2 exemples : *l'infection à COVID et la chronothérapie.*

Professor Atul PATHAK, MD, PhD.

Atul.pathak@chpg.mc

@AtulPathak31

Head of Cardiovascular Medicine

Grace Hospital

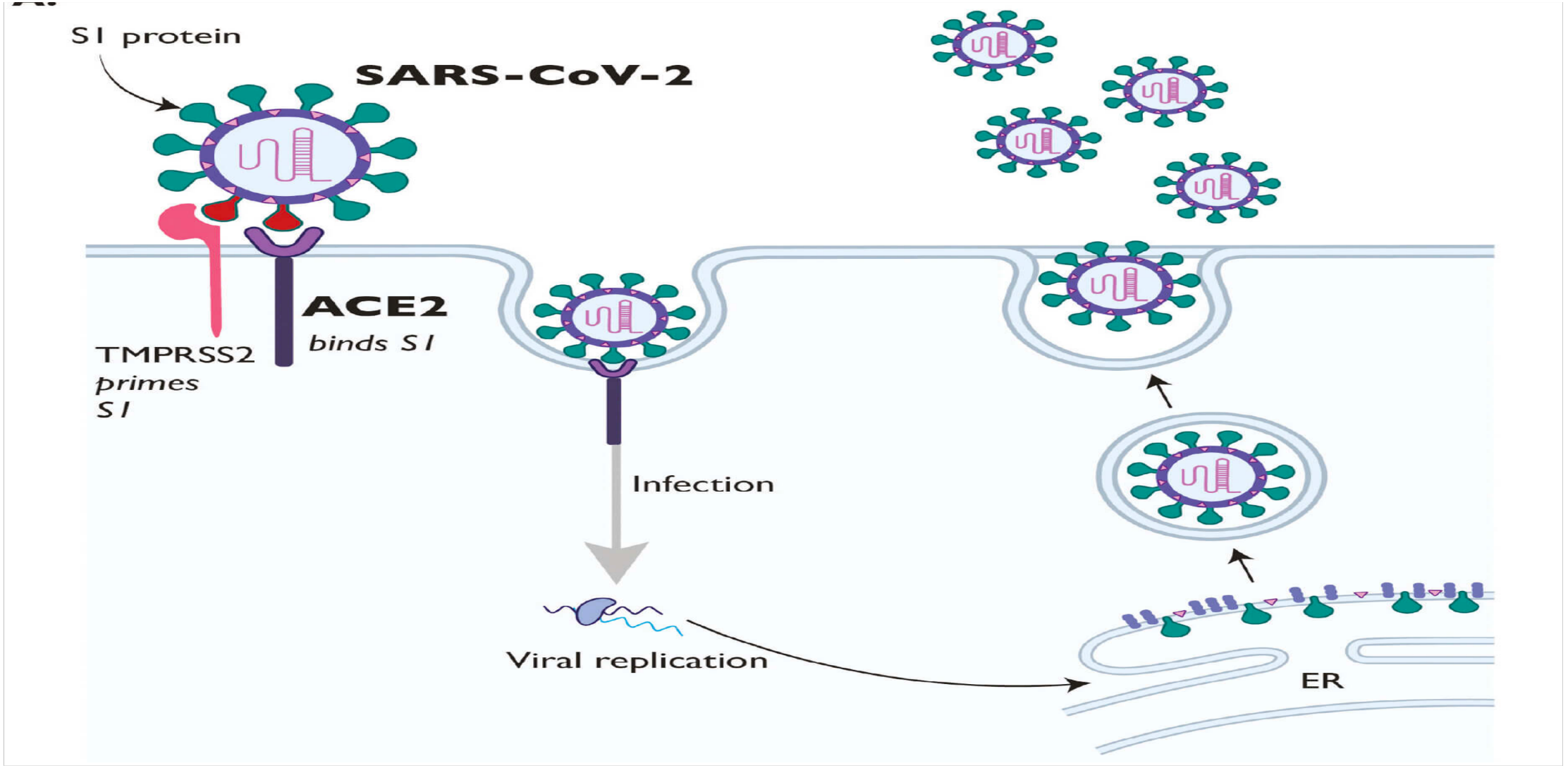
MONACO

University of Pennsylvania

PHILADELPHIE

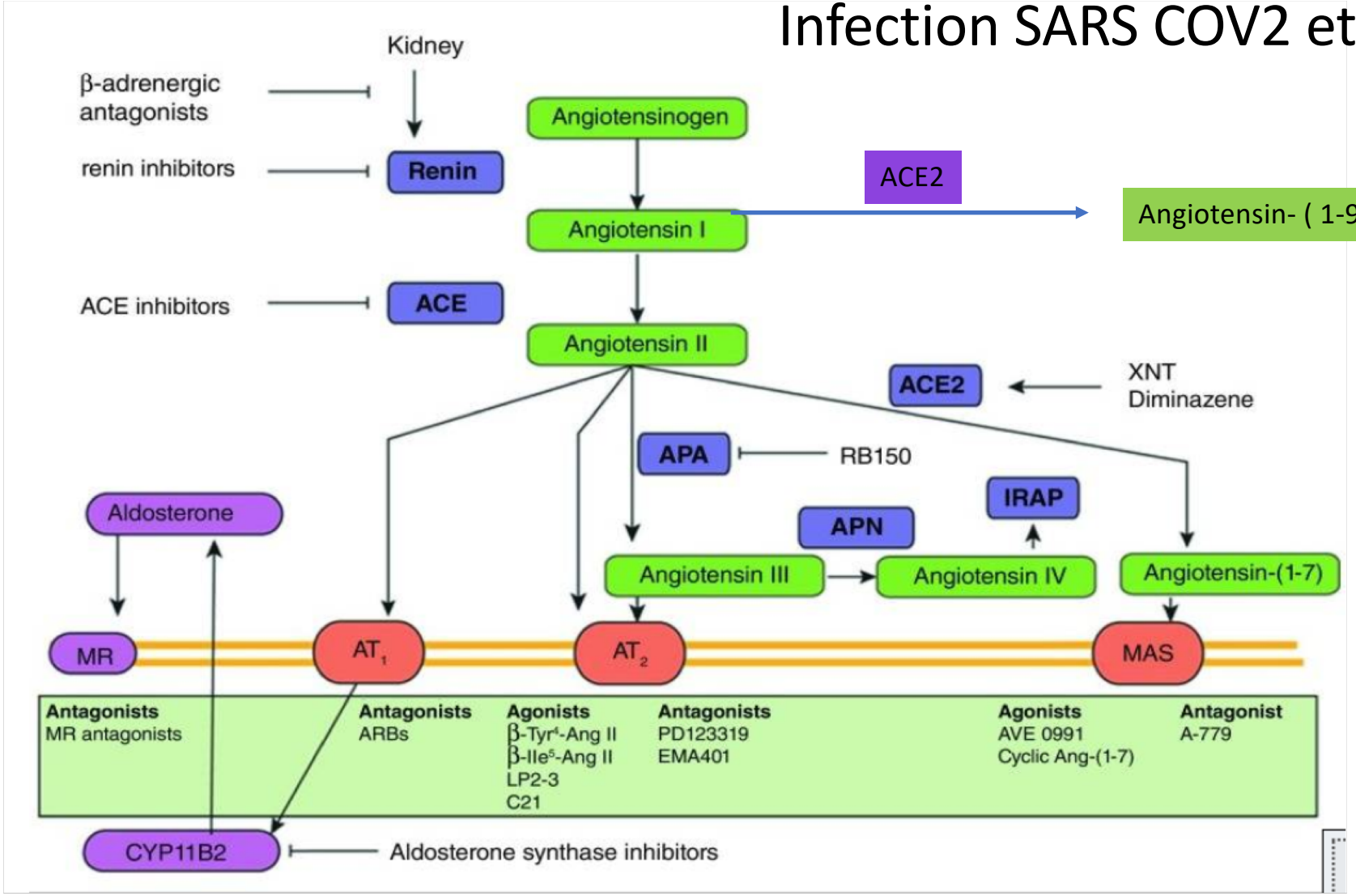
USA

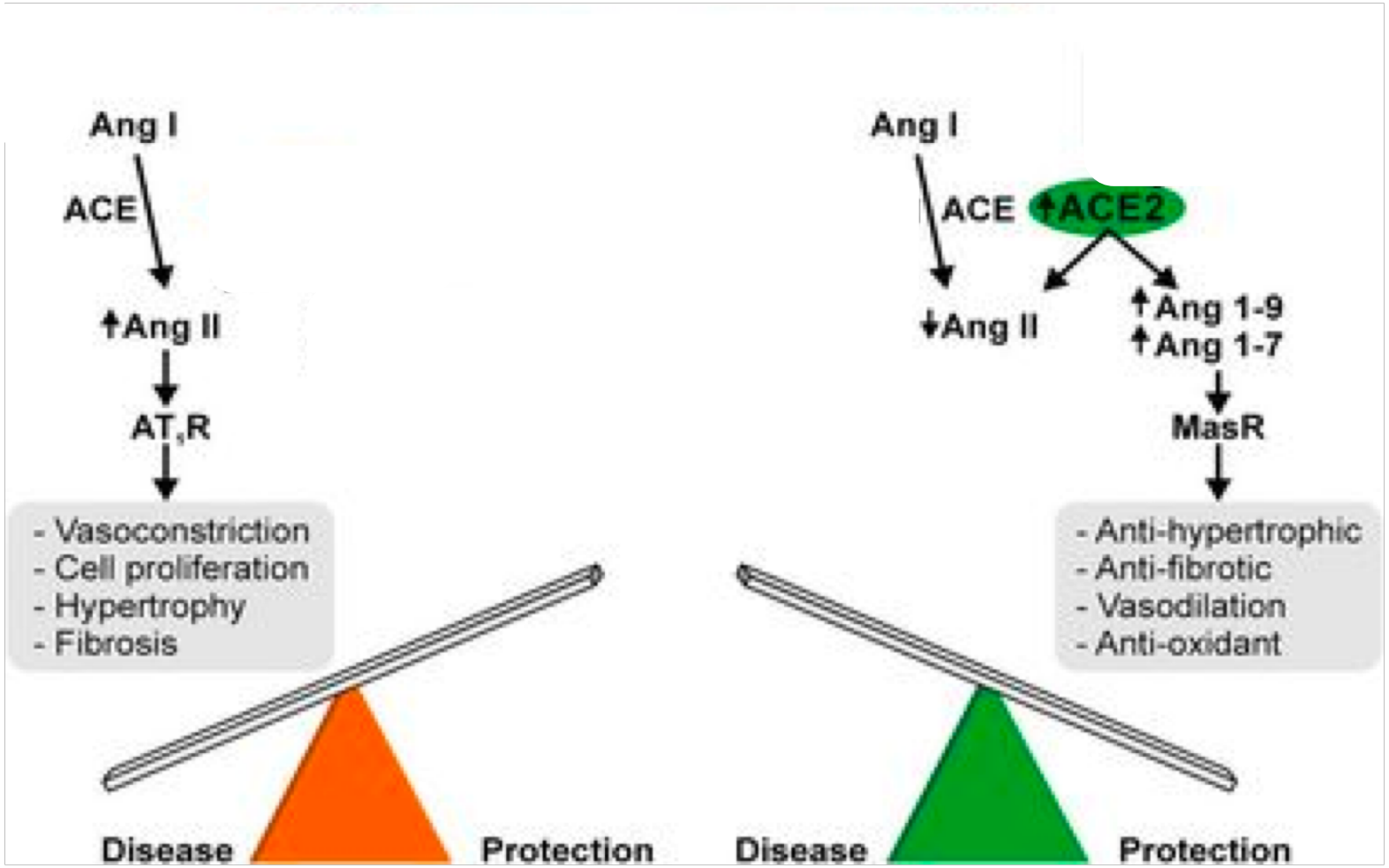
ACE2 porte d'entrée du Coronavirus



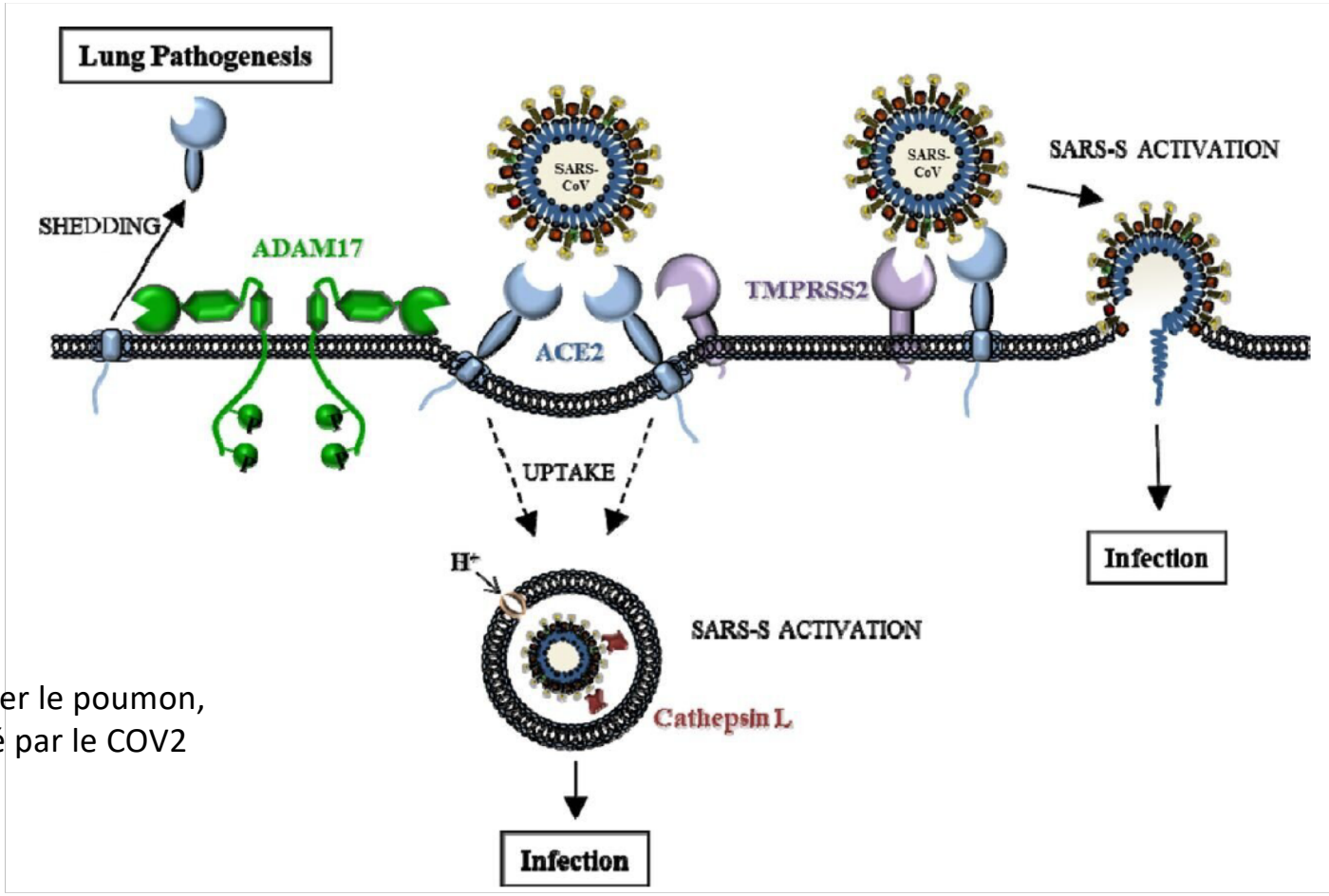
