La réanimation personnalisée

Jean-Daniel Chiche, MD PhD

jean-daniel.chiche@chuv.ch

Service de Médecine Intensive Adulte
CHUV, Lausanne. Suisse.

UNIL | Université de Lausanne
Faculty of Biology and Medicine

CHUV

I·CARE LAUSANNE

ONE ON ONE
ADVANCING INTENSIVE CARE


TOP SECRET

Adapter pour mieux soigner

La révolution de la recherche clinique en réanimation

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I·CARE LAUSANNE

ONE TO ONE
ADVANCING INTENSIVE CARE

Dans les coulisses de ONE ONE

“Je me sens plus forte et tellement heureuse de vivre ma « deuxième » vie.”

HISTOIRE DE SECONDES VIES

Marine,
Ancienne patiente en réanimation

“J’ai eu toutes les complications qu’on peut prévoir en réanimation : choc septique, trachéotomie, arrêt cardio-respiratoire, pneumothorax, hémorragies digestives, embolisation artérielle digestive, insuffisance rénale, thromboses veineuses...

Mon passage en réanimation a été pour moi une descente aux enfers. Chaque jour, j’avais la sensation de « vouloir » mourir. Ma souffrance psychique m’emmenait dans des rêves mortifères pendant les périodes de coma.

ONE IOI ONE

LA RÉANIMATION EST UN ENJEU

Développement connexions neuronales

Elagage

Stabilisation

Nombre de connexions neuronales

Pourquoi (WHY)

Mouvements

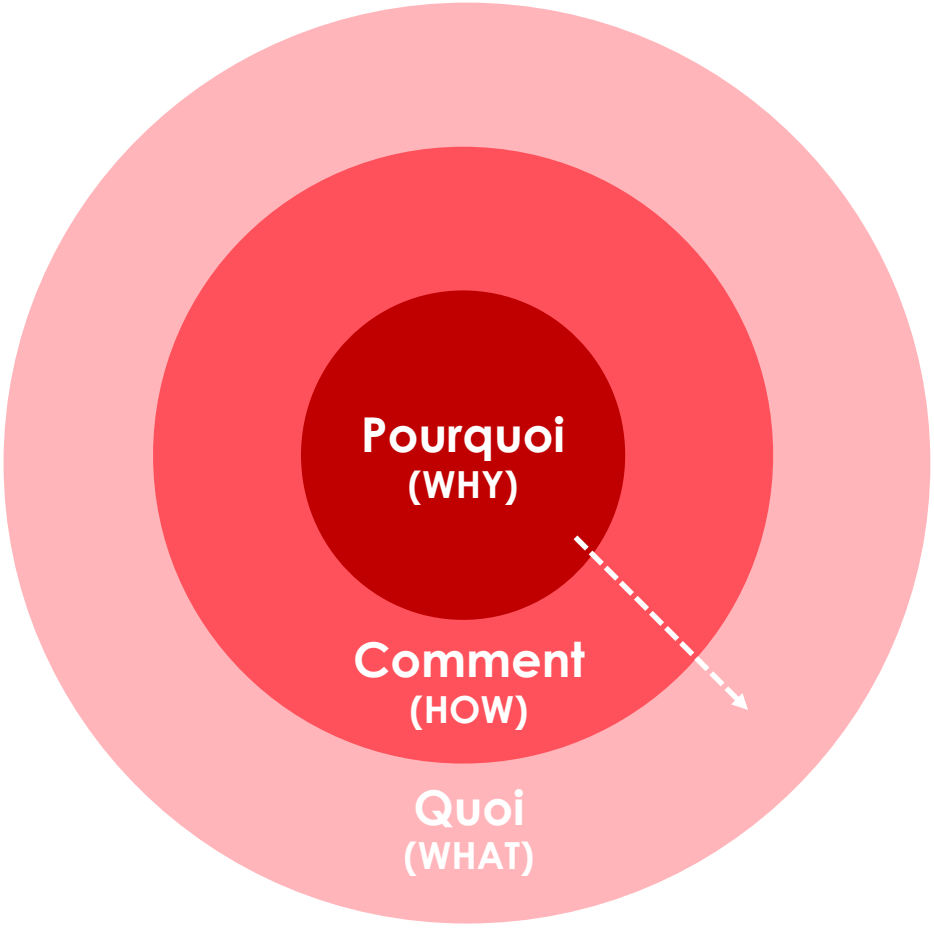
Raisonnements complexes

Naissance

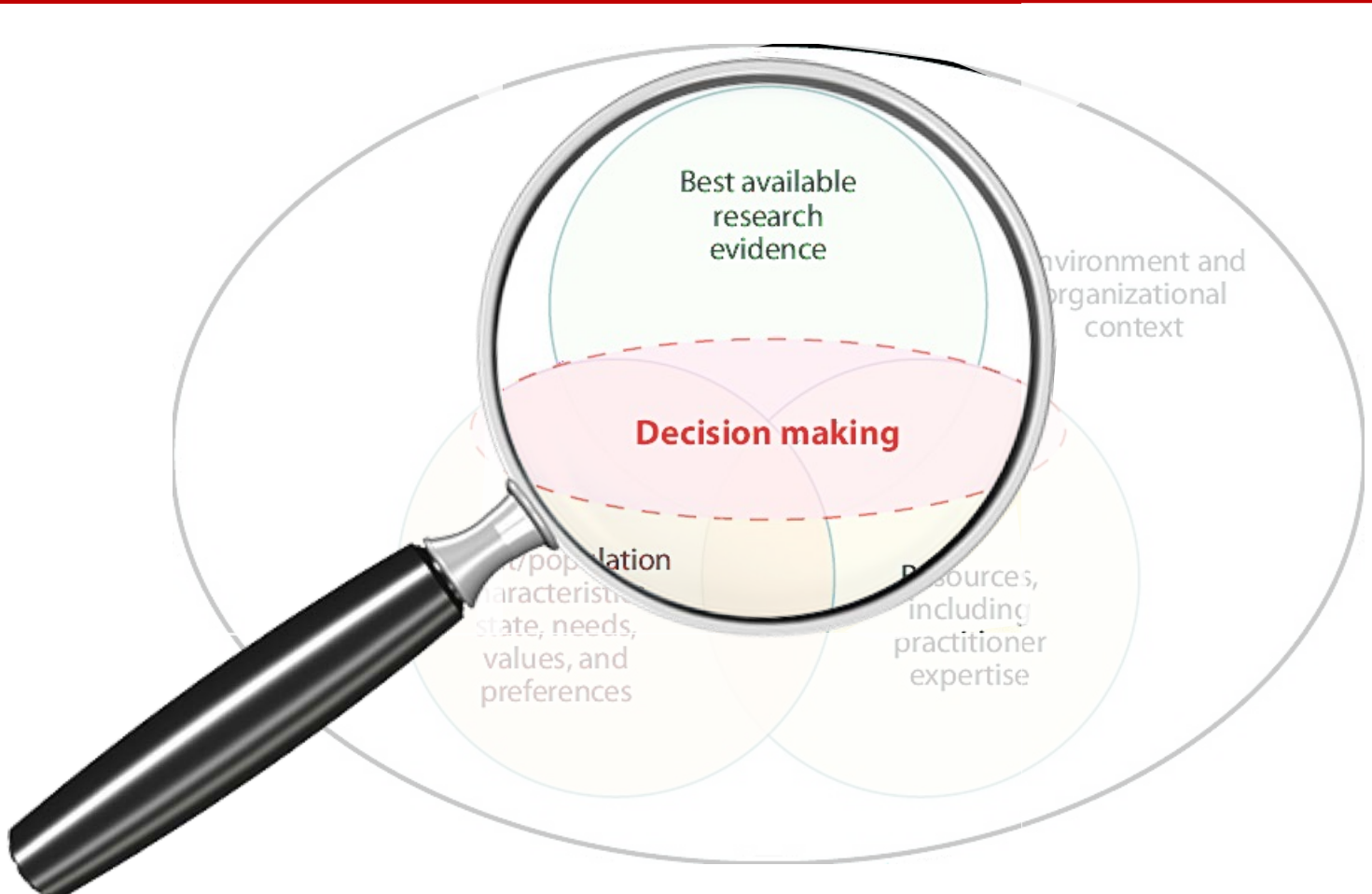
Enfance

Adolescence

Adulte


Pourquoi
(WHY)
Comment
(HOW)
Quoi
(WHAT)

Sur quoi reposent nos décisions au lit du patient?



Détermine l'effet moyen d'un traitement sur une population

Détermine le meilleur traitement pour un patient

Une question de philosophie…

- Si vous (ou un de vos amis) avez besoin de soins intensifs, vous souhaitez…

A. L'art des soins intensifs?

B. La science des soins intensifs?

C. L'ingénierie des soins intensifs?

Vous (ou votre ami) partez en Australie…

A. Un pilote amateur et le Spirit of St Louis

B. Chuck Yaeger et un Bell XS-1 test jet

C. Un équipage Swiss et son Airbus A380

Pourquoi l'option 'C' est préférable ?

- **Les vols commerciaux sont sûrs…**
  - **Approche systémique et rigoureuse**
    - Contrôles, procédures dégradées, redondances & SOPs
    - **Incorporation constante & immédiate d'informations nouvelles**
  - **Minimise les risques d'erreur & tire bénéfice de l'expérience disponible concernant chaque risque**
  - **0,4 accident mortel pour 1 million de décollages**
  - **La première cause d'accident reste l'erreur humaine**

Redéfinir « évidence » aux soins intensifs

Art des soins intensifs

- En l'absence d'évidence pour guider nos décisions dans des situations exceptionnelles
  La physiologie, le bon sens et l'expertise au lit du malade

Science des soins intensifs

- En l'absence de preuves alors que le problème fréquent, la recherche est un devoir!

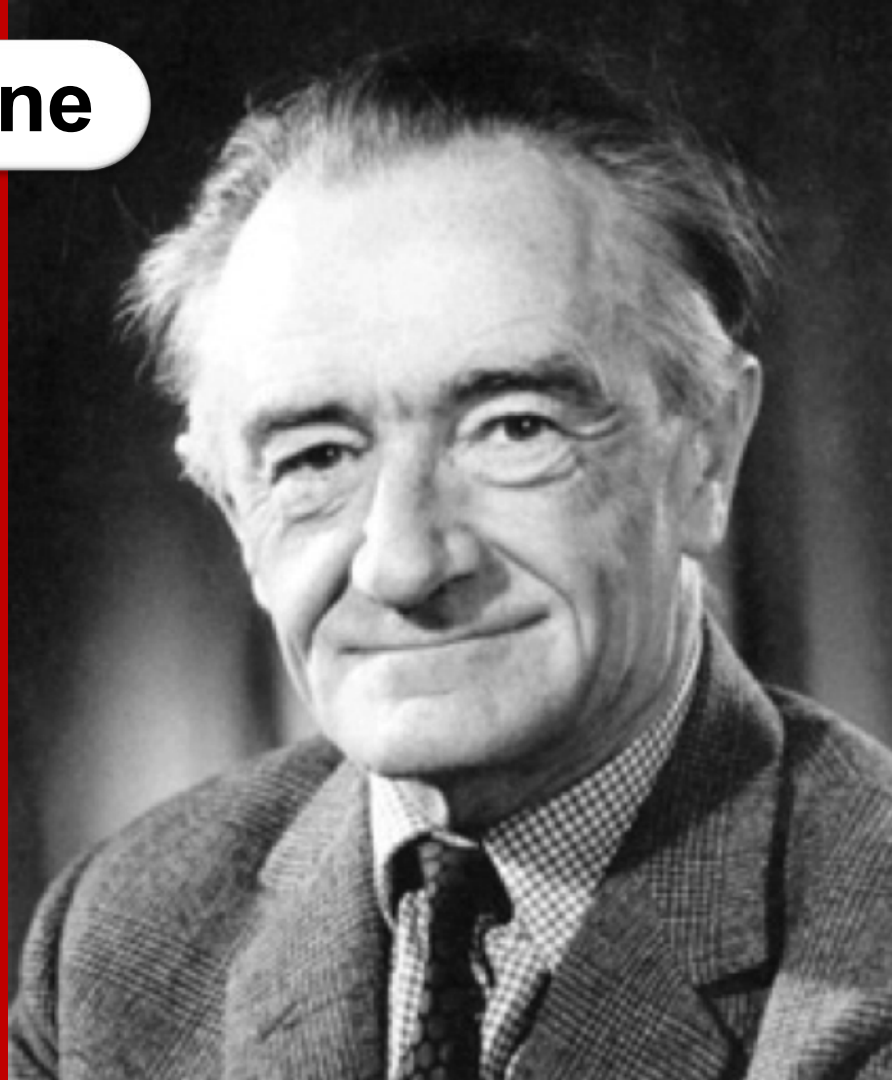
Ingénierie des soins intensifs

- Lorsque les preuves existent, il faut soigner avec rigueur !!

Evidence-based medicine

"Doctors must base what they do on randomized clinical trials (RCTs)"

Archie Cochrane



We should abandon randomized controlled trials in the intensive care unit

Jean-Louis Vincent, MD, PhD, FCCM

Intervention	Comment
Demonstrated to improve outcomes in RCTs	
Activated protein C in severe sepsis and septic shock	Results challenged–new placebo-controlled trial started
Gastric tonometry	Abandoned
Gamma-globulins in severe sepsis	Seldom used
Selective digestive decontamination	Used only in selected centers
Steroid administration before extubation	Seldom applied
Hypothermia for postanoxic brain damage	
Demonstrated to worsen outcomes in RCTs	
Tumor necrosis factor receptor in severe sepsis	Development stopped
Hemoglobin solutions in polytrauma	Development stopped
Growth hormone	Not used
High tidal volume in acute respiratory distress syndrome	Lower tidal volumes used (although perhaps not universally)
Tight blood sugar control	Still controversial

Crit Care Med 2010; 38[Suppl.]:S534–S538

Jean-Louis

@jlvincen Vous su

critical care

intensive.org

Inscrit en janvi

Jean-Louis Vincent
@jlvincen

Abonné

Negative trials are wonderful - if we continue like this we will keep only old respirators and norepinephrine - icu care will be very cheap!

Traduire le Tweet

01:30 - 2 août 2017

58 Retweets **107** J'aime

12 58 107

Tweeter votre réponse

Luis Felipe Jurado C @ludovicojc · 2 août 2017

En réponse à @jlvincen

😍 The best icu therapy so far: common sense and informed clinical judgement.

Les études « négatives » peuvent nous conduire à arrêter des interventions dangereuses!

A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

Paul C. Hébert, M.D., George Wells, Ph.D., Morris A. Blajchman, M.D., John Marshall, M.D., Claudio Martin, M.D., Giuseppe Pagliarello, M.D., Martin Tweeddale, M.D., Ph.D., Irwin Schweitzer, M.Sc., Elizabeth Y

Transfusion Strategies for Patients in Pediatric Intensive Care Units

Jacques Lacroix, M.D., Paul C. Hébert, M.D., James S. Hutchison, M.D., Heather A. Hume, M.D., Marisa Tucci, M.D., Thierry Ducruet, M.Sc., France Gauvin, M.D., Jean-Paul Collet, M.D., Ph.D., Baruch J. Toledano, M.D., Pierre Robillard, M.D., Ari Joffe, M.D., Dominique Biarent, M.D.,

;356:1609-19.

Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery

Jeffrey L. Carson, M.D., Michael L. Terrin, M.D., M.P.H., Helaine Noveck, M.P.H., David W. Sanders, M.D., Bernard R. C Lauren Beau Donald Richard C Rebecc

CARING FOR THE CRITICALLY ILL PATIENT

Transfusion Requirements

JAMA

Liberal or Restrictive Transfusion after Cardiac Surgery

Gavin J. Murphy, F.R.C.S., Katie Pike, M.Sc., Chris A. Rogers, Ph.D., Sarah Wordsworth, Ph.D., Elizabeth A. Stokes, M.Sc., Gianni D. Angelini, F.R.C.S., and Barnaby C. Reeves, D.Phil., for the TITRe2 Investigators*

N Engl J Med 2015;372:997-1008

Lib pat

Jeffrey Sheryl Oscar C. Marroquin, MD,[g] Sunil V. Rao, MD,[h] Helaine Noveck, MPH,[a] Elizabeth Passano, MS,[b] Regina M. Hardison, MS,[b] Thomas Smitherman, MD,[g] Tudor Vagaonescu, MD,[i] Neil J. Wimmer, MD,[j] and David O. Williams, MD[j]

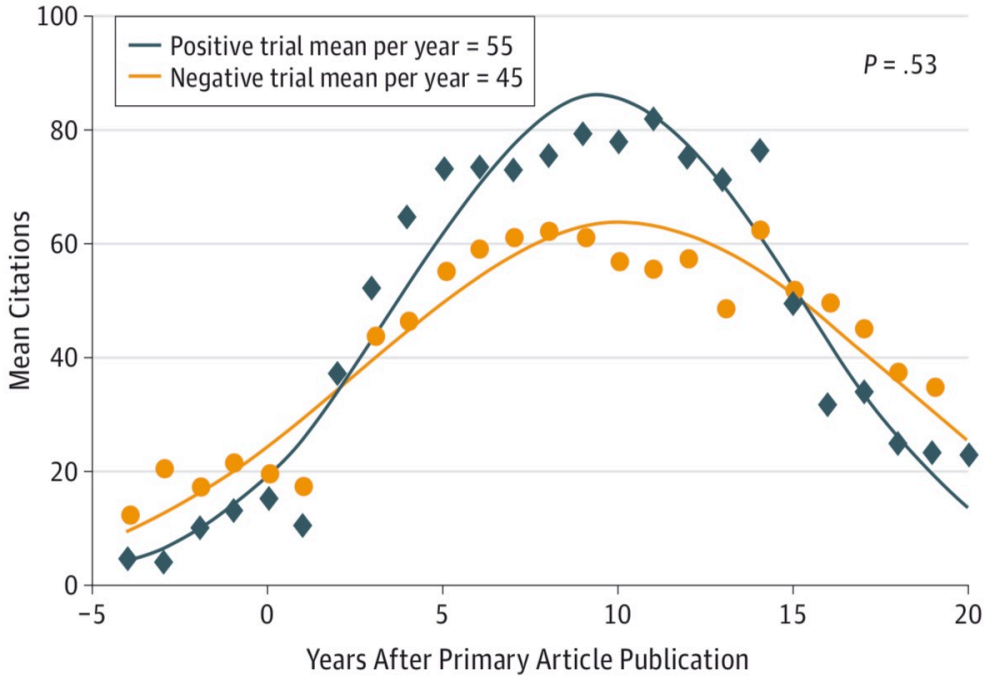
Am Heart J 2013;165:964-

Original Investigation

The Scientific Impact of Positive and Negative Phase 3 Cancer Clinical Trials

Joseph M. Unger, PhD; William E. Barlow, PhD; Scott D. Ramsey, MD; Michael LeBlanc, PhD; Charles D. Blanke, MD; Dawn L. Hershman, MD

B Primary and secondary article publications



Key Points

Question Is the scientific impact of positive ph… cer clinical treatment trials greater than that of ne…

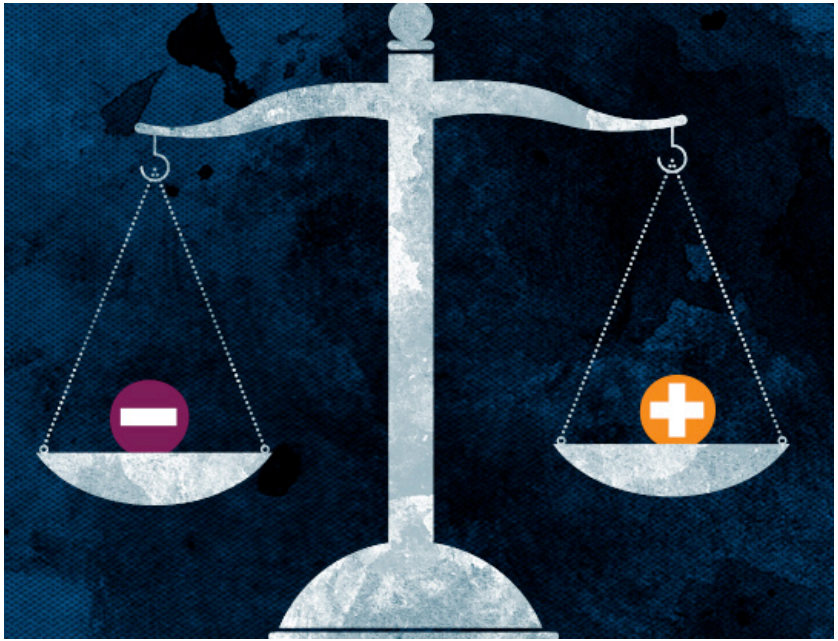
Findings Using SWOG's ph… 985 through 2014, primary result… published in high-impact j… ere cited more frequently than n… tion rate from all primary and second… t significantly differ between positive and negative …

Meaning When all articles derived from phase 3 cancer treatment trials were considered, the scientific impact between positive and negative trials was similar.

IDENTIQUE

JAMA Oncol. 2016;2(7):875-881.

3 types d'études négatives?



- Celles que l'on ne finit pas…
- Les études importantes que l'on ne fait pas!
- Les études mal conçues et mal exécutées…

Il n’y pas d’étude négative…

Pour autant que…

- La question soit importante
- L'étude est bien conçue
- L'étude est bien conduite
- Il y a une hypothèse plausible
- Les résultats sont bien interprétés
- Cela conduit à changer les pratiques

Traduire la recherche en pratique…

Temps '*requis*' pour changer les pratiques…

17

Heures

Jours…

Semaines

Mois

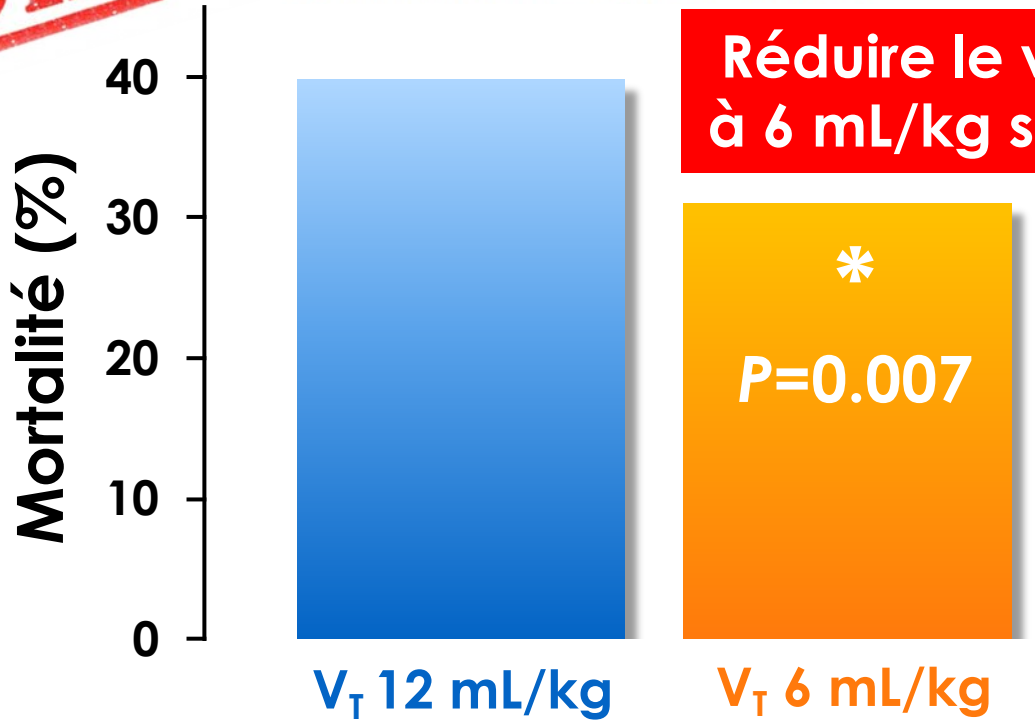
ANS

Après 17 ans, 14% des résultats de recherche se traduisent par un changement de pratiques

EVIDENCE

VENTIL… …H LOWER TIDAL VOLUMES AS COMPARED WITH …TIDAL VOLUMES FOR ACUTE LUNG INJURY …UTE RESPIRATORY DISTRESS SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK*



Réduire le volume insufflé à 6 mL/kg sauve des vies!!