https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance

Infection SARS COV2 et SRAA




Ang I
ACE
↑Ang II
AT1R
- Vasoconstriction
- Cell proliferation
- Hypertrophy
- Fibrosis
Disease
Protection
Ang I
ACE
↑ACE2
↓Ang II
↑Ang 1-9
↑Ang 1-7
MasR
- Anti-hypertrophic
- Anti-fibrotic
- Vasodilation
- Anti-oxidant
Disease
Protection

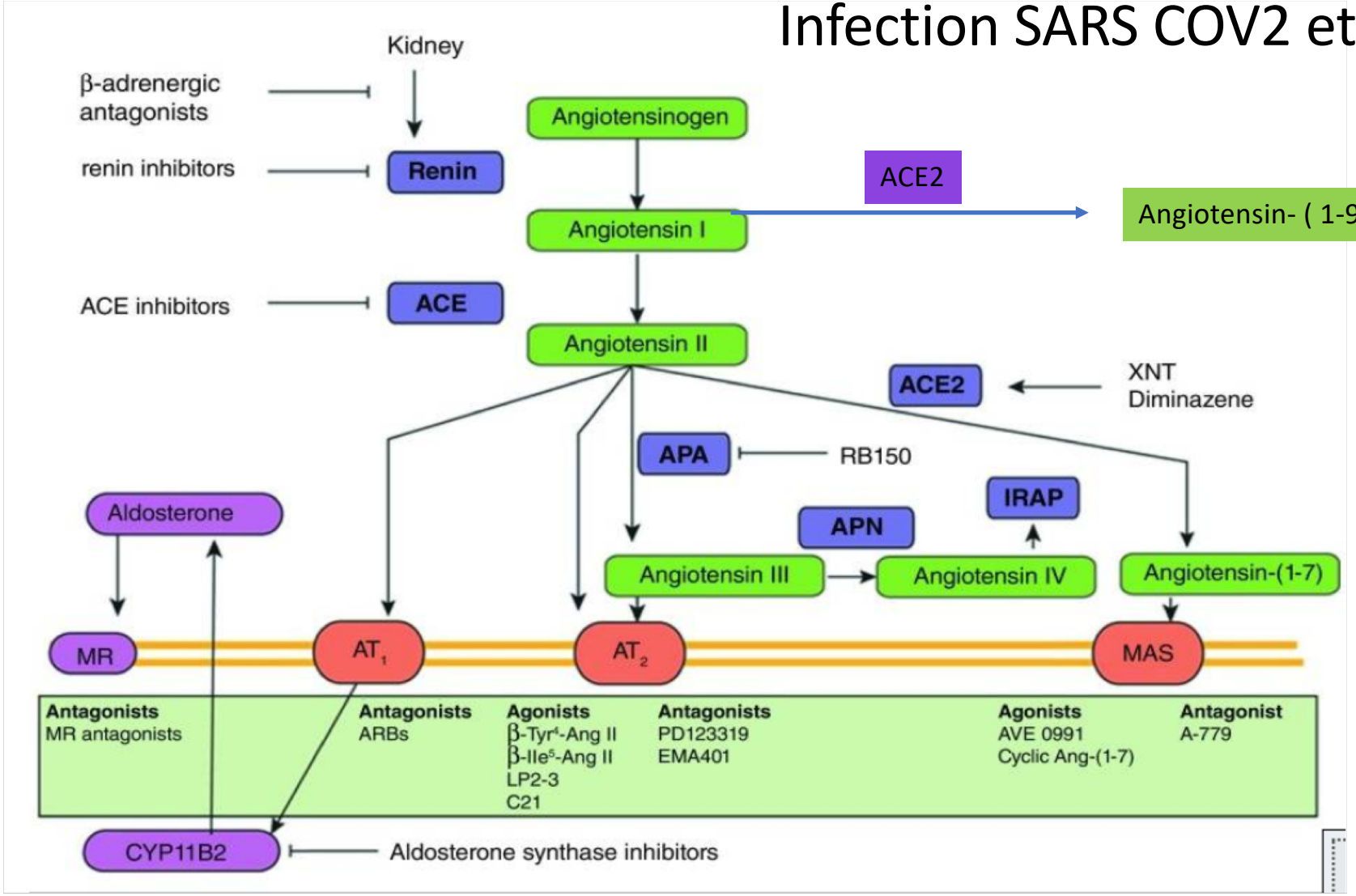
Pneumocytes et Enterocytes expliquent donc la sémiologie clinique

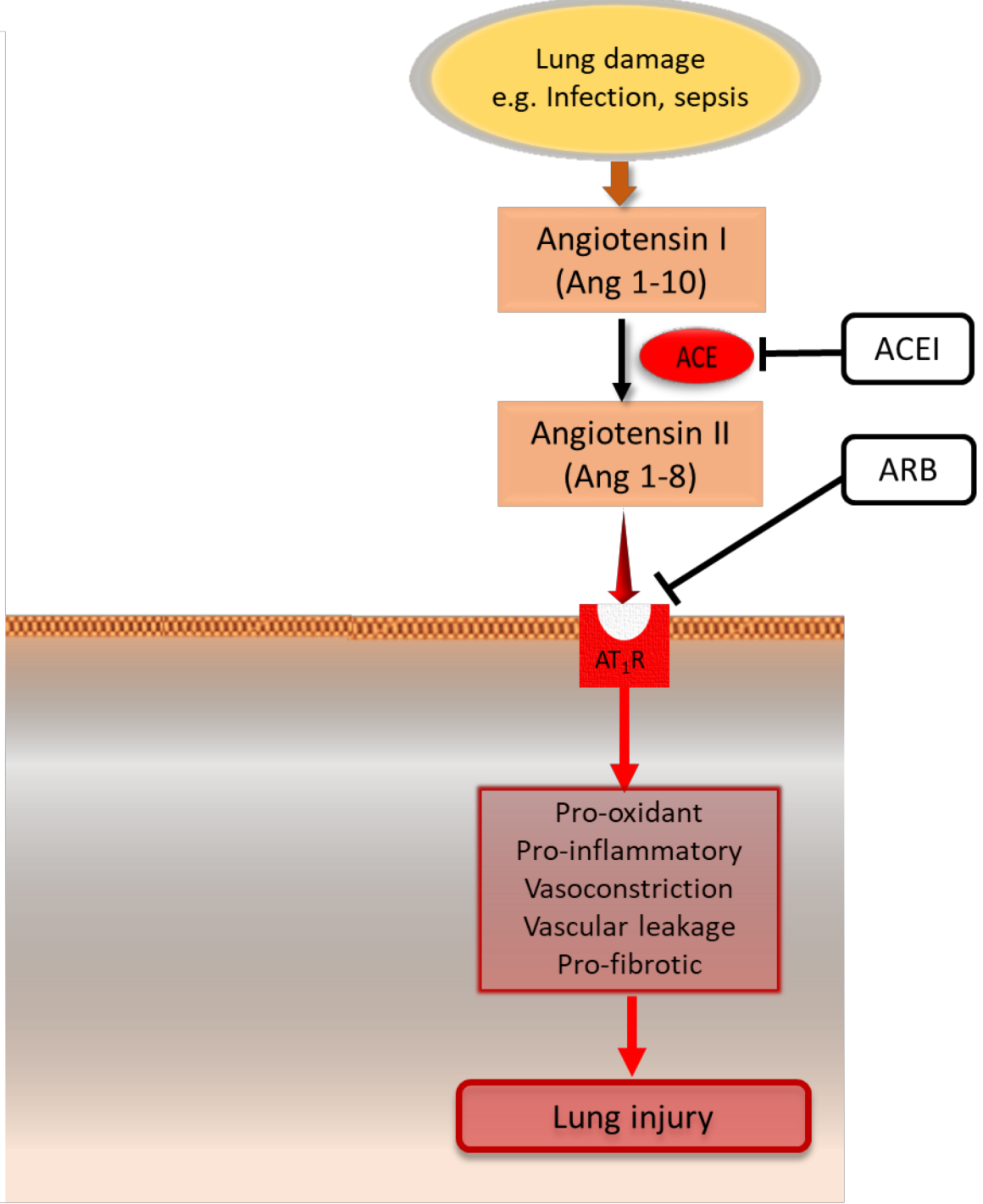


Endocytose

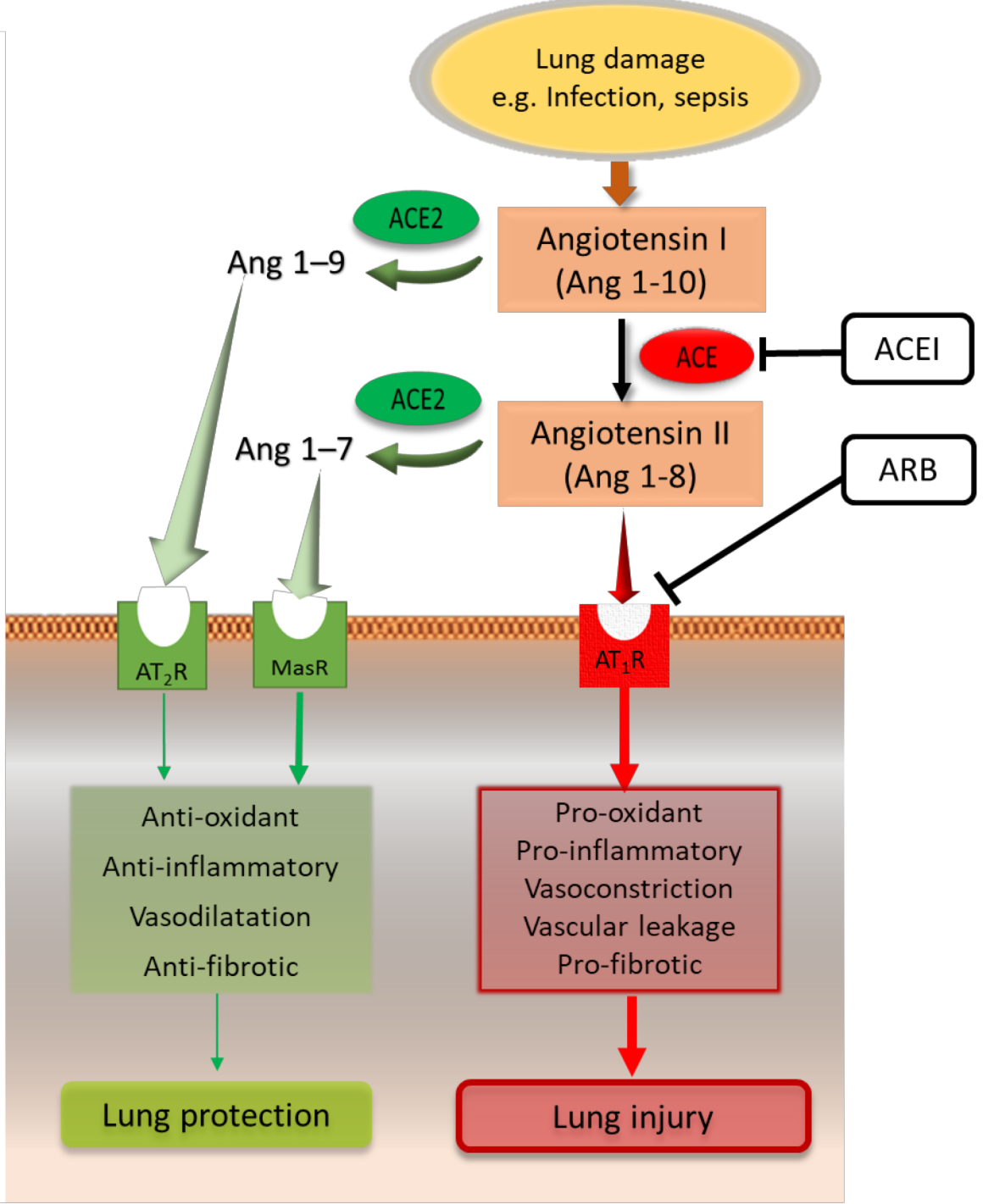
ACE2 sert à protéger le poumon,
mécanisme bloqué par le COV2

Infection SARS COV2 et SRAA

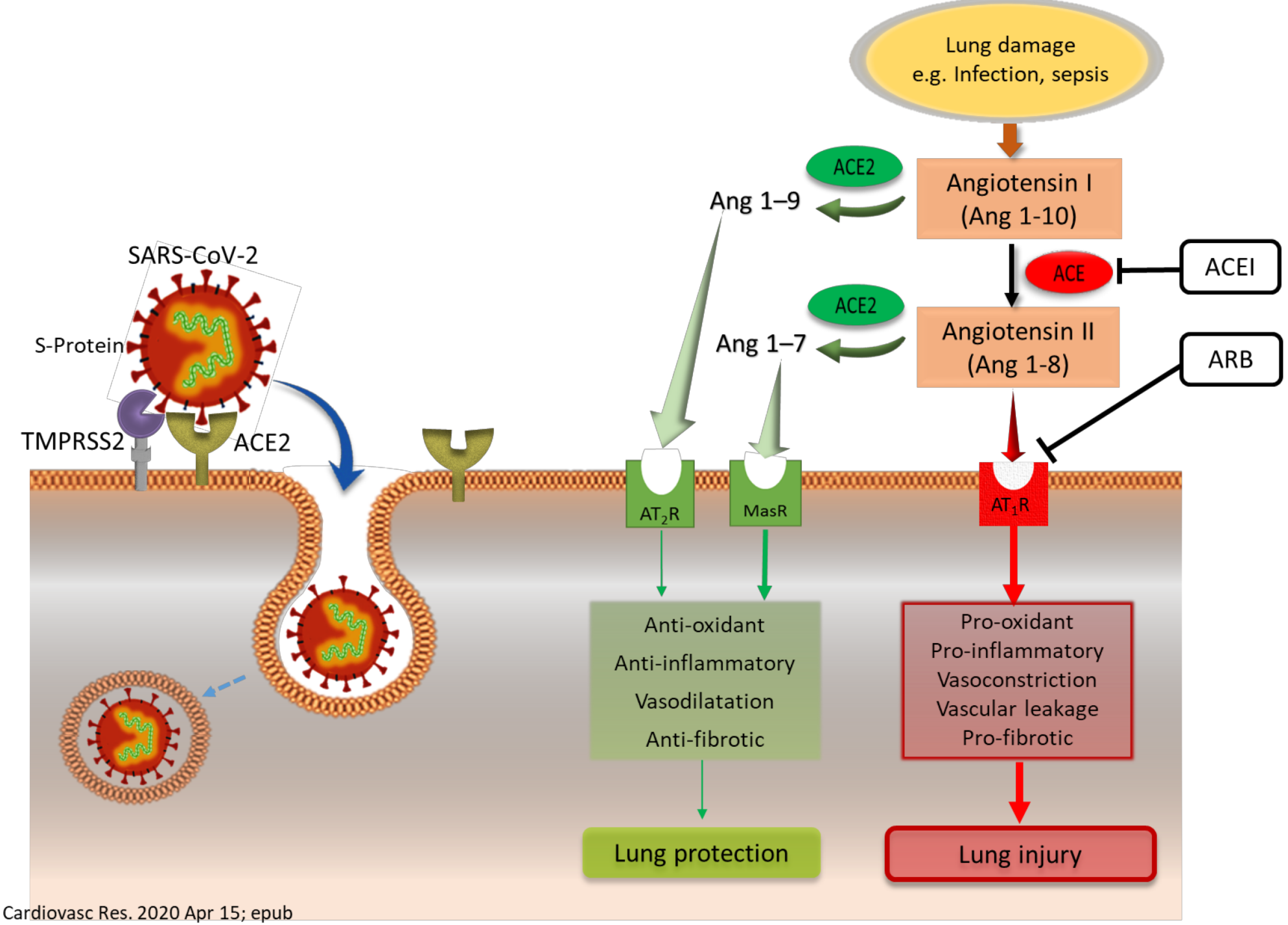




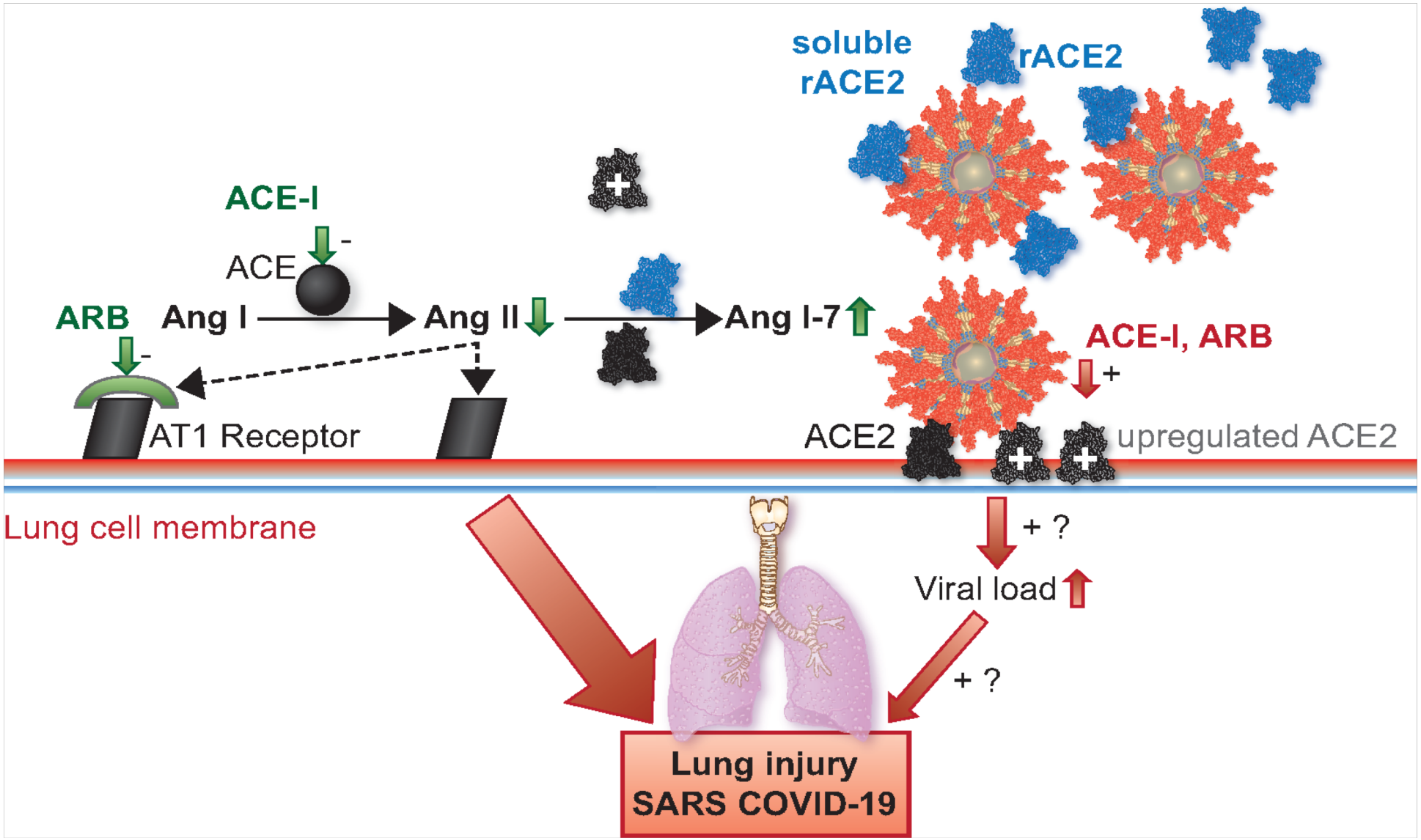
Kreutz R. et al. Cardiovasc Res. 2020 Apr 15; epub



Kreutz R. et al. Cardiovasc Res. 2020 Apr 15; epub

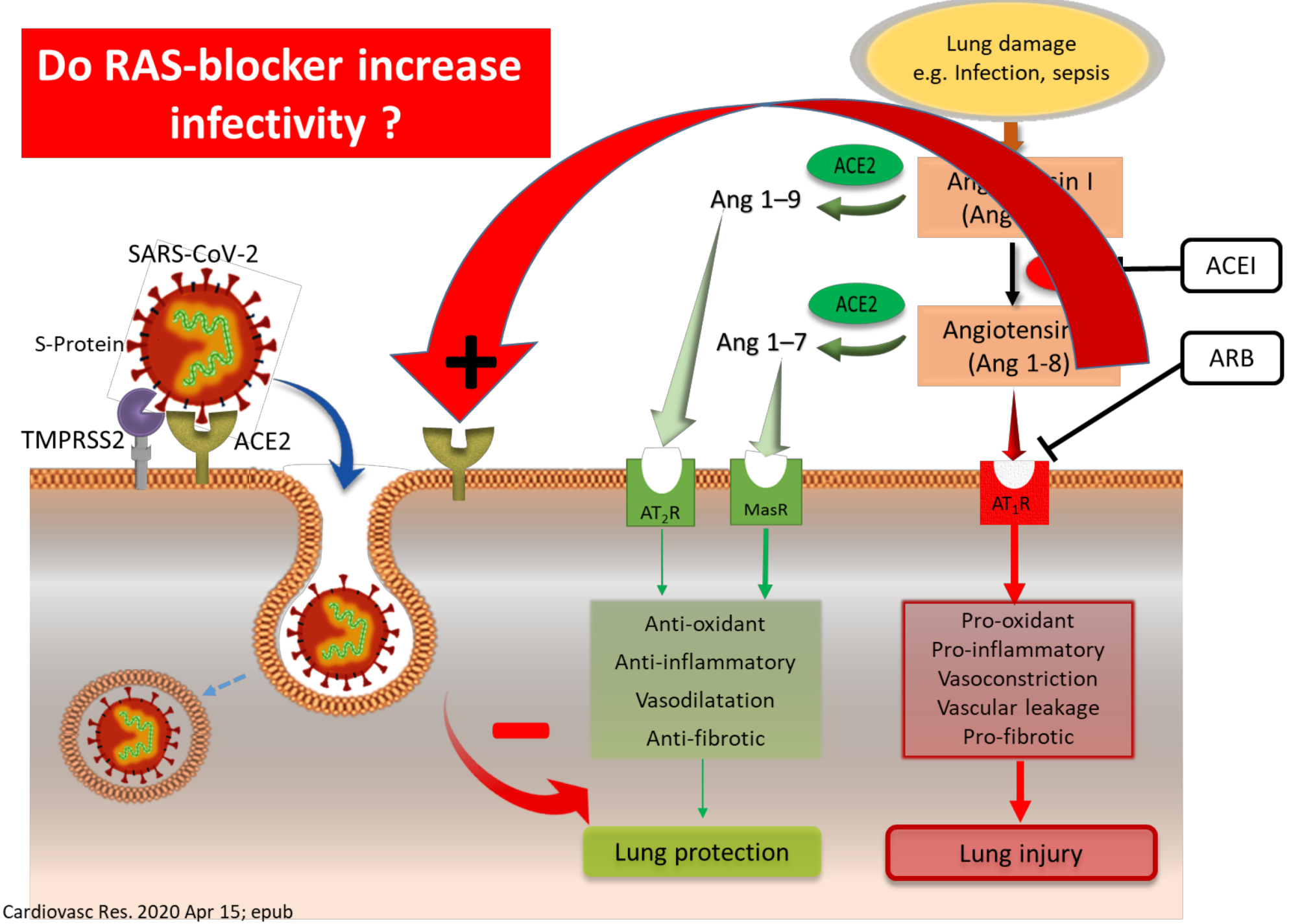


Kreutz R. et al. Cardiovasc Res. 2020 Apr 15; epub



Eur Heart J, Volume 41, Issue 19, 14 May 2020, Pages 1801–1803, https://doi.org/10.1093/eurheartj/ehaa235

Do RAS-blocker increase infectivity ?