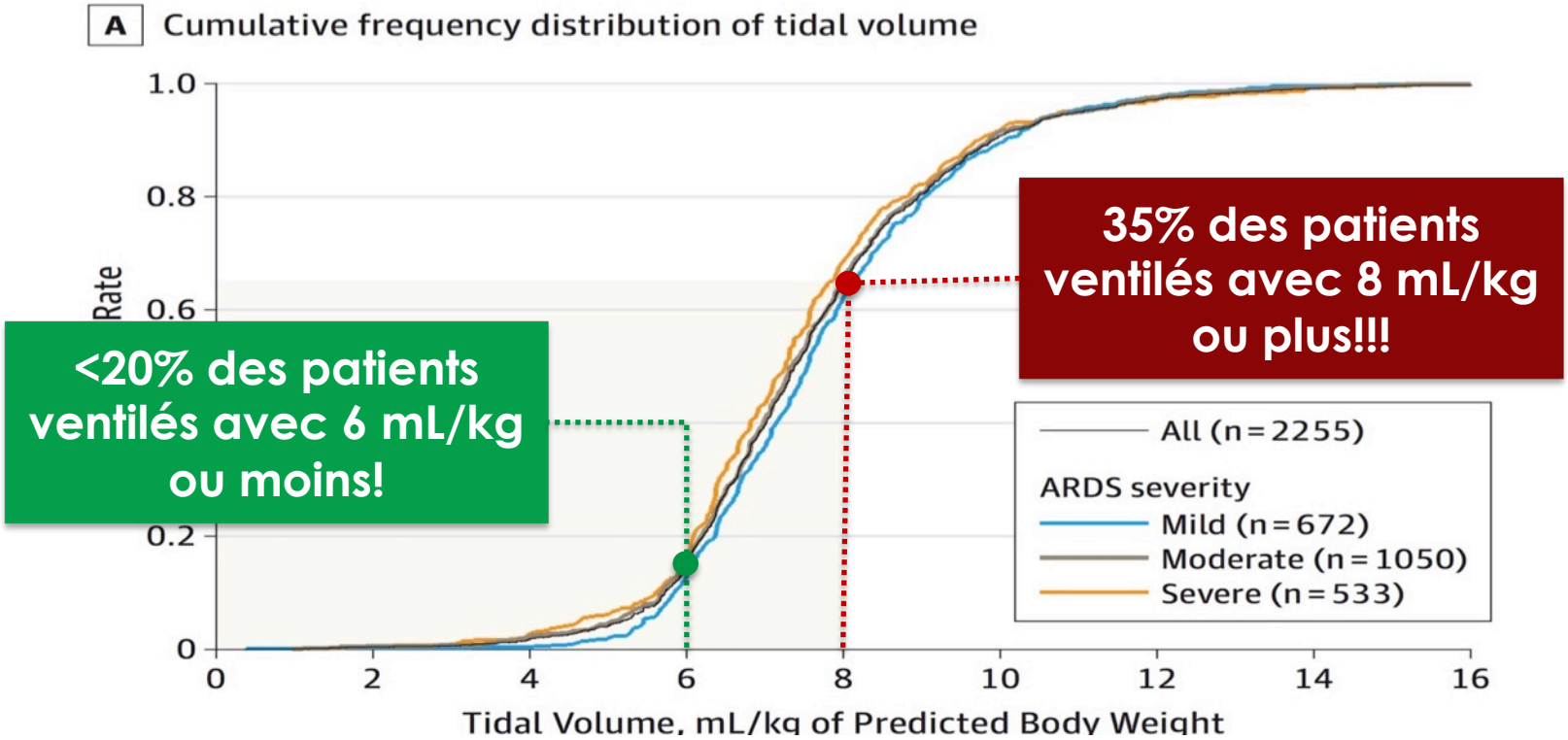
N Engl J Med 2000;342:1301-8.

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

JAMA. 2016;315(8):788-800.

Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

Giacomo Bellani, MD, PhD; John G. Laffey, MD, MA; Tài Pham, MD; Eddy Fan, MD, PhD; Laurent Brochard, MD, HDR; Andres Esteban, MD, PhD; Luciano Gattinoni, MD, FRCP; Frank van Haren, MD, PhD; Anders Larsson, MD, PhD; Daniel F. McAuley, MD, PhD; Marco Ranieri, MD; Gordon Rubenfeld, MD, MSc; B. Taylor Thompson, MD, PhD; Hermann Wrigge, MD, PhD; Arthur S. Slutsky, MD, MASc; Antonio Pesenti, MD; for the LUNG SAFE Investigators and the ESICM Trials Group



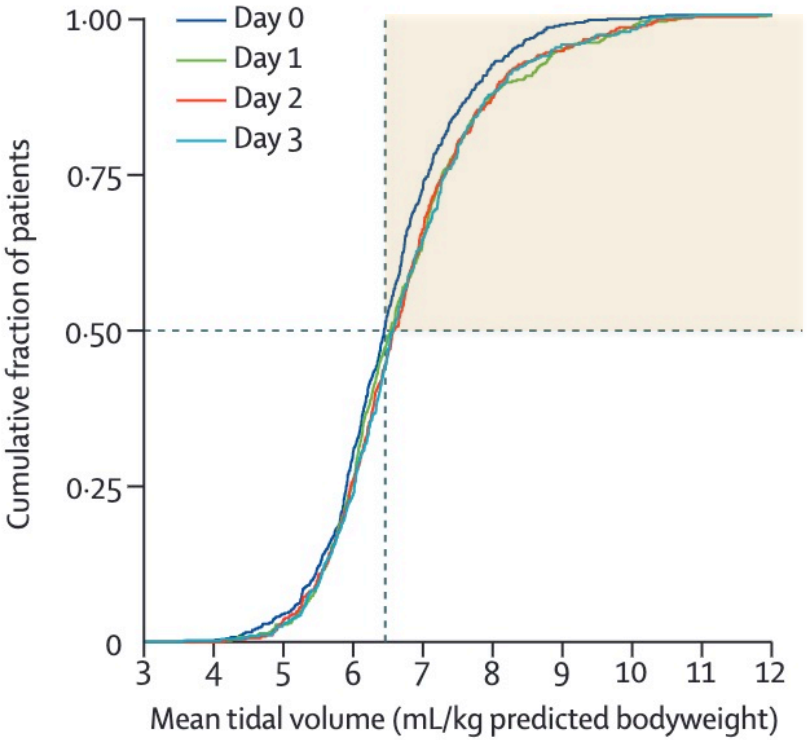
Battling COVID-19-related mortality: from a fight for ventilators to a cry for oxygen

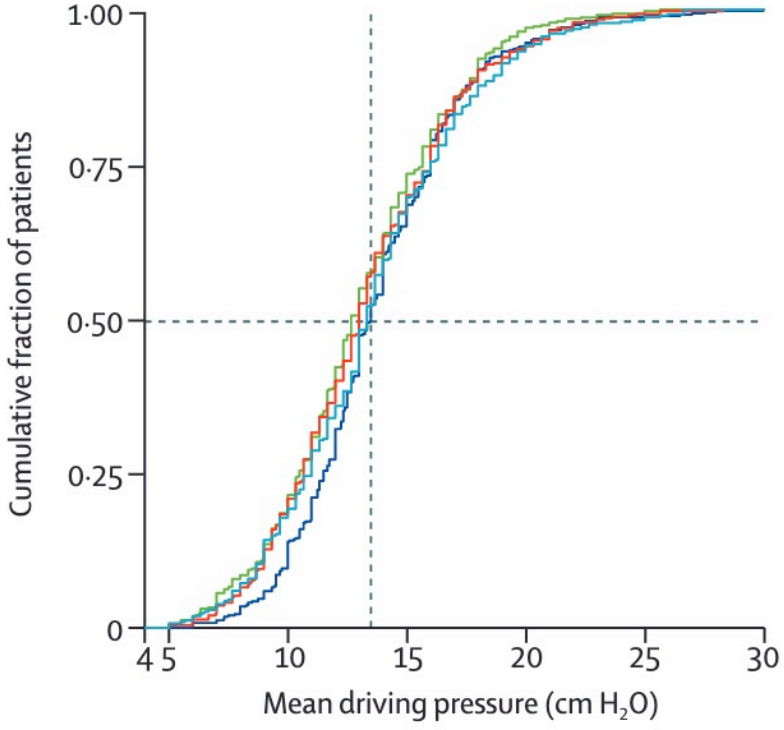
	SATICOVID (n=1909)[6]	PRoVENT-COVID (n=533)[1]	Ferrando et al (n=742)[2]	REVA network (n=4244)[3]	Grasselli et al (n=301)[4]	Cummings et al (n=257)[5]
Country	Argentina	Netherlands	Spain	France, Belgium, and Switzerland*	Italy	USA
Period of inclusion	March–October, 2020	March–April, 2020	March–June, 2020	February–May, 2020	March, 2020	March–April, 2020
Patient characteristics						
Age, years	62 (52–70)	67 (59–73)	64 (56–71)	64 (54–71)*	63 (55–70)	62 (51–72)
Sex						
Female	615 (32%)	136 (25%)	236/740 (32%)	1085 (26%)	69 (23%)	86 (33%)
Male	1294 (68%)	417 (75%)	504/740 (68%)	3159 (74%)*	232 (77%)	171 (67%)
PaO_2/FiO_2, mm Hg	160 (111–218)	159 (129–200)	120 (83–177)	154 (106–223)	124 (89–164)	103 (82–134)
Ventilatory variables at day 1						
Tidal volume, mL/kg predicted bodyweight	6·1 (6·0–7·0)	6·3 (5·7–7·1)	6·9 (6·3–7·8)	6·1 (5·8–6·7)	7·0 (6·3–7·6)	6·2 (5·9–7·2)
PEEP, cm H_2O	10 (8–12)	14 (11–15)	12 (11–14)	12 (10–14)	13 (10–15)	15 (12–18)
Respiratory system compliance, mL/cm H_2O	36 (29–44)	32 (26–40)	35 (27–45)	33 (26–42)	41 (33–52)	27 (22–36)
Outcomes						
Duration of ventilation, days	13 (7–22)	13 (7–22)	14 (7–24)	11 (7–17)	..	18 (9–28)
Hospital mortality	1101 (58%)	210 (42%)	..	1173 (37%)	..	101 (39%)
28-day mortality	966 (51%)	186 (35%)	241 (32%)	1019 (30%)	93 (36%)	..

Ventilation management and clinical outcomes in invasively ventilated patients with COVID-19 (PRoVENT-COVID): a national, multicentre, observational cohort study

Lancet Respir Med 2021; 9: 139–48

*Michela Botta, Anissa M Tsonas, Janesh Pillay, Leonoor S Boers, Anna Geke Algera, Lieuwe D J Bos, Dave A Dongelmans, Marcus W Hollmann, Janneke Horn, Alexander P J Vlaar, Marcus J Schultz, Ary Serpa Neto, Frederique Paulus, for the PRoVENT-COVID Collaborative Group**





SCIENCES • MÉDECINE

Covid-19 : de nouvelles données sur la mortalité en réanimation

En Lombardie (Italie), un patient sur deux admis en soins intensifs est décédé ; aux Etats-Unis, la proportion est de 40 %, selon deux études. Le taux serait de 30 % en France, un chiffre qui reste à consolider.