Kreutz R. et al. Cardiovasc Res. 2020 Apr 15; epub

Lancet May 16, 2020

Use of renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study

*Francisco J de Abajo, Sara Rodríguez-Martín, Victoria Lerma, Gina Mejía-Abril, Mónica Aguilar, Amelia García-Luque, Leonor Laredo, Olga Laosa, Gustavo A Centeno-Soto, Maria Ángeles Gálvez, Miguel Puerro, Esperanza González-Rojano, Laura Pedraza, Itziar de Pablo, Francisco Abad-Santos, Leocadio Rodríguez-Mañas, Miguel Gil, Aurelio Tobías, Antonio Rodríguez-Miguel, Diego Rodríguez-Puyol, on behalf of the MED-ACE2-COVID19 study group**

COVID patients / Controls

N=1139 / 11,390

Take home message

- ACEi or ARBs do not significantly affect COVID-19 !

The NEW ENGLAND JOURNAL of MEDICINE

Recently Published, May 1, 2020

The following articles are now available on NEJM.org. For more articles and other resources on the Covid-19 outbreak, visit NEJM.org/coronavirus.

COVID patients / Controls

ORIGINAL ARTICLE

Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19

M.R. Mehra and Others

FREE

N=8910 / na

ORIGINAL ARTICLE

Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19

G. Mancia and Others

FREE

N=6272 / 30,759

ORIGINAL ARTICLE

Renin–Angiotensin–Aldosterone System Inhibitors and Risk of Covid-19

H.R. Reynolds and Others

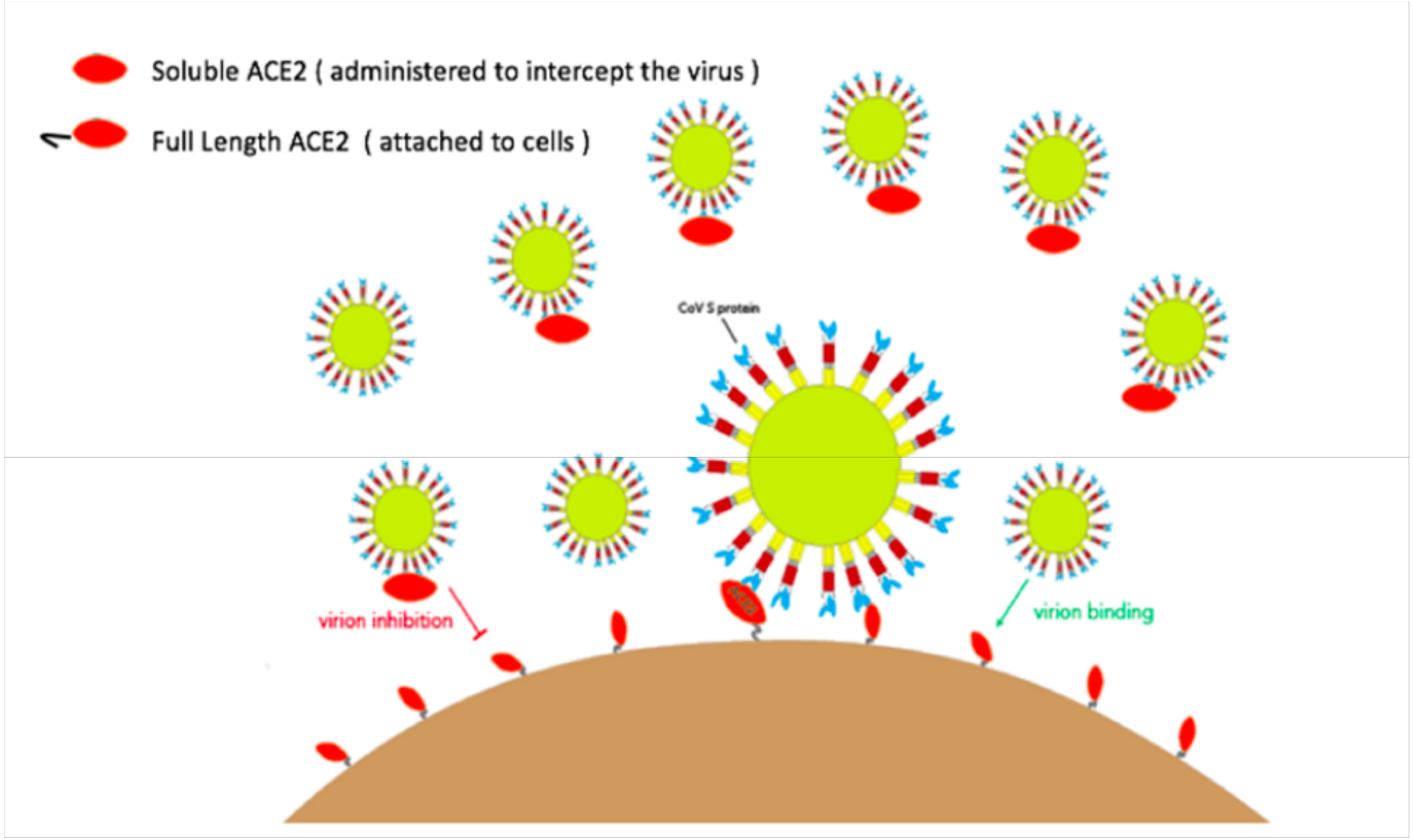
FREE

N=5894 / na

EDITORIAL

Inhibitors of the Renin–Angiotensin–Aldosterone System and Covid-19

J.A. Jarcho and Others


Soluble ACE2 (administered to intercept the virus)
Full Length ACE2 (attached to cells)
CoV S protein
virion inhibition
virion binding

Modulation ACE 2 : downregulation

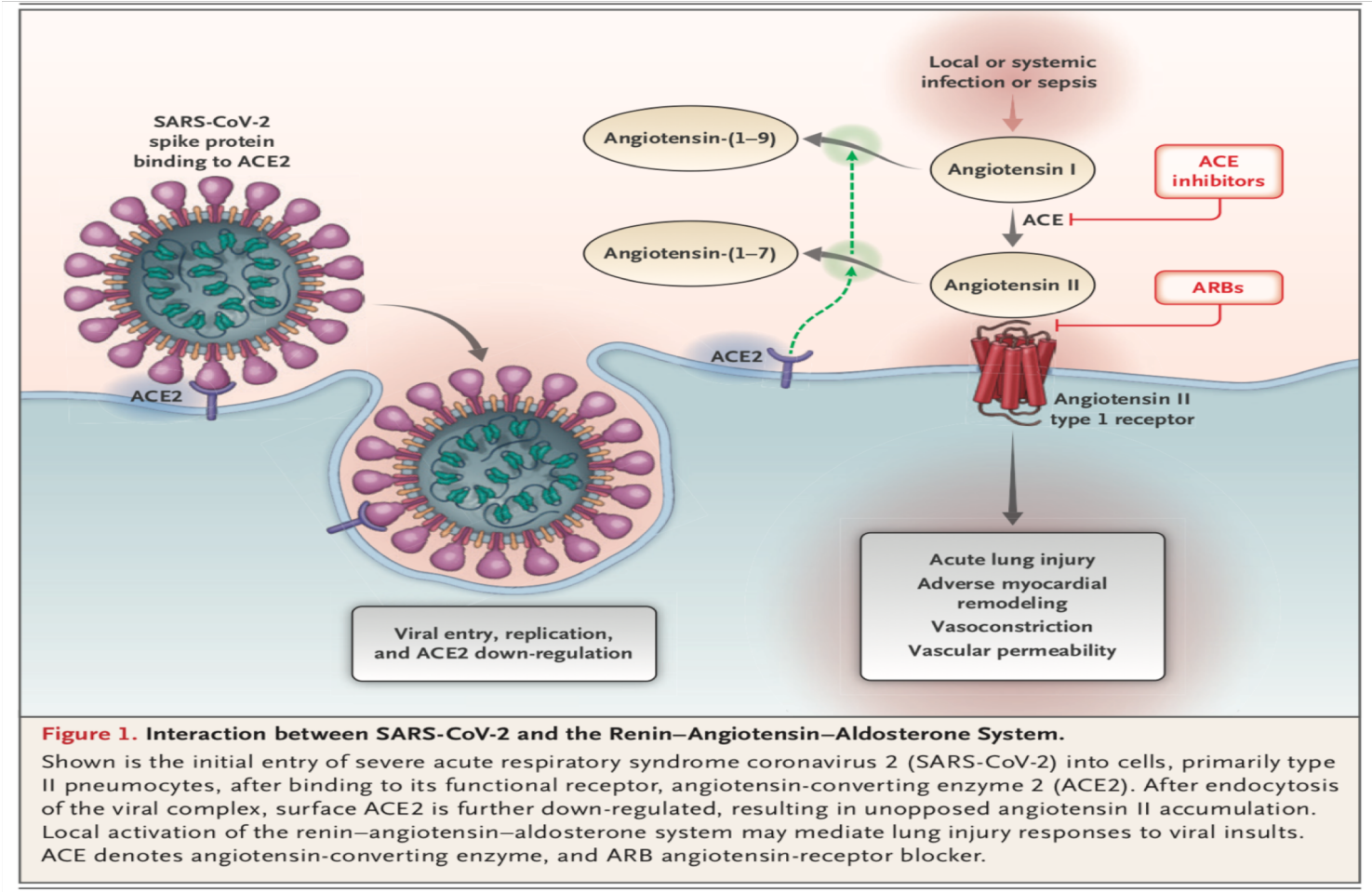
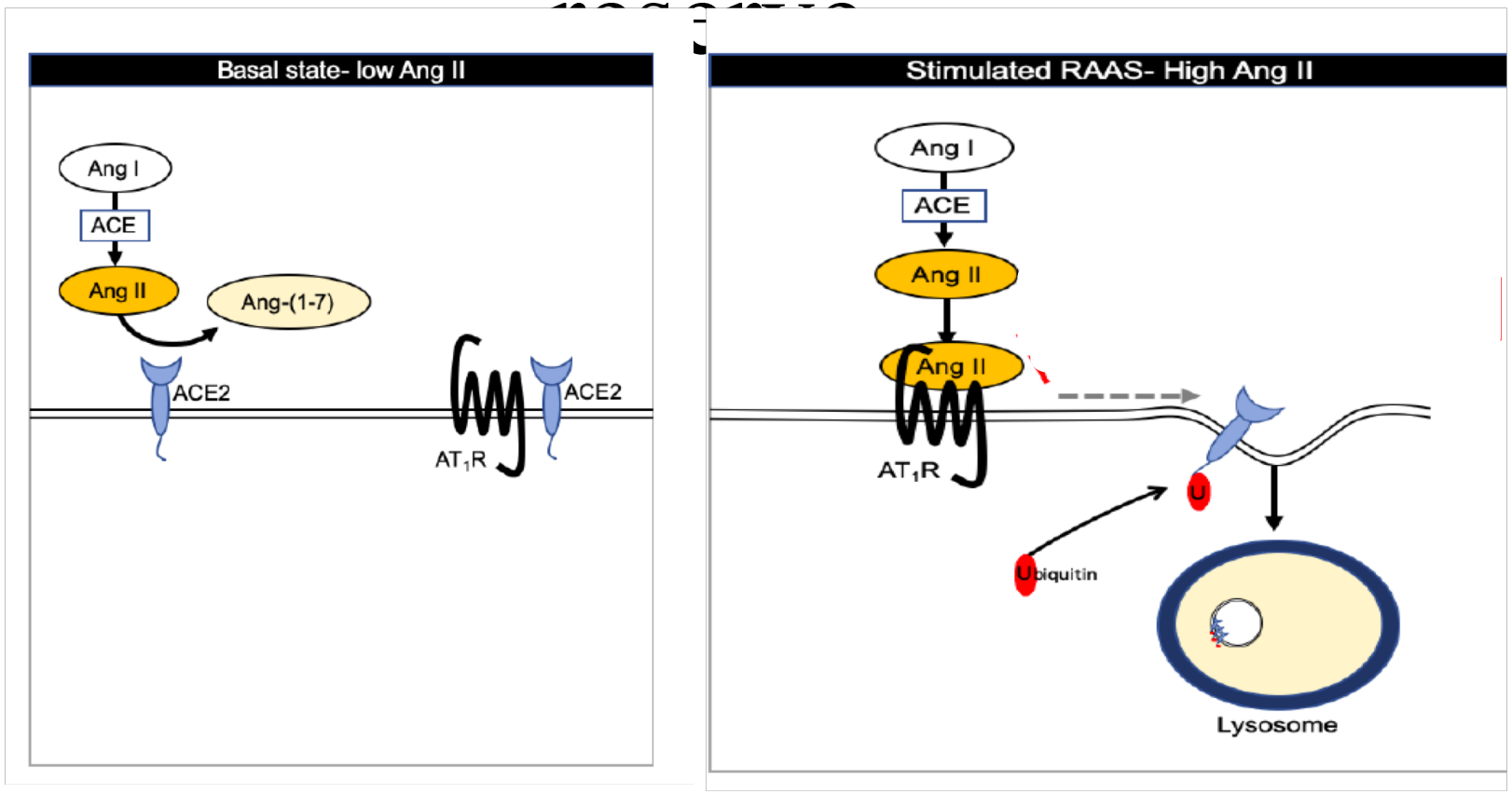
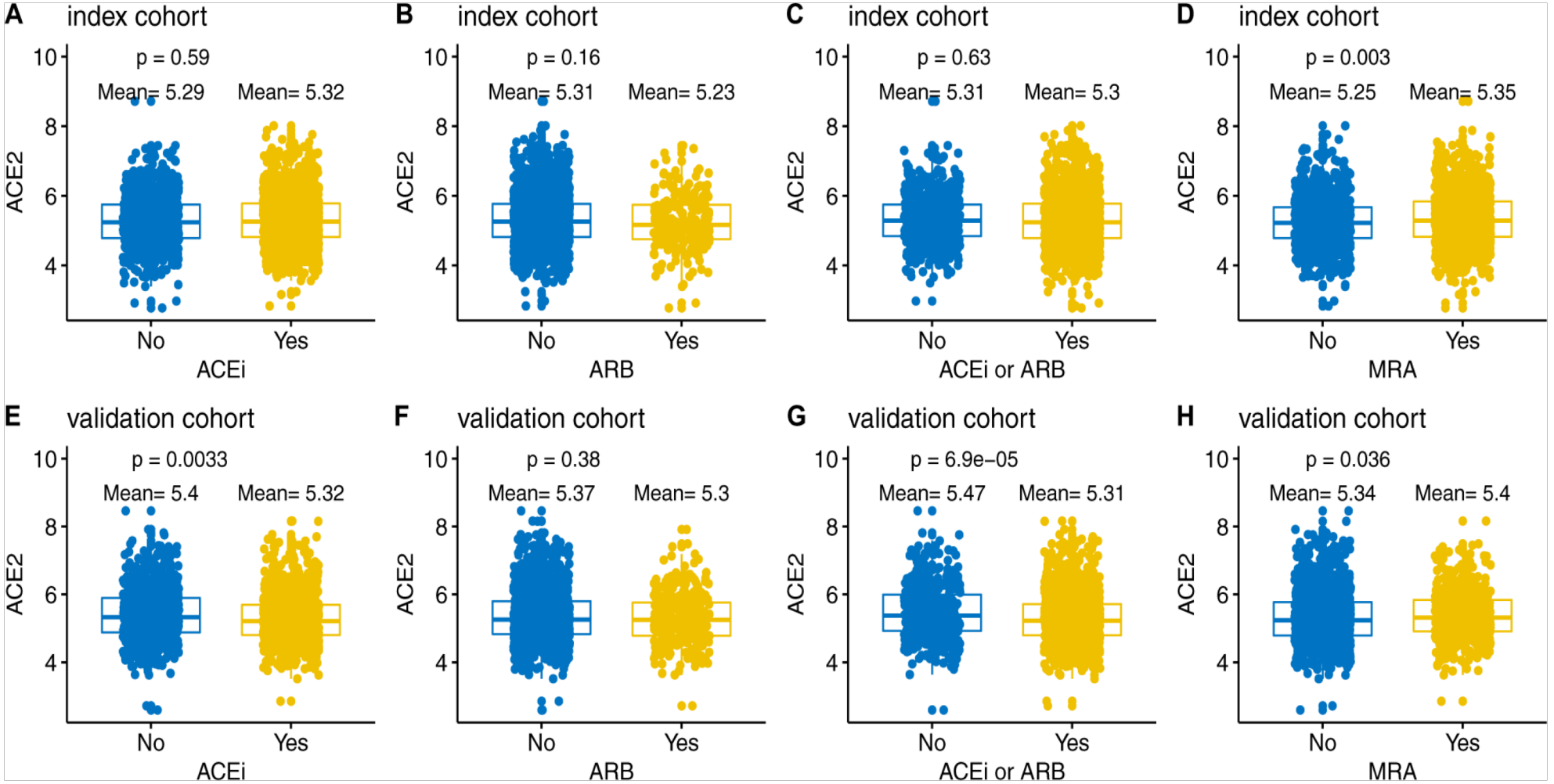