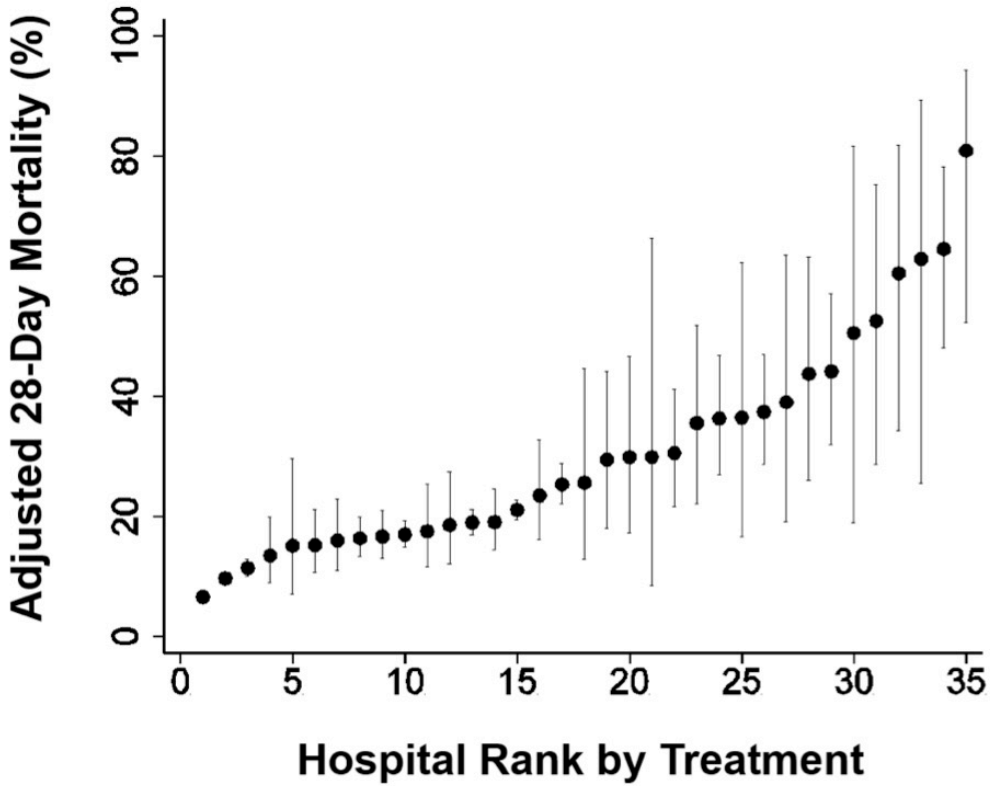
Dans une cohorte américaine de 2215 patients admis en soins intensifs, le taux de mortalité est évalué à 35,4% à vingt-huit jours, avec de fortes disparités entre les 65 centres (de 6,6 % à 80,8 %), selon un article publié le 15 juillet dans JAMA Internal Medicine.

JAMA Internal Medicine | Original Investigation

JAMA Intern Med. doi:10.1001/jamainternmed.2020.3596
Published online July 15, 2020.Last corrected on September 10, 2020.

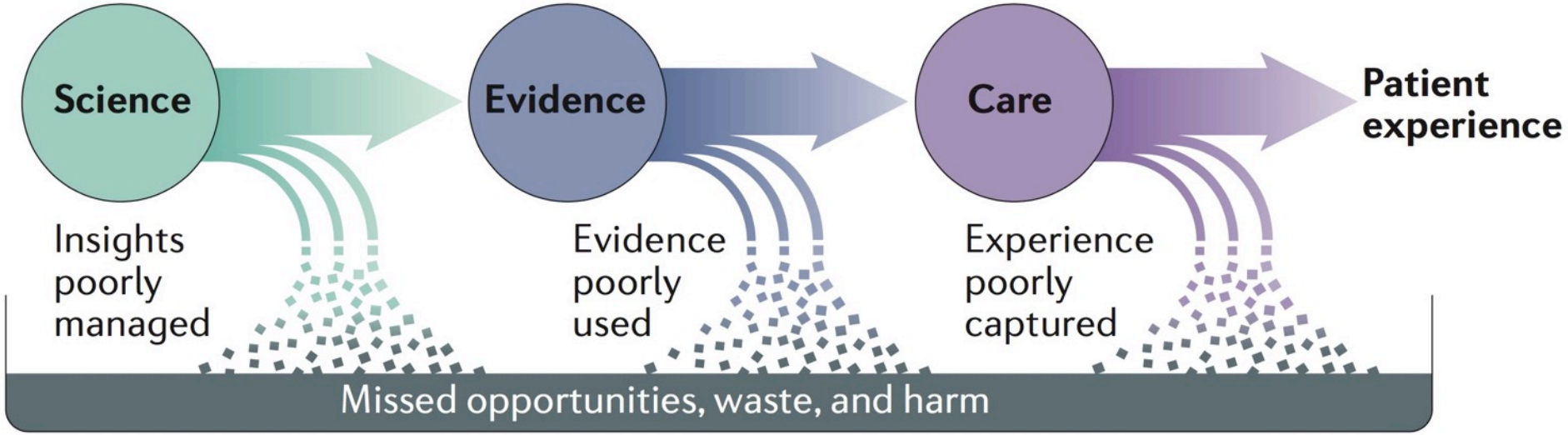
Factors Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US

Shruti Gupta, MD, MPH; Salim S. Hayek, MD; Wei Wang, PhD; Lili Chan, MD, MSCR;



Innover pour mieux soigner: une démarche agile!

Objectif: des soins de haute qualité pour chaque patient



John S. Rumsfeld[1,2], Karen E. Joynt[3,4] and Thomas M. Maddox Nat Rev Cardiol, 2016 vol. 13 (6)


ACT
WAIT


& TRIALS
TRIBULATIONS

La bonne nouvelle…

- Des essais cliniques nombreux
  - 5819 essais à promotion industrielle en 2018-2019
  - Tous les médicaments et dispositifs médicaux
- Nos essais cliniques sont mieux conduits
  - Méthodologie
  - Ethiques
  - Publications

Bonne nouvelle mais…

- **Essais cliniques trop précis**
  - Patients sélectionnés; “ce n’est pas la vraie vie”…

- **Pas d’essais réellement comparatifs**
  - A vs. B ? Mais dans quel contexte ?
  - A vs. B, vs. C, vs. D,…
    - Et si on donne E ou F …

- **Je veux juste la réponse**
  - Mes patients ne sont pas des cobayes…


Recherche
clinique
ctrl
alt

FOCUS ON SEPSIS

Trial failure prompts soul-searching for critical-care specialists

In late May, researchers delivered the final analysis of the boldly named PROWESS-SHOCK trial. Despite the study's gallant moniker, though, the antisepsis drug Xigris (activated protein C) showed little prowess—and the results came as no shock, as Eli Lilly, the Indiana-based drugmaker behind the medicine, had already withdrawn Xigris from worldwide markets in October 2011. At the end of the day, global sales of Xigris came in at only $104 million in 2010, the last full year the agent was in use. But the PROWESS-SHOCK study continues to be a point of contention in the sepsis field as researchers dispute whether the results of randomized trials in the sepsis arena can fully be trusted.

"The outcome of [PROWESS-SHOCK] was not only bad for Lilly and activated protein C, but it was really bad for the entire field," says Steven Opal, an infectious disease specialist at the Brown University School of Medicine in Providence, Rhode Island.

For one thing, says Derek Angus, a critical-care physician at the University of Pittsburgh in Pennsylvania who sat on the data and safety monitoring board for the PROWESS-SHOCK trial, the whole Xigris story is "a bit of a faith shaker around how much of a house of sand are we building here" with clinical trials for sepsis. "The whole potential fickleness of this is quite disconcerting," he says.

Lilly's decision to pull Xigris came nearly a decade after US and European regulators approved the drug off the back of the first phase 3 PROWESS trial. That 1,700-person study was stopped early, in June 2000, because Xigris's results seemed so amazing: a reduction in 28-day mortality from 31% in the placebo group to 25% in Xigris-treated individuals (*N. Engl. J. Med.* **344,** 699–709, 2001). Yet subsequent findings proved disappointing. Additional trials requested by the US Food and Drug Administration (FDA), one in less ill adults and another in children with severe sepsis, did not show a benefit for Xigris (*N. Engl. J. Med.* **353,** 1332–1341, 2005; *Lancet* **369,** 836–843, 2007), and, like PROWESS, both studies were stopped prematurely—in these cases, however, for futility, rather than efficacy, reasons.

The PROWESS-SHOCK trial came about at the behest of the European Medicines Agency, which requested another large study of Xigris after numerous critics pointed out aspects of the original PROWESS design and implementation that may have helped yield a favorable result. For example, organizers changed the enrollment criteria halfway through the PROWESS trial to include more participants at high risk of death. Upon retesting, Xigris ultimately failed to reduce mortality in patients with septic shock in the PROWESS-SHOCK trial, a finding that has cast further doubt on the integrity of the first study.

Lilly-livered: The post-marketing PROWESS-SHOCK trial spurred Lilly to withdraw its antisepsis drug.

Which trial results do you believe?

Some researchers now think both trials were valid but came to different conclusions simply because of improvements in general sepsis management over the past decade that improved the survival rate of the control group and thereby diminished the comparative influence of the drug. Researchers involved in PROWESS-SHOCK had originally expected a 28-day survival rate in the placebo group below 70%, as was seen in PROWESS. But what they eventually saw was a rate of 76%. "When you have a moving target of placebo mortality and improvements in the standard of care, that adds additional challenges to running these types of studies, which are already very complicated and difficult," notes Jonathan Janes, medical director for acute care with Lilly.

Against that backdrop, PROWESS-SHOCK may have been underpowered to detect a significant benefit for Xigris. "This is a study that's negative for Xigris but positive for critical-care medicine," says Marco Ranieri, an anesthesiologist and intensive-care physician at the University of Turin in Italy. Or, perhaps, Xigris is now superfluous given the state of modern medicine, notes Taylor Thompson, director of the medical intensive care unit at the Massachusetts General Hospital in Boston who, together with Ranieri, led the PROWESS-SHOCK trial. "What we've got is a clinical trial of well-resuscitated, well-treated patients, and in that setting you don't need Xigris," he says.

But not everyone has such confidence in the latest study's results, given the logistical issues of running a placebo-controlled trial of an already approved medicine. Opal notes that many of the clinical centers that participated in the original PROWESS trial refused to take part in the follow-up, and he suspects that those sites that did enroll individuals in PROWESS-SHOCK—and were thus willing to give a placebo—might have been prejudiced, subconsciously or otherwise, against the drug from the get-go. "If you take the better places out of the globe and you exclude them from the study, it's possible that you've biased the study for failure rather than success," he says.

Guido Bertolini, a clinical epidemiologist who specializes in intensive care at the Mario Negri Institute for Pharmacological Research in Bergamo, Italy, also worries about the "dangerous precedent" that such a trial poses. "The idea to look for a confirmatory trial on efficacy without withdrawing the drug from the market is unbelievable from an ethical perspective," he says.

Not to worry, argues Thompson. "Reading the tea leaves from the FDA, my guess is that they'll never do this again," he says. "They'll ask for two trials" before granting approval for antisepsis drugs.

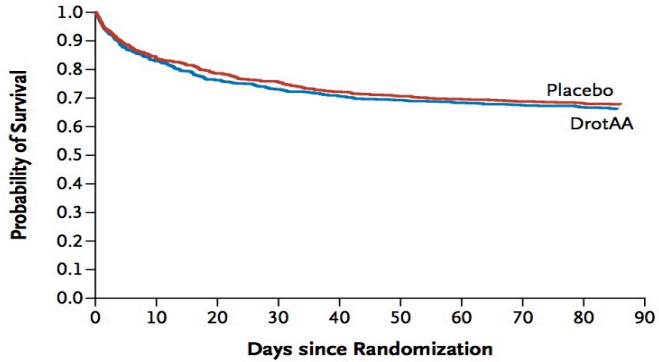
That may help mitigate some concerns. But, given the cost and uncertainty of such trials, the need for large-scale replication could have a chilling effect on the whole field. "It's going to take the financial incentive that was mildly present in the past to do these sepsis trials out of the equation," Opal says.