Figure 1. Interaction between SARS-CoV-2 and the Renin–Angiotensin–Aldosterone System.
Shown is the initial entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into cells, primarily type II pneumocytes, after binding to its functional receptor, angiotensin-converting enzyme 2 (ACE2). After endocytosis of the viral complex, surface ACE2 is further down-regulated, resulting in unopposed angiotensin II accumulation. Local activation of the renin–angiotensin–aldosterone system may mediate lung injury responses to viral insults. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

Modulation ACE 2 : recepteurs de



ACE2 concentrations in patients with and without use of an ACE inhibitor, ARB, and MRA (HF PATIENT)



Eur Heart J, Volume 41, Issue 19, 14 May 2020, Pages 1810–1817, https://doi.org/10.1093/eurheartj/ehaa373

Variables associated with plasma ACE2 concentrations

The strongest predictor of elevated plasma concentrations of ACE2 in the index and validation cohort was male sex (estimate = 0.26, $P < 0.001$; and 0.19, $P < 0.001$, respectively). In the index cohort, neither ACE inhibitors, ARBs, nor MRAs were associated with plasma ACE2 concentrations (*Table* 2). In the validation cohort, ACE inhibitors (estimate = −0.17, $P = 0.002$) and ARBs (estimate = −0.15, $P = 0.03$) were associated with lower plasma ACE2 concentrations, but MRAs (estimate = 0.11, $P = 0.04$) were associated with higher concentrations (Supplementary material online, *Table S4*).

ESH STATEMENT ON COVID-19

Statement of the European Society of Hypertension (ESH) on hypertension, Renin-Angiotensin System (RAS) blockers and COVID-19

European Society of Hypertension

- https://www.eshonline.org/spotlights/esh-statement-covid-19/

- In stable patients with COVID-19 infections or at risk for COVID-19 infections, treatment with ACEIs and ARBs should be executed according to the recommendations in the 2018 ESC/ESH guidelines.

- The currently available data on COVID-19 infections do not a support a differential use of RAS blockers (ACEI or ARBs) in COVID-19 patients.

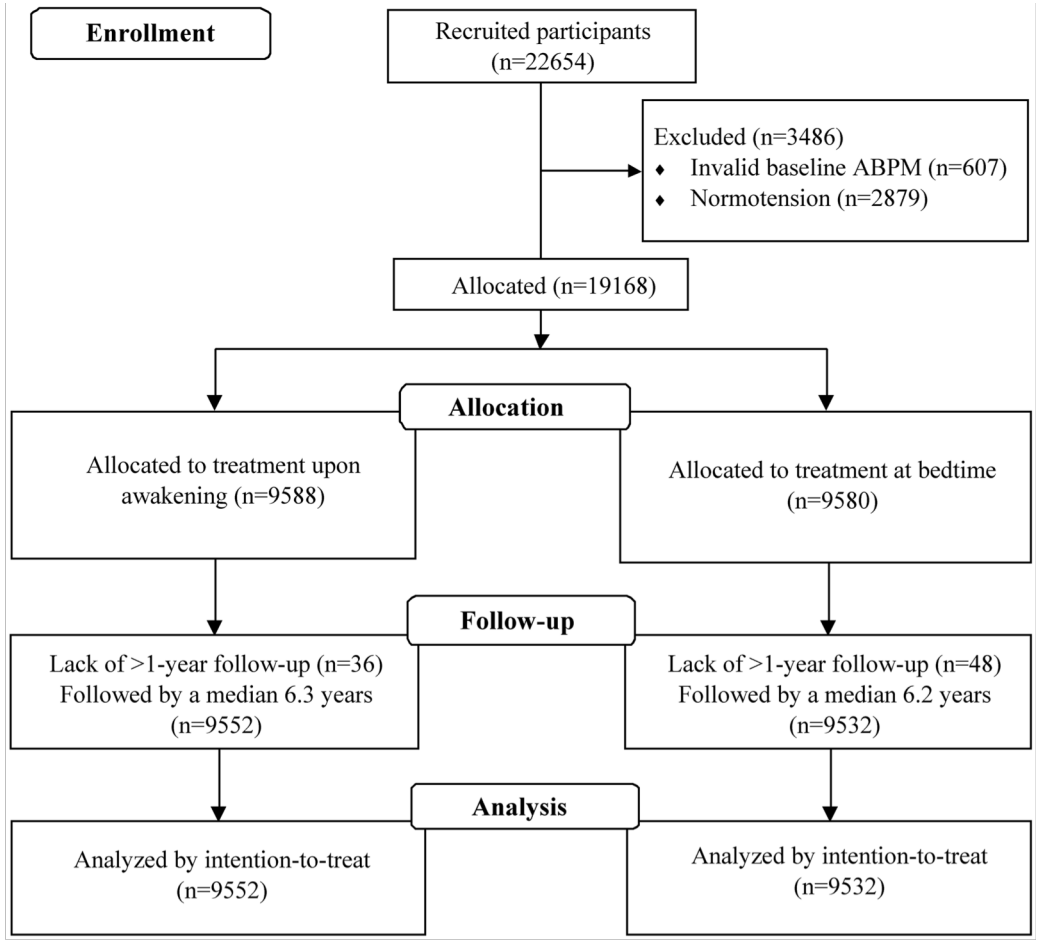
Williams, Mancia et al. J Hypertens 2018;36:1953-2041 and Eur Heart J 2018;39:3021-3104

Pourquoi parler de chronopharmacologie ?

- Papier Herrada

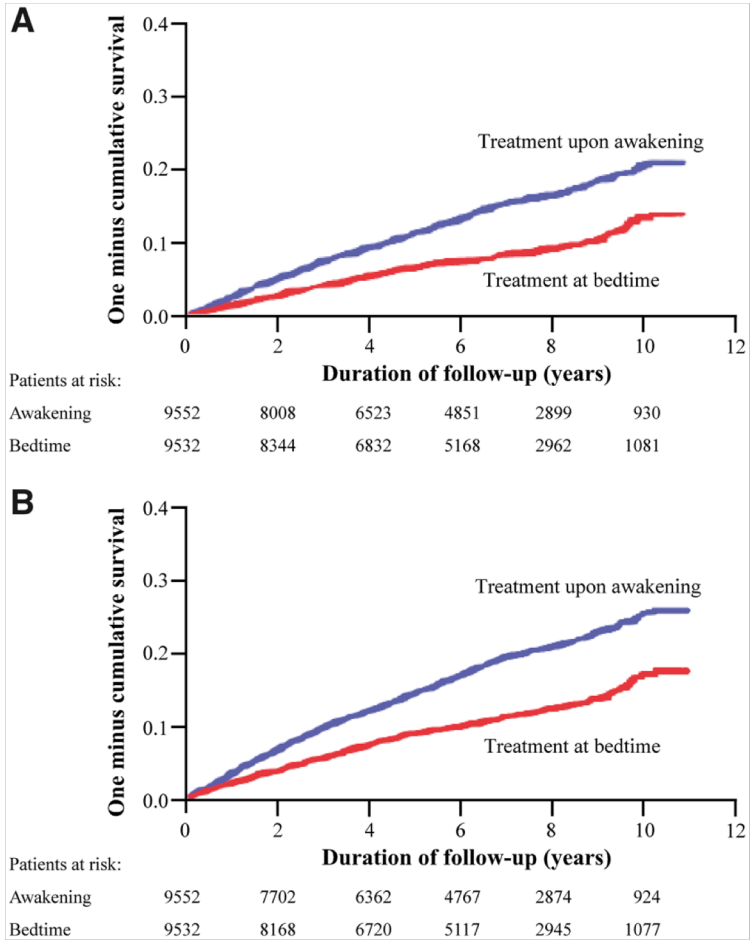
- Prise de jour ? Prise de nuit ? Différence ?

Figure 1 Flow diagram of participants in the study.



Eur Heart J, ehz754, https://doi.org/10.1093/eurheartj/ehz754

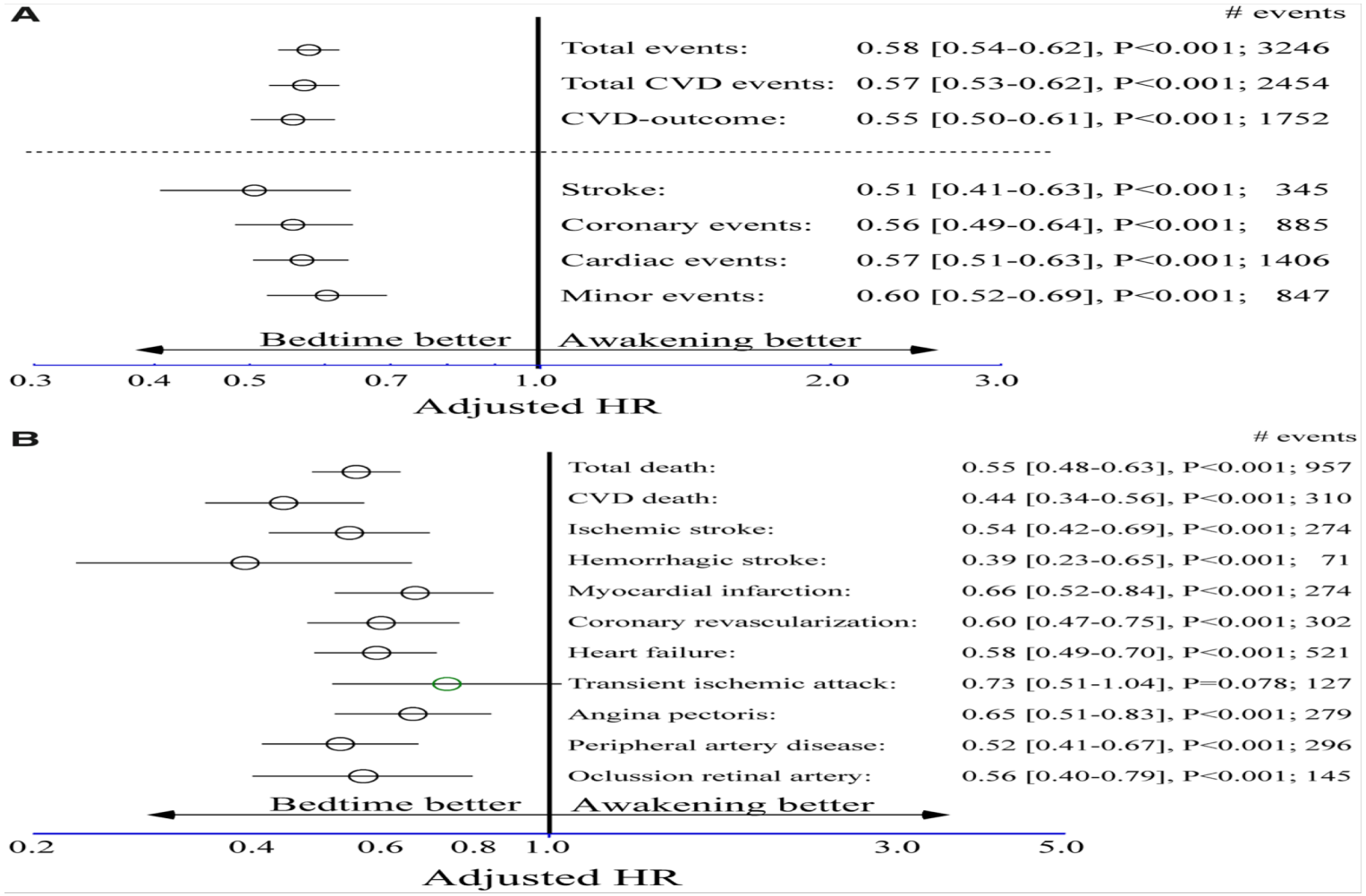
Figure 3 Kaplan–Meier cumulative hazard curves for cardiovascular disease outcome as a function of hypertension ...



(A) Cardiovascular disease outcome: composite of cardiovascular disease death, myocardial infarction, coronary revascularization, heart failure, and stroke; log-rank: 140.1, $P < 0.001$.
(*B*) Total cardiovascular disease events: composite of cardiovascular disease death, myocardial infarction, coronary revascularization, heart failure, stroke, angina pectoris, peripheral artery disease, and transient ischaemic attack; log-rank: 174.0, $P < 0.001$.

Eur Heart J, ehz754, https://doi.org/10.1093/eurheartj/ehz754

Figure 2 Adjusted hazard ratio of cardiovascular disease outcome as a function of hypertension treatment-time regimen ...



Eur Heart J, ehz754, https://doi.org/10.1093/eurheartj/ehz754

Relates to: 'Bedtime Hypertension Treatment Improves Cardiovascular Risk Reduction: Hygia Chronotherapy Trial'

European Heart Journal, Volume 41, Issue 16, 21 April 2020, Page 1600,
https://doi.org/10.1093/eurheartj/ehaa339
Published: 21 April 2020

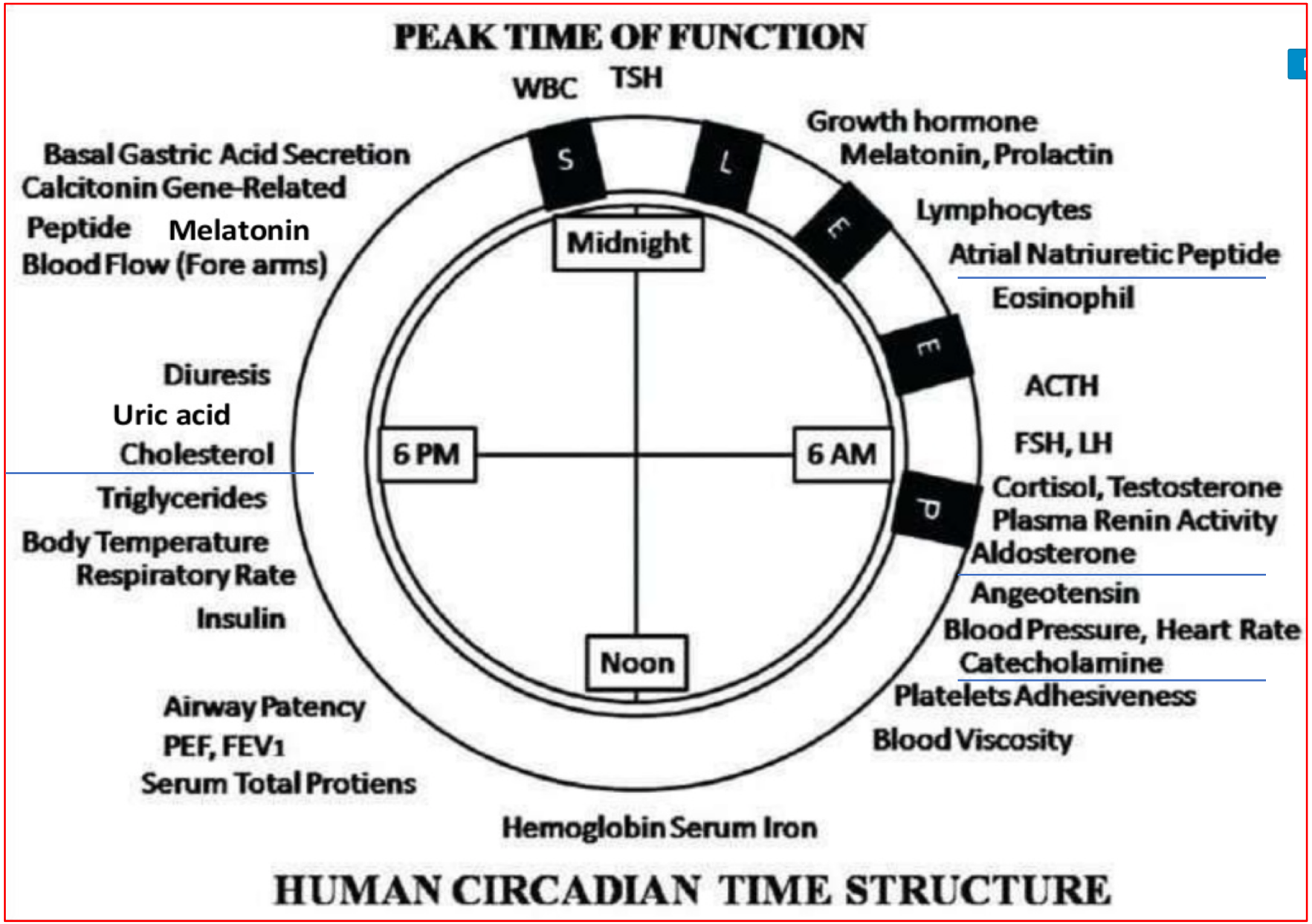
This is a correction to:
European Heart Journal, ehz754,
https://doi.org/10.1093/eurheartj/ehz754

Issue Section: EXPRESSION OF CONCERN

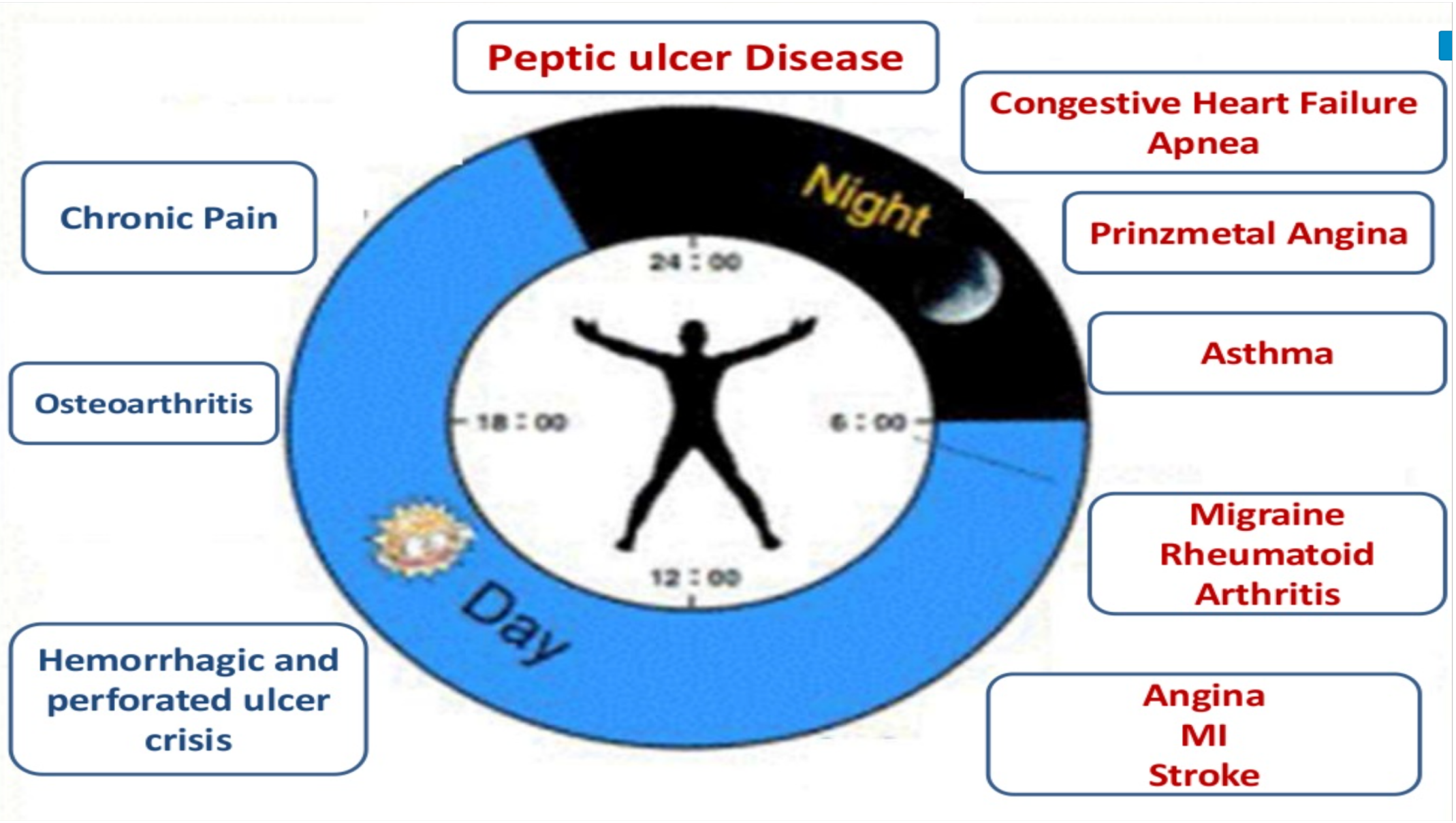
This is an Expression of Concern for: (https://doi.org/10.1093/eurheartj/ehz754)

> The editors would like to inform the readers of the article 'Bedtime Hypertension Treatment Improves Cardiovascular Risk Reduction: Hygia Chronotherapy Trial' by Ramon C. Hermida et al. *Eur Heart J* 2020; online that the content and conduct of this randomized clinical trial is currently under investigation. They therefore recommend to interpret the major results and conclusions with caution until further notice.