Elie Dolgin

Nature Medicine 2012;18(7)

Drotrecogin Alfa (Activated) in Adults with Septic Shock

V. Marco Ranieri, M.D., B. Taylor Thompson, M.D., Philip S. Barie, M.D., M.B.A., Jean-François Dhainaut, M.D., Ivor S. Douglas, M.D., Simon Finfer, F.R.C.P., Bengt Gårdlund, M.D., John C. Marshall, M.D., Andrew Rhodes, M.D., Antonio Artigas, M.D., Ph.D., Didier Payen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D., Hussein R. Al-Khalidi, Ph.D., Vivian Thompson, M.P.H., Jonathan Janes, M.B., B.Ch., William L. Macias, M.D., Ph.D., Burkhard Vangerow, M.D., and Mark D. Williams, M.D., for the PROWESS-SHOCK Study Group*



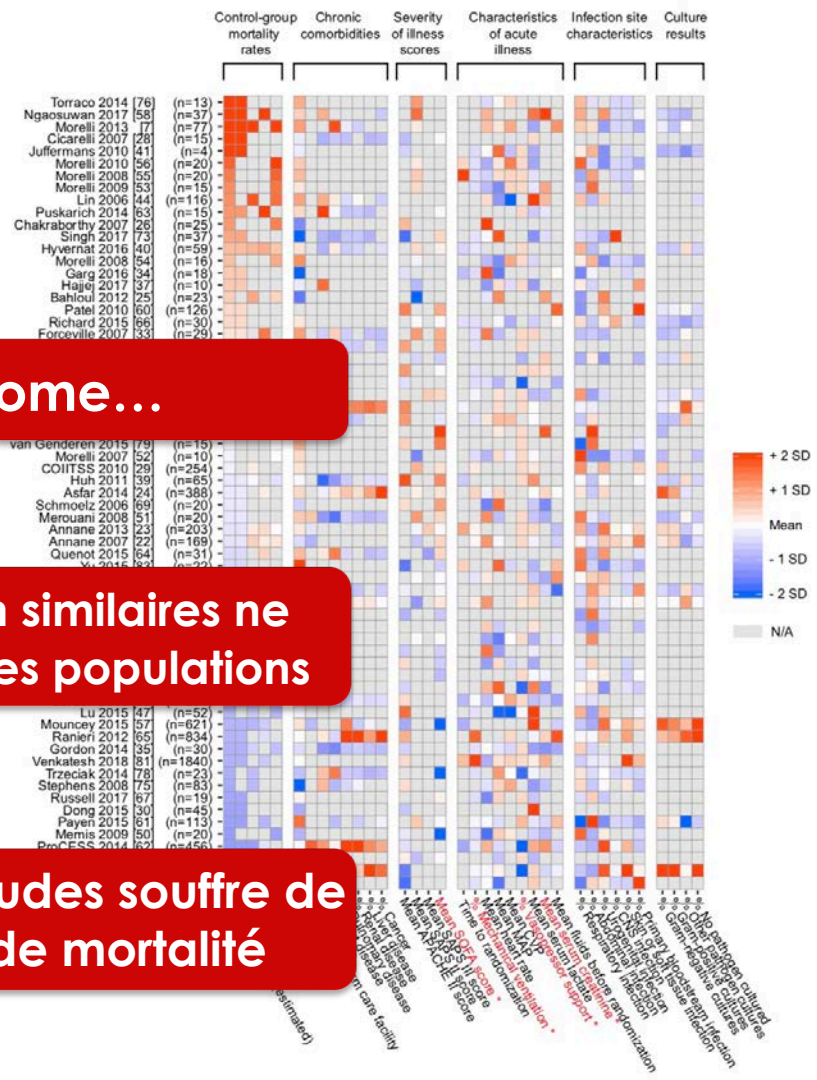
No. at Risk

Placebo	845	703	656	622	593	579	569	563	557	553
DrotAA	851	701	645	616	596	584	576	567	561	555

N Engl J Med 2012;366:2055-64.

Unexplained mortality differences between septic shock trials: a systematic analysis of population characteristics and control-group mortality rates

Harm-Jan de Grooth[1,2*], Jonne Postema[2], Stephan A. Loer[2], Jean-Jacques Parienti[3,4], Heleen M. Oudemans-van Straaten[1] and Armand R. Girbes[1]



1 Le sepsis reste un syndrome…

2 Des critères d'inclusion/exclusion similaires ne garantissent pas l'homogénéité des populations

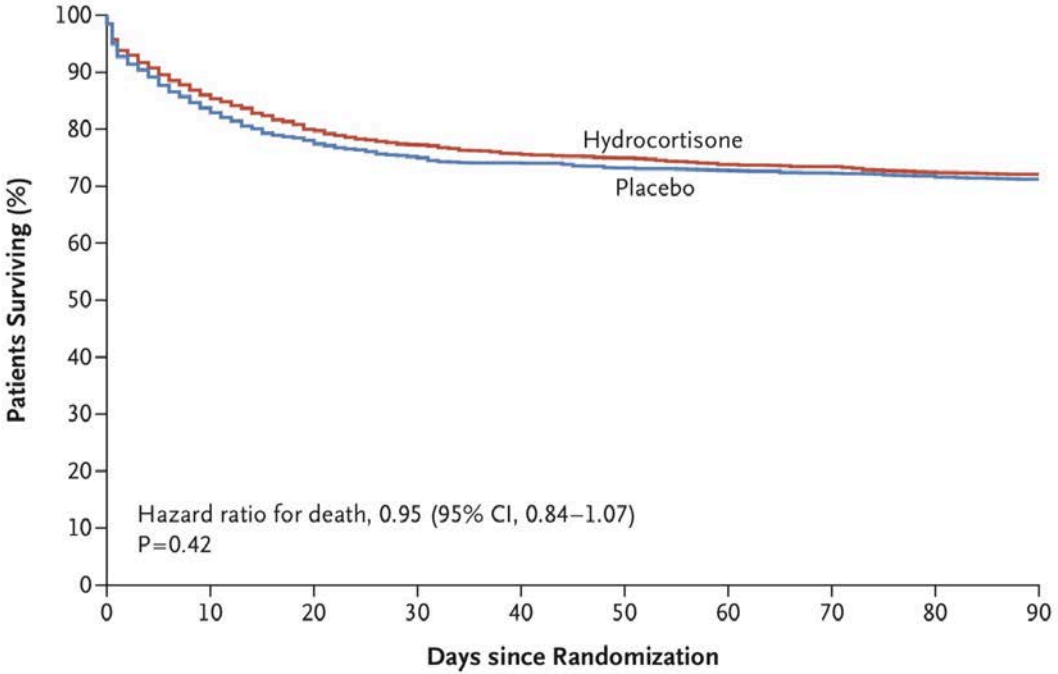
3 Le calcul de puissance de nos études souffre de l'imprécision des prédictions de mortalité

Mortalité: le bon critère de jugement?

- Mortalité aux soins intensifs?
- Mortalité hospitalière?
- J14, J28, J90 ?
- Toute cause ou liée au choc ?
- Influencé par des facteurs indépendants du traitement à l'étude
- Autres critères?

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*



Hydrocortisone	1832	1591	1481	1418	1388	1374	1356	1348	1328	1321
Placebo	1826	1546	1433	1376	1354	1337	1330	1322	1312	1300

N Engl J Med 2018;378:797-808.

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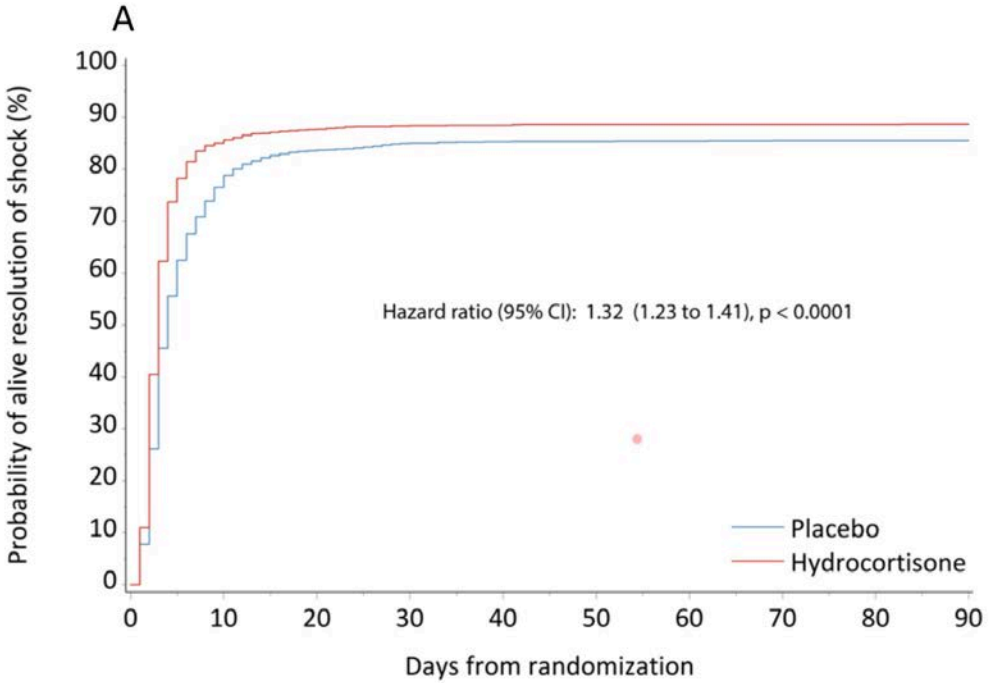

No. at Risk										
Hydrocortisone	1843	104	34	9	6	3	3	2	1	0
Placebo	1854	213	53	19	8	6	4	0	0	0

Moins de temps sous vasopresseurs

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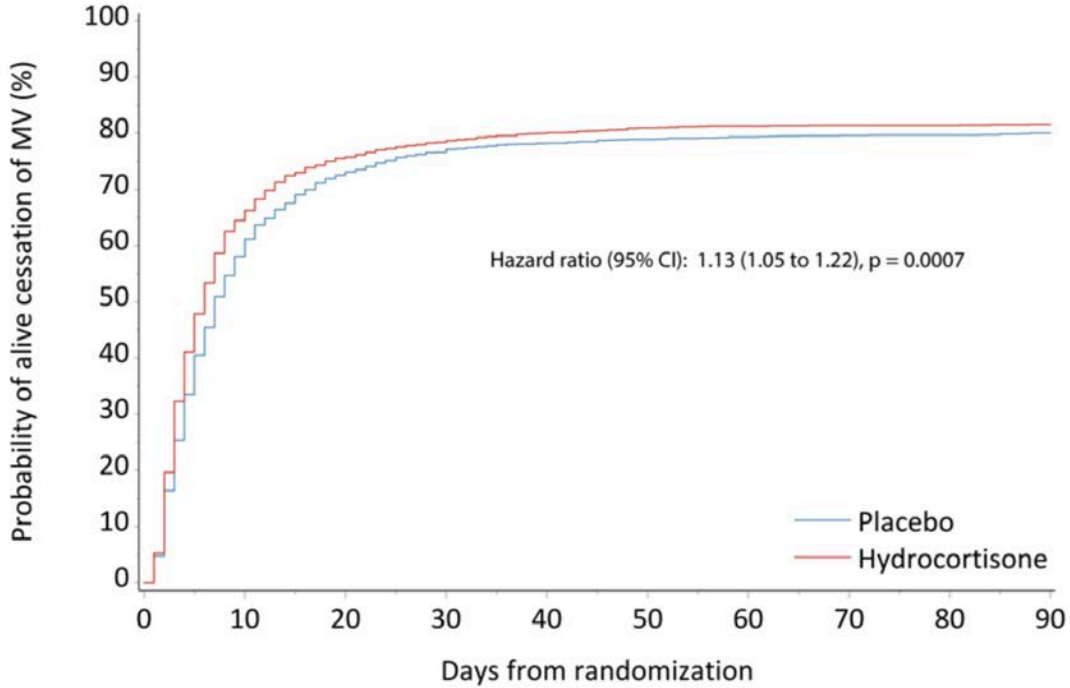

No. at Risk										
Hydrocortisone	1842	439	175	90	50	31	18	14	11	8
Placebo	1849	513	182	85	51	31	24	17	15	8

Moins de temps sous ventilation mécanique

N Engl J Med 2018;378:797-808.