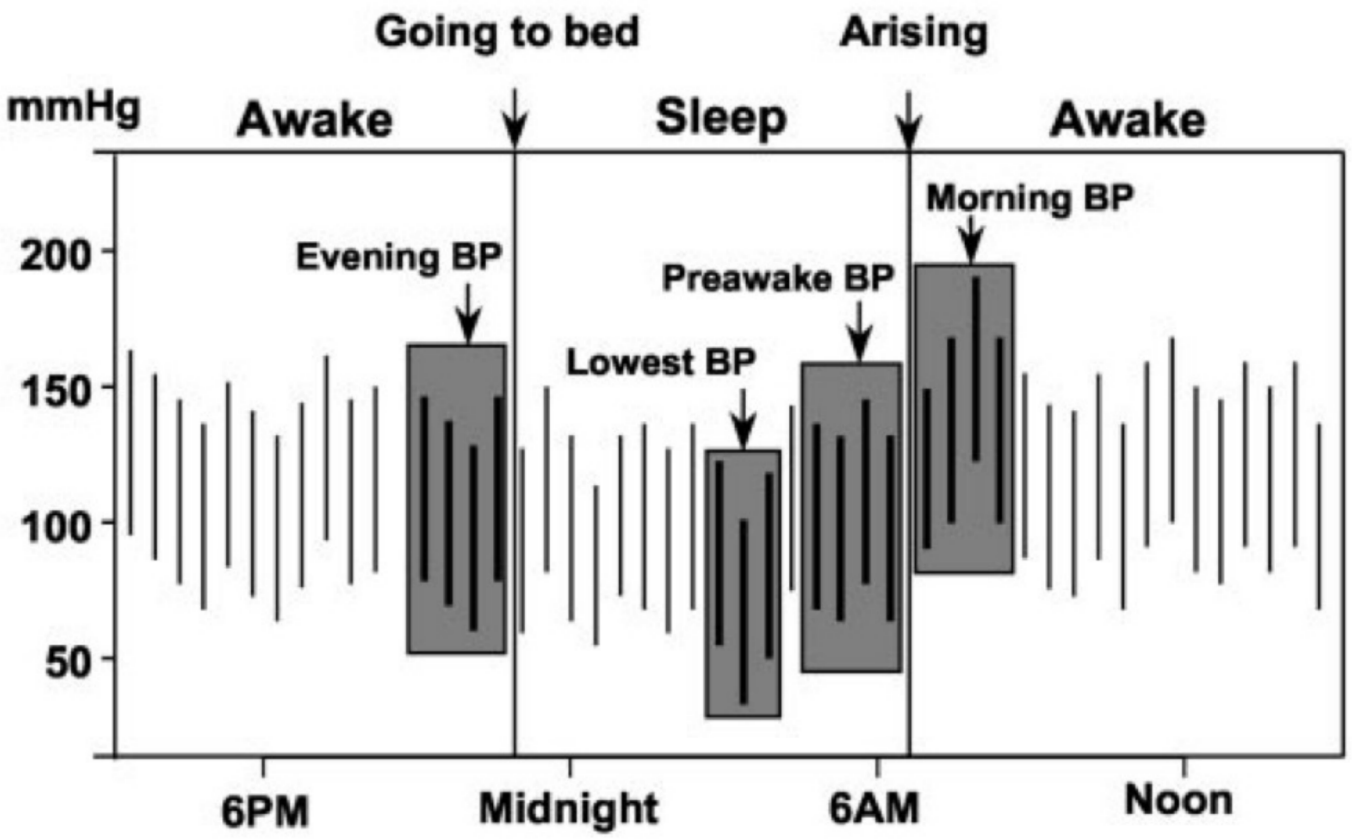
Tout est rythme !



Chronosémiologie

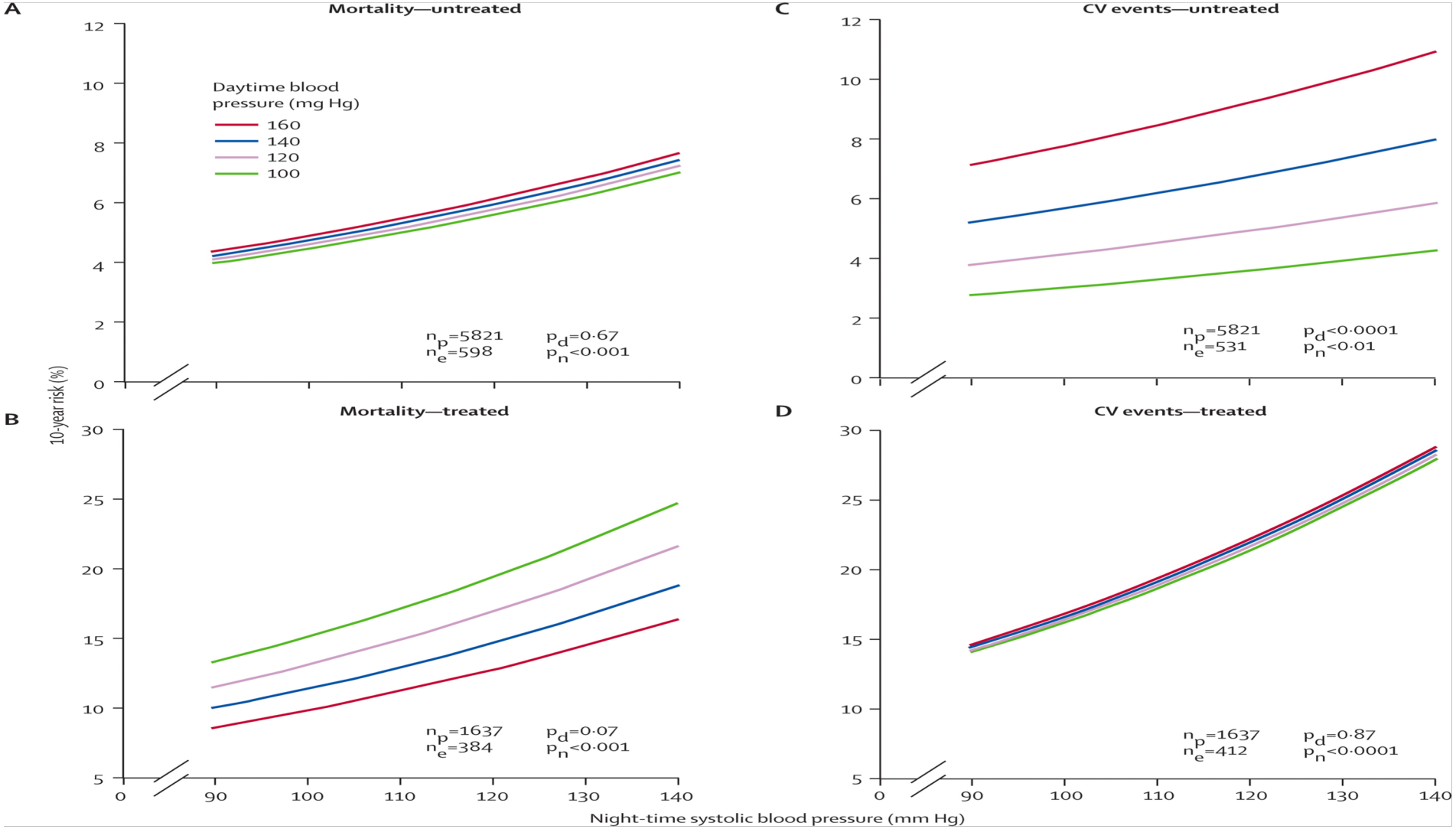


Variabilité de la PA : une cible ?



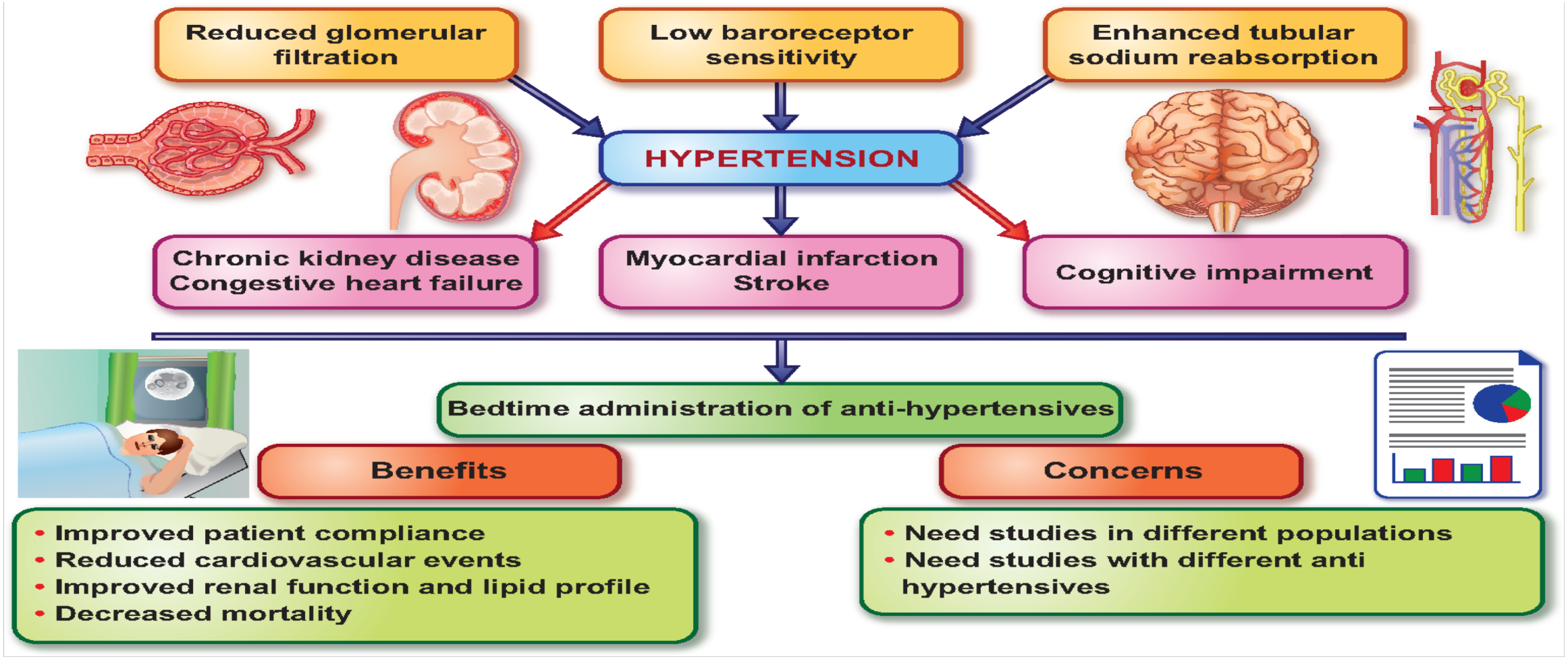
Source: Kario et coll. Circulation 2003

On sous estime les méfaits de la PA nocturne



Boggia J et al. *Lancet* 2007 ;370 :1219–1229

Chronotherapy for hypertension: pathophysiology, benefits, and concerns.



Eur Heart J, ehz836, https://doi.org/10.1093/eurheartj/ehz836

Les avantages de la prise nocturne

- Hermida *et al*. 2012 hypertensive patients without diabetes, and showed that bedtime ingestion of antihypertensive medications reduced the risk of new-onset diabetes and incident chronic kidney disease.

- Wang *et al*. Meta-analysis comprising 3732 patients observed that bedtime administration of medications was effective in lowering blood pressure in non-dippers among chronic kidney disease patients.

- Bowles *et al*. reviewed this topic and observed an improved 24-h blood pressure and dipping blood pressure profile, with at least one medication taken in the evening.

- The Japan Morning Surge-Target Organ Protection (J-TOP) open-label multicentre trial of 450 patients showed that reduction in night-time home blood pressure with an evening dose of the angiotensin receptor blocker candesartan was significantly correlated with a decrease in left ventricular hypertrophy and microalbuminuria.