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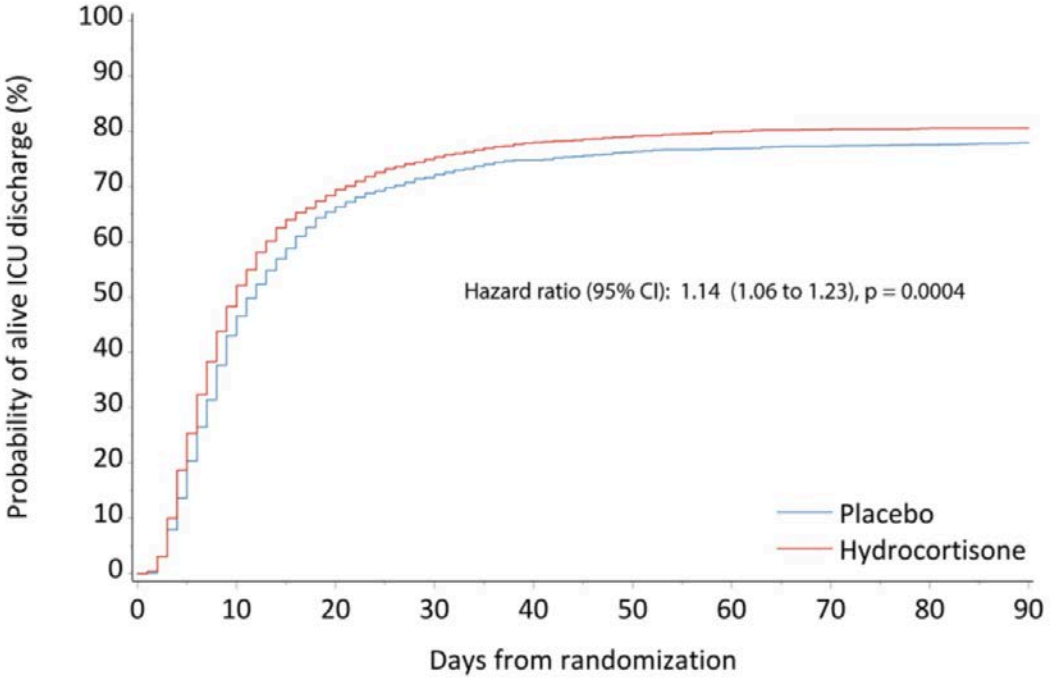


No. at Risk										
Hydrocortisone	1843	731	284	128	63	40	16	10	3	2
Placebo	1849	780	289	138	74	41	29	20	14	8

Moins de temps aux soins intensifs

N Engl J Med 2018;378:797-808.

Implications of Heterogeneity of Treatment Effect for Reporting and Analysis of Randomized Trials in Critical Care

Theodore J. Iwashyna[1,2,3], James F. Burke[4], Jeremy B. Sussman[1,3], Hallie C. Prescott[1], Rodney A. Hayward[1,3], and Derek C. Angus[5]

Une étude clinique détermine l'effet moyen d'un traitement sur une population

Conclusions

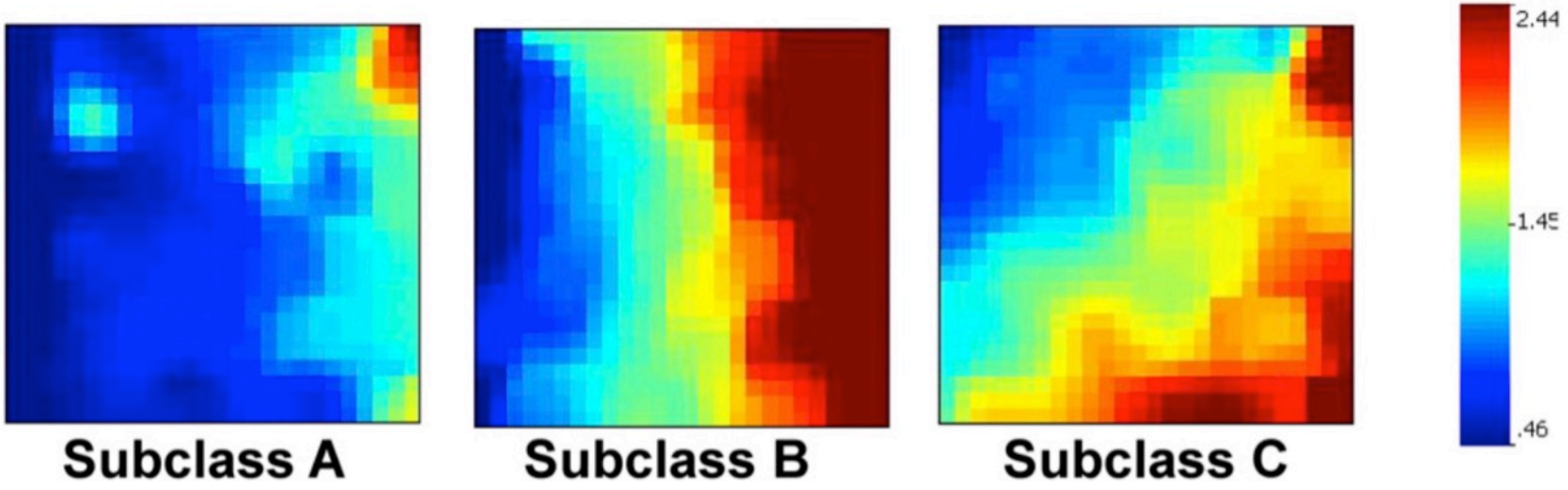
En conclusion, ce travail suggère que l'effet global du traitement évalué par un essai peut être un guide trompeur quand à l'utilité de ce traitement chez un patient individuel tant que nous ignorons quelles 'caractéristiques patient' conditionnent l'efficacité (ou la toxicité) du traitement pour lui/elle.

Am J Respir Crit Care Med Vol 192, Iss 9, pp 1045–1051, Nov 1, 2015

Developing a Clinically Feasible Personalized Medicine Approach to Pediatric Septic Shock

Hector R. Wong[1,2], Natalie Z. Cvijanovich[3], Nick Anas[4], Geoffrey L. Allen[5], Neal J. Thomas[6], Michael T. Bigham[7], Scott L. Weiss[8], Julie Fitzgerald[8], Paul A. Checchia[9], Keith Meyer[10], Thomas P. Shanley[11], Michael Quasney[11], Mark Hall[12], Rainer Gedeit[13], Robert J. Freishtat[14], Jeffrey Nowak[15], Raj S. Shekhar[16], Shira Gertz[17], Emily Dawson[18], Kelli Howard[1], Kelli Harmon[1], Eileen Beckman[1], Erin Frank[1], and Christopher J. Lindsell[19]

Evaluation of gene expression for 100 « class-defining genes ».
Color & intensity indicate increased / decreased gene expression

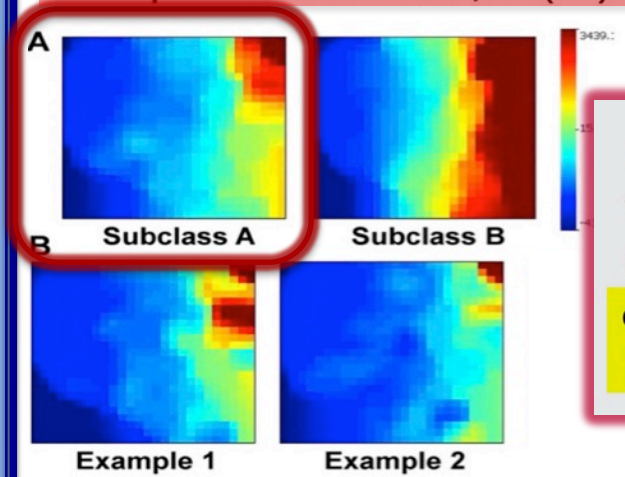


Am J Respir Crit Care Med Vol 191, Iss 3, pp 309–315, Feb 1, 2015

Developing a Clinically Feasible Personalized Medicine Approach to Pediatric Septic Shock

Hector R. Wong[1,2], Natalie Z. Cvijanovich[3], Nick Anas[4], Geoffrey L. Allen[5], Neal J. Thomas[6], Michael T. Bigham[7], Scott L. Weiss[8], Julie Fitzgerald[8], Paul A. Checchia[9], Keith Meyer[10], Thomas P. Shanley[11], Michael Quasney[11], Mark Hall[12], Rainer Gedeit[13], Robert J. Freishtat[14], Jeffrey Nowak[15], Raj S. Shekhar[16], Shira Gertz[17], Emily Dawson[18], Kelli Howard[1], Kelli Harmon[1], Eileen Beckman[1], Erin Frank[1], and Christopher J. Lindsell[19]

	Subclass A	Subclass B
n	57	111
Median age (IQR), yr	1.4 (0.2–2.9)	3.0 (1.5–7.3)*
Males, n (%)	36 (63)	64 (58)
28-d mortality, n (%)	12 (21)	11 (10)†
Complicated course, n (%)	24 (42)	26 (23)†



Allocation to this subclass was independently associated with mortality (odds ratio = 2.7; CI_{95} = 1.2–6.0; P = 0.016), and adjunctive corticosteroids prescribed at physician discretion were independently associated with mortality in this subclass (odds ratio = 4.1; CI_{95} = 1.4–12.0; P = 0.011).

Am J Respir Crit Care Med Vol 191, Iss 3, pp 309–315, Feb 1, 2015

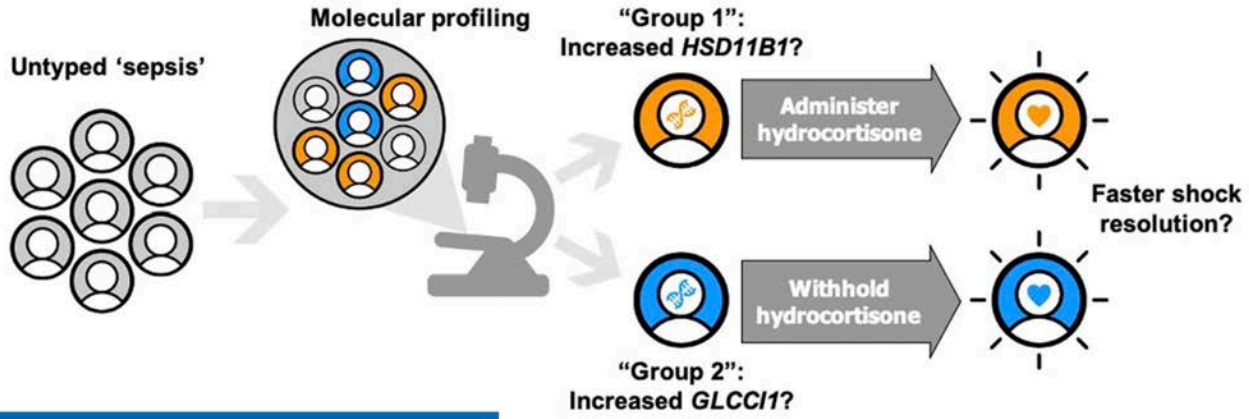
ORIGINAL

The relationship between adrenocortical candidate gene expression and clinical response to hydrocortisone in patients with septic shock

Jeremy Cohen[1,2,3,4*], Antje Blumenthal[5], Gabriel Cuellar-Partida[5], David M. Evans[5,6], Simon Finfer[1,7,8,9], Qiang Li[1], Johanna Ljungberg[5], John Myburgh[1,7,10], Elizabeth Peach[5], Joseph Powell[11,12], Dorrilyn Rajbhandari[1], Andrew Rhodes[13], Anne Senabouth[11] and Balasubramanian Venkatesh[1,3,7,14]

Genes tested

NR3C1	Glucocorticoid receptor (including Beta splice variant)
NR3C2	Mineralocorticoid receptor
MC2R	Adrenocorticotrophin receptor
CRHR1	Corticotrophin releasing hormone receptor
LINC02210-CRHR1	Corticotrophin releasing hormone receptor isoform
CRHBP	Corticotrophin releasing hormone binding protein
CRH	Corticotrophin releasing hormone
GLCCI1	Glucocorticoid induced transcript protein
HSD11B1	Intracellular conversion cortisone to cortisol
HSD11B2	Intracellular conversion cortisol to cortisone



Take-home message

In patients with septic shock, variation in gene expression may alter the clinical response to adjunctive corticosteroids.

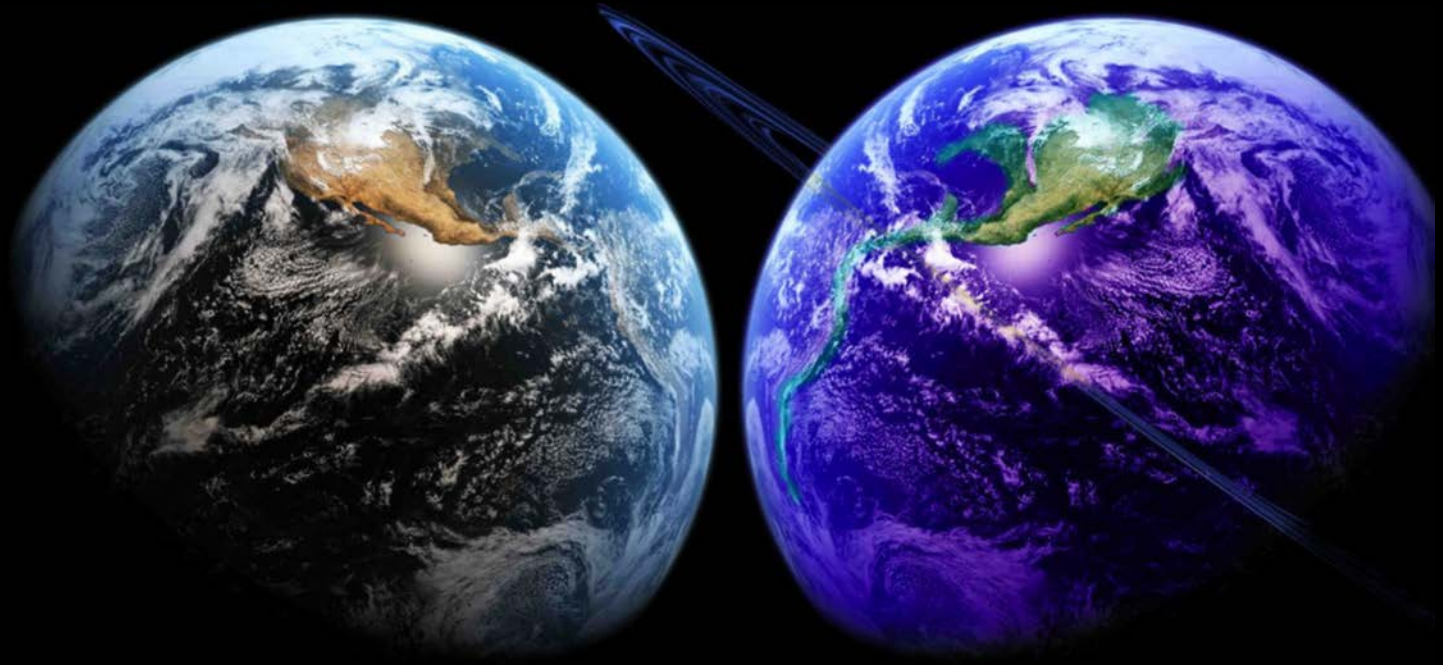
Intensive Care Med (2021) 47:974–983

AUSSI POUR LE SEPSIS & LES SOINS INTENSIFS

PRECISION HEALTH

Individualized treatments to maximize the benefits of any particular intervention for one single individual.

Parallel universes …



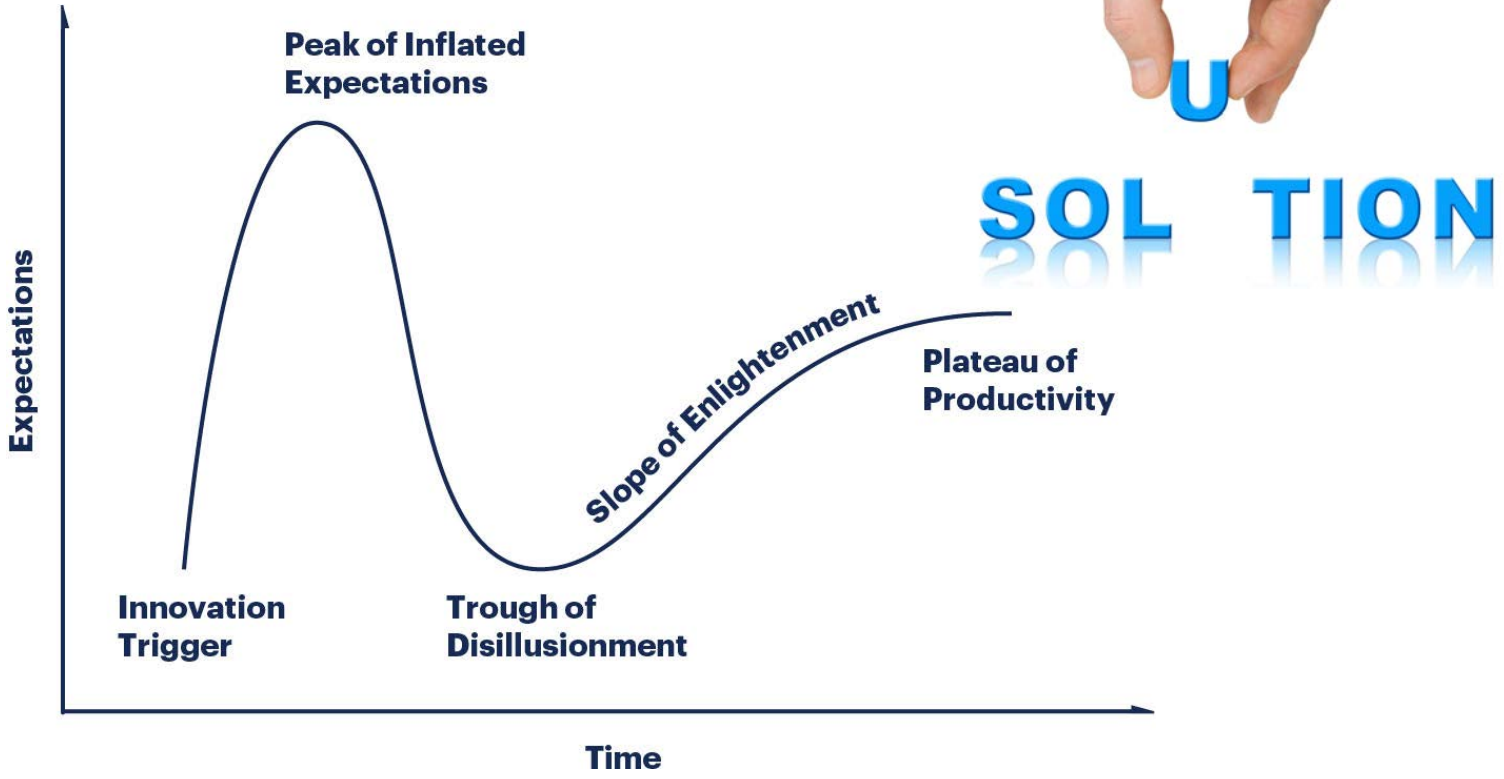
Clinical care

Clinical research

A quoi sert la recherche clinique?

- Obtenir des publications
- Obtenir des fonds
- Obtenir plus de fonds…
- Convertir les patients en billets d'avion
- Générer l'évidence nécessaire pour guider et, le cas échéant, changer les pratiques cliniques
- Mieux comprendre

The Revolution of Trial Design



L'ére des 'Big Data' et de l'intelligence artificielle

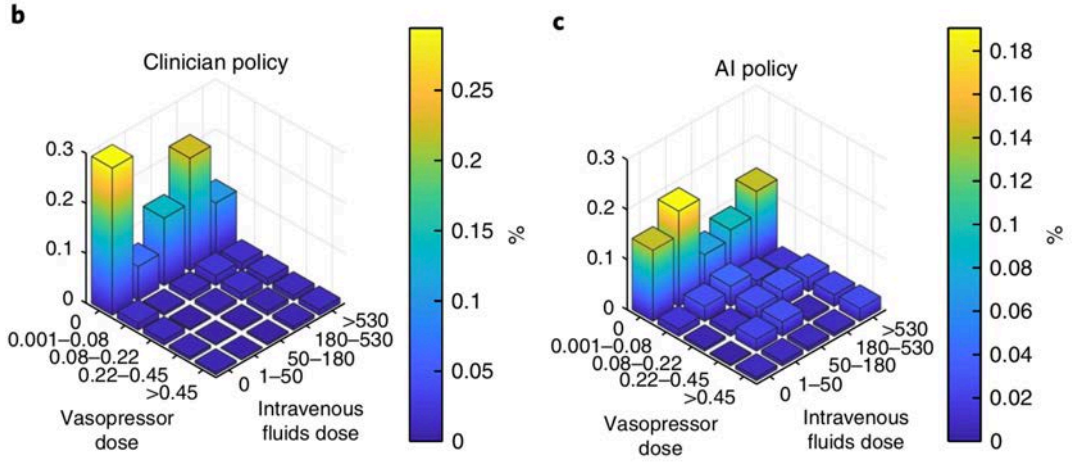
- **Intégration de données personalisées et 'denses'**
  - **Pour informer sur les soins optimaux**
  - **Des données – 'vie réelle' et pratique quotidienne**
  - **Pour des estimations de bénéfice 'personnel'**
  - **Le carburant de l'intelligence artificielle**

The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care

Matthieu Komorowski[1,2,3], Leo A. Celi[3,4], Omar Badawi[3,5,6], Anthony C. Gordon[1*] and A. Aldo Faisal[2,7,8,9*]

nature medicine

Les patients reçoivent plus de remplissage vasculaire et moins de vasopresseurs que ce recommanderait un algorithme d'IA entraîné pour détecter les combinaisons optimales pour la survie.