Chronopharmacodynamique

Réaction physicochimique

Variations temporelles de la perméabilité membranaire

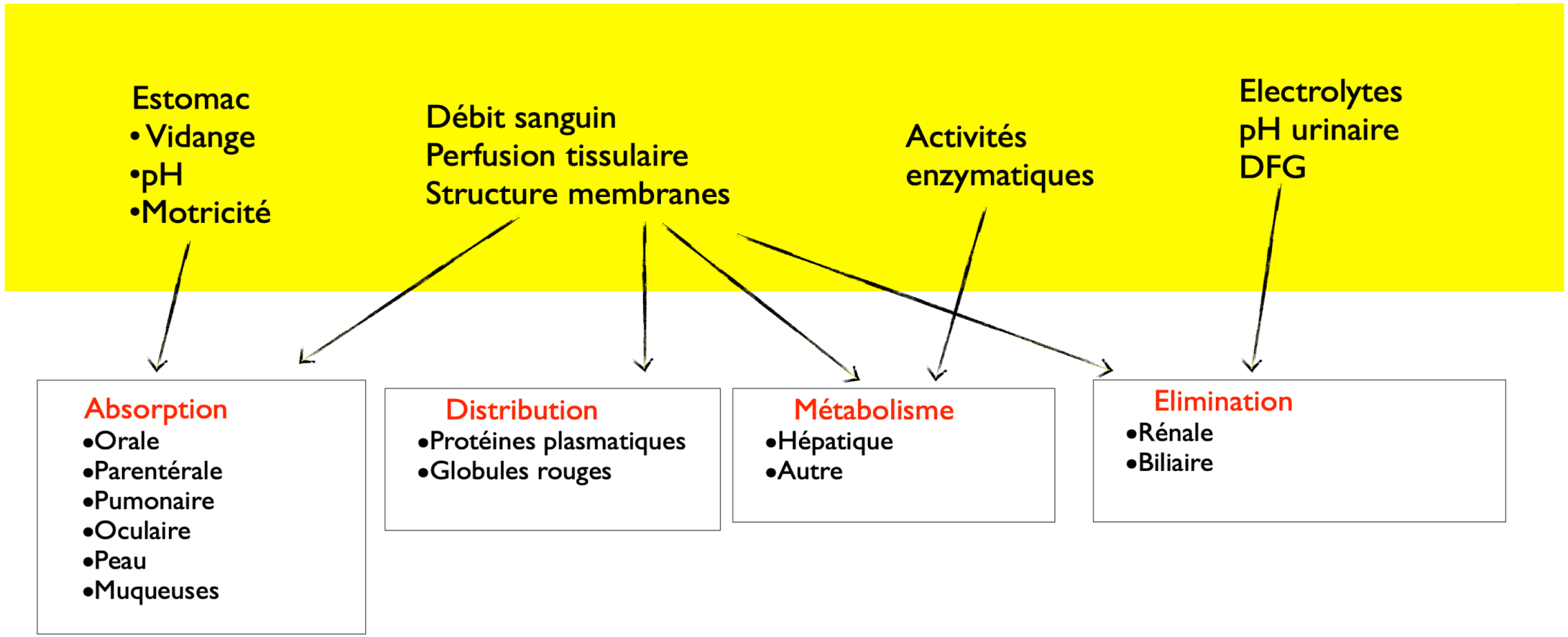
ex: anesthésiques locaux

Action spécifique via des récepteurs

Variations temporelles du nombre et/ou de l'affinité des récepteurs

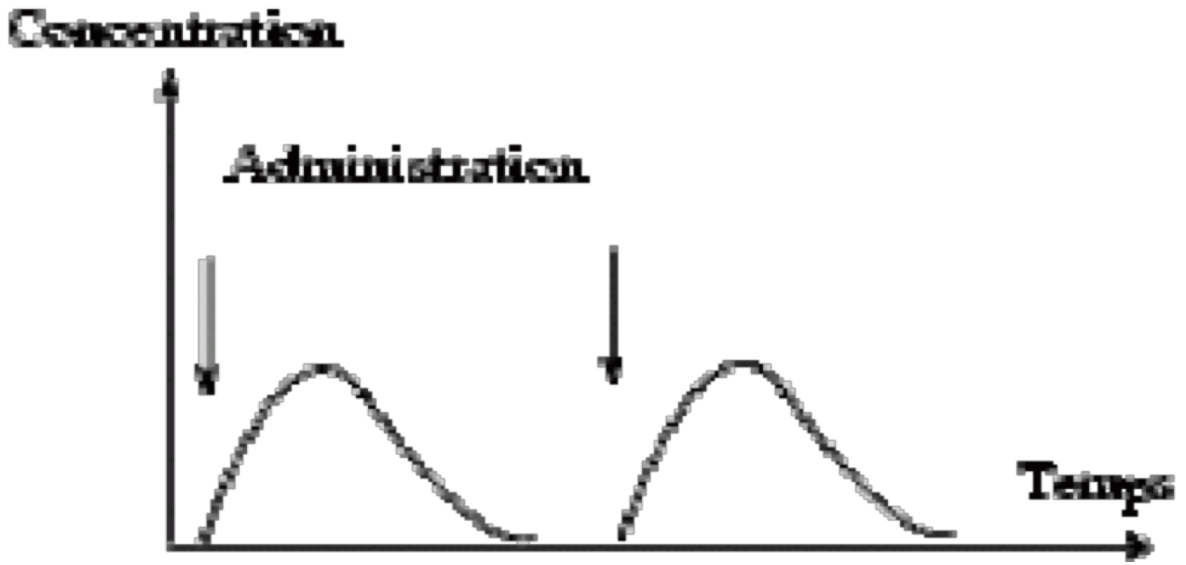
ex: β bloquants

chronopharmacocinétique



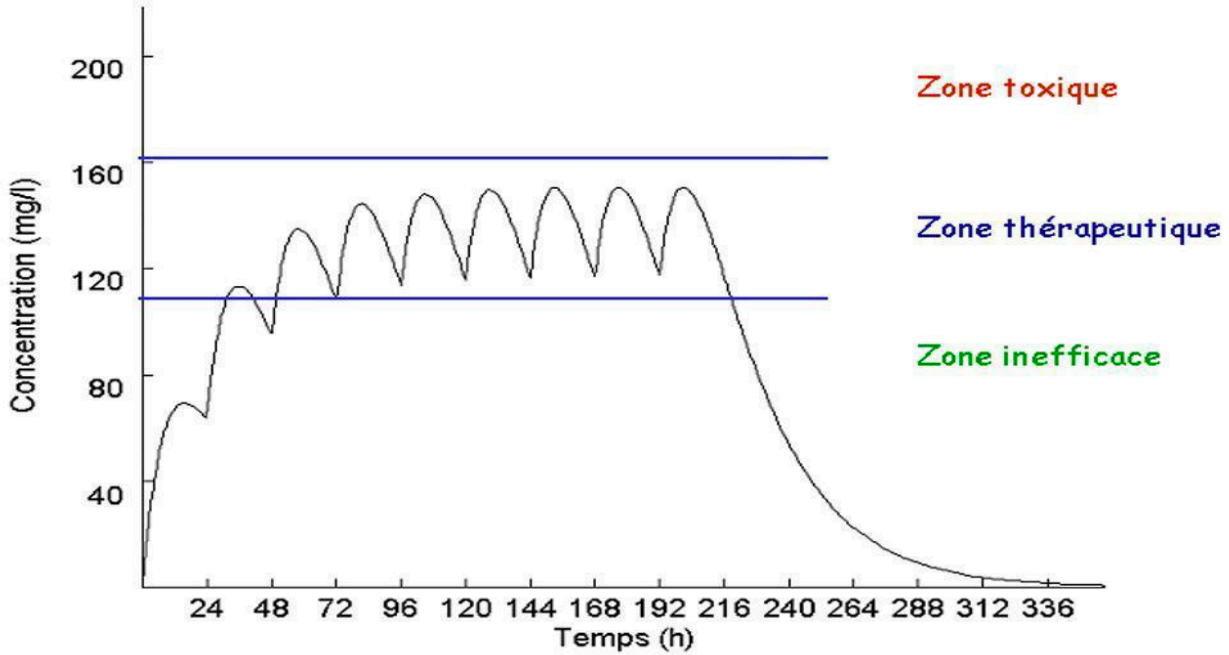
En pratique

- Variabilité des systèmes
- Variabilité des cibles
- Variabilité des concentrations



Pour une administration chronique

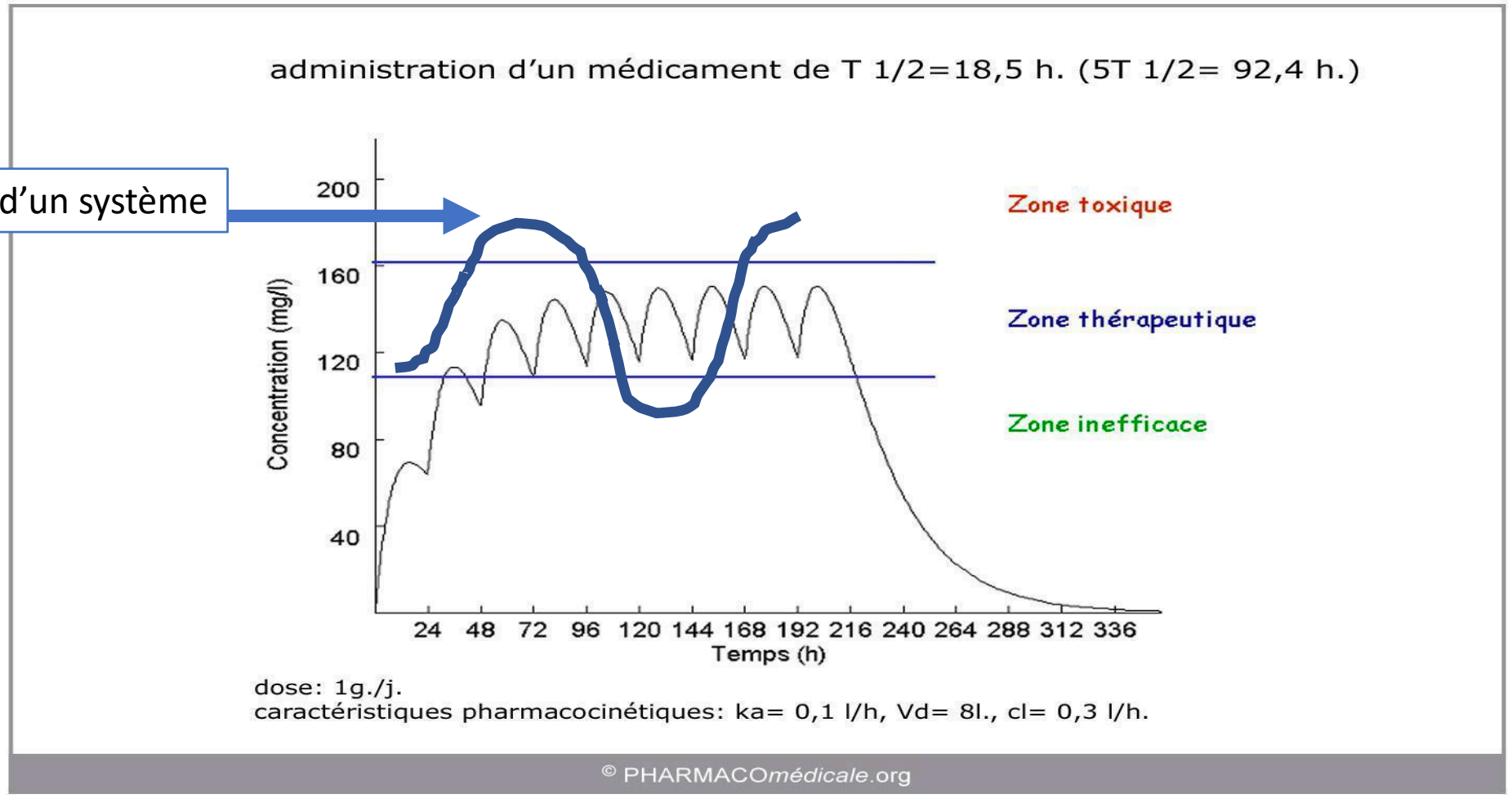
administration d'un médicament de T 1/2=18,5 h. (5T 1/2= 92,4 h.)



dose: 1g./j.
caractéristiques pharmacocinétiques: ka= 0,1 l/h, Vd= 8l., cl= 0,3 l/h.

Pour une administration chronique

Activité d'un système



En pratique

- Donner un médicament la nuit c’est mieux …:
- Si le médicament est pris

- Si les effets indésirables ne sont pas genants la nuit (diurese, hypotension)

- Optimisation thérapeutique (relation PK / PD)