- 36% des patients reçoivent la quantité de liquides suggérée par l'algorithme
- Seuls 17% des patients reçoivent des vasopresseurs, alors que l'IA traiterait 30% des patients

Nature Medicine **24**, 1716–1720 (2018)

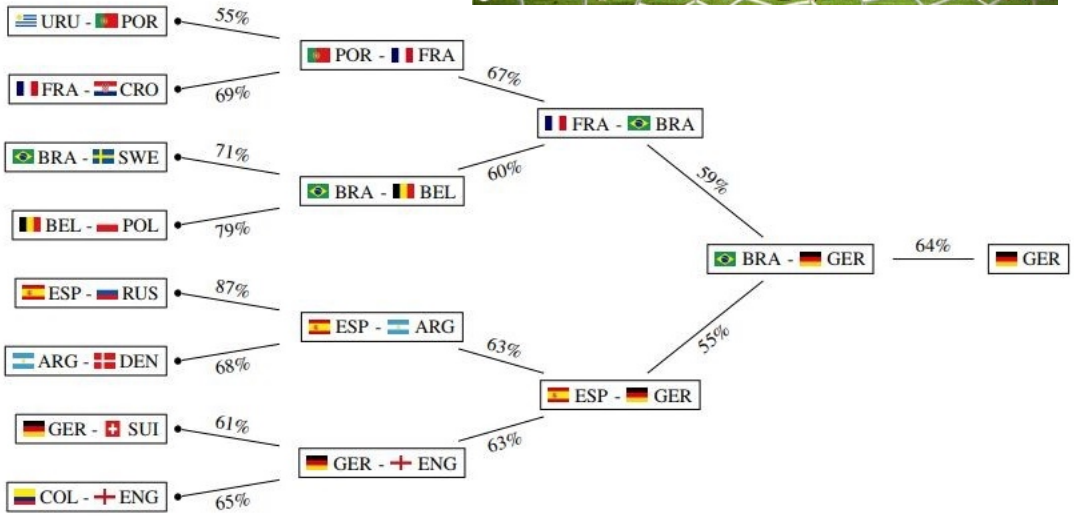
Intelligent Machines

Machine learning predicts World Cup winner

Researchers have predicted the outcome after simulating the entire soccer tournament 100,000 times.

The predictions arrived at through this process differ from others in some important ways. For a start, the random-forest method picks out Spain as the most likely winner, with a probability of 17.8 percent.

However, a big factor in this prediction is the structure of the tournament itself. If Germany clears the group phase of the competition, it is more likely to face strong opposition in the 16-team knockout phase. Because of this, the random-forest method calculates Germany's chances of reaching the quarter-finals as 58 percent. By contrast, Spain is unlikely to face strong opposition in the final 16 and so has a 73 percent chance of reaching the quarter-finals.

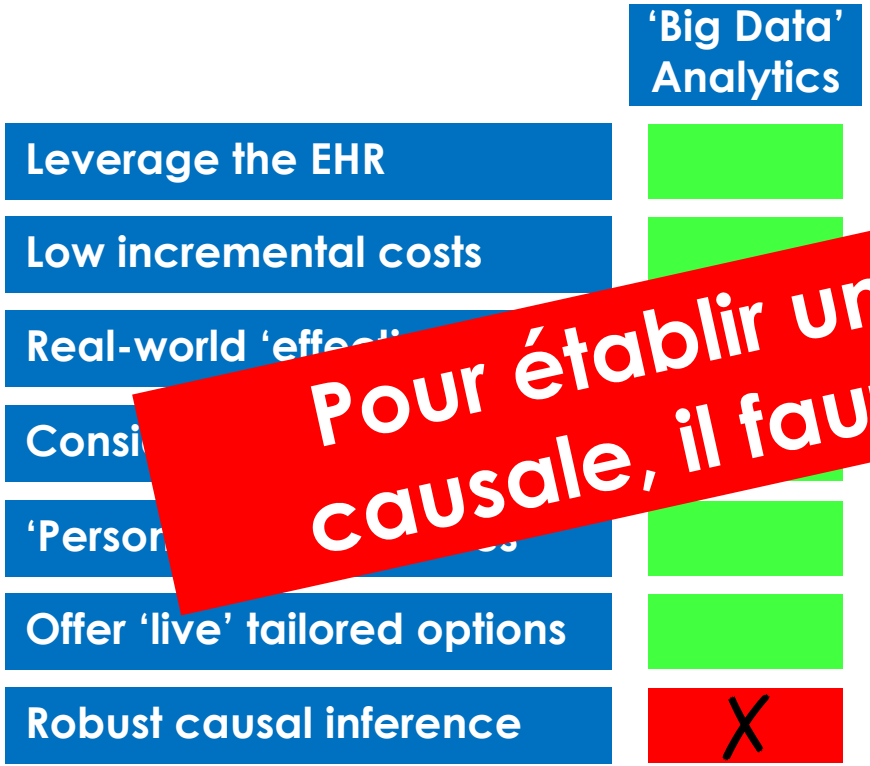


VIEWPOINT

Fusing Randomized Trials With Big Data

The Key to Self-learning Health Care Systems?

Derek C. Angus, MD, MPH



Pour établir une inférence causale, il faut randomiser!

Les essais Point-of-care (POC)

- Un évènement clinique dans le système d'information 'déclenche' l'essai clinique
- VA EHR system
  - Patients diabétiques non équilibrés
  - Lorsque l'on prescrit de l'insuline, le système propose de ransomiser…
    - Protocole selon glycémie vs algorithme base sur le poids
      - Fiore et al. Clinical Trials 2011
- Dans la cour des grands essais 'pragmatiques'
  - 2 diurétiques thiazidiques, >13k patients hypertendus (NCT02185417)
  - 2 doses d'aspirine, 20k patients coronariens (ADAPTABLE) (PCORI)

VIEWPOINT

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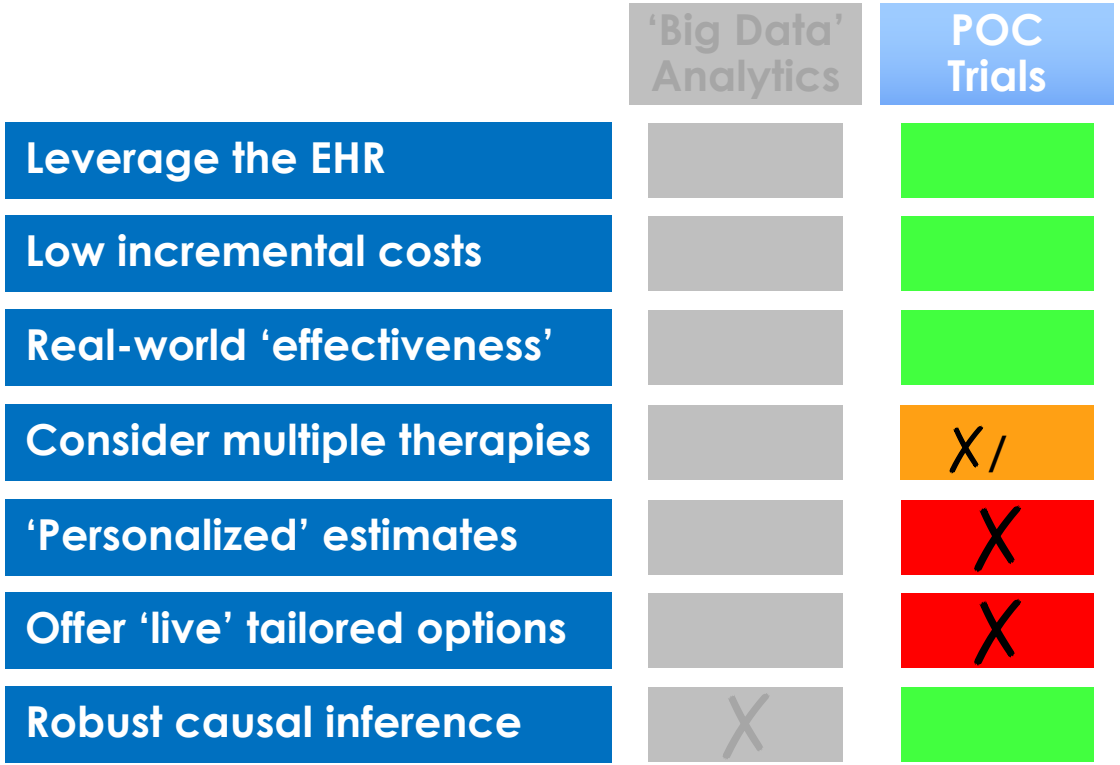


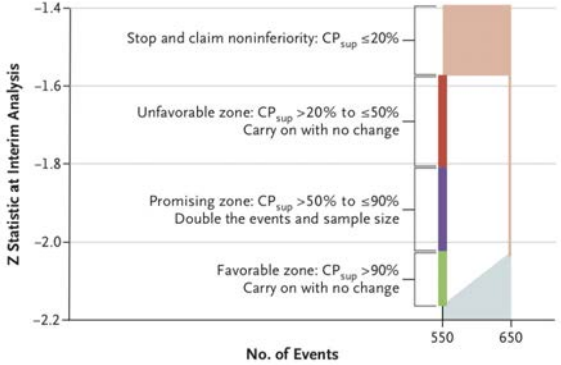
Adapter pour mieux soigner

- **Essais adaptatifs: vers des essais cliniques avec bénéfice individuel direct**
  - Pour garantir à chaque patient le meilleur traitement connu à l'instant T
  - Des interventions mutliples et des essais qui s'adaptent au fil du temps
  - Essais 'perpétuels', conduits pendant les soins courants
  - Technologie: modèles & statistiques bayesiennes
- **Focus sur les maladies plus que sur les traitements**
  - Objectif: établir l'efficacité et la sécurité sans exposer des patients inutilement alors que la réponse devient disponible
  - S'adaptent à l'arrivée de nouveaux traitements

JAMA. 2015;313(16):1619-1620.

Essais adaptatifs: les principes

- **Simulation *in silico* & adapter le modèle en cours d'essai**
- **Randomiser des patients dans plusieurs bras**
  - Randomisation basée sur la probabilité de succès
  - Proche d'interventions "qualité" – participation?
- **Des seuils pour abandonner/continuer un bras**
  - 'Play the winner' – randomiser dans les bras les plus prometteurs
  - Taille de l'échantillon variable! Le nombre de bras et les schémas de randomisation sont influencés pendant l'étude par les résultats de l'étude
- **Randomisation sélective pour …**
  - Différents types de patients ou contextes cliniques distincts
  - Différentes co-interventions



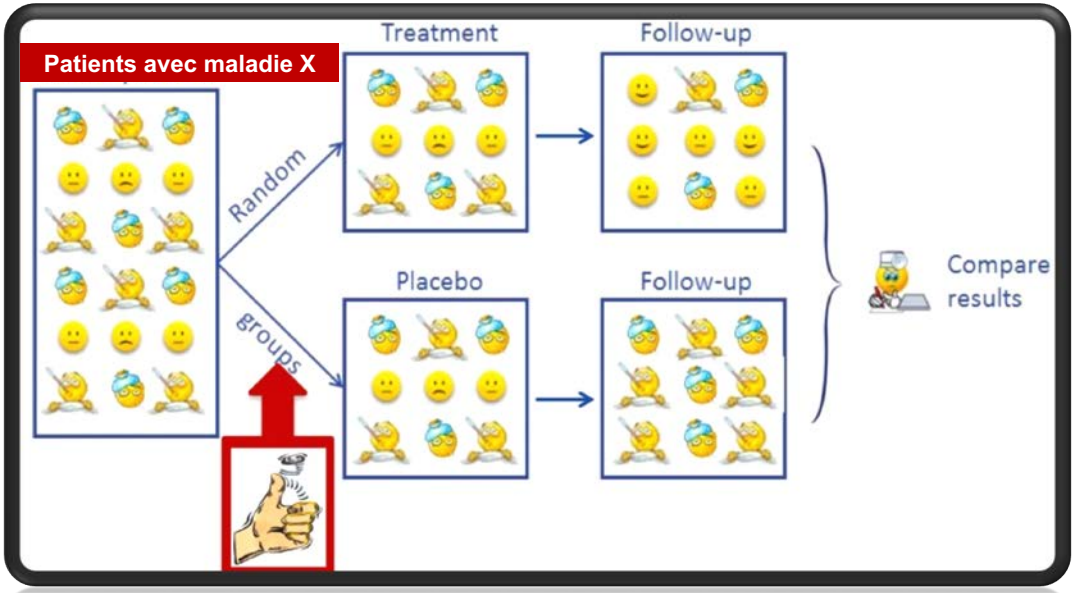
L'essai clinique traditionnel…

Patients avec maladie X

2 options de traitement (A ou B)

Au début,
50% chance
Que A > B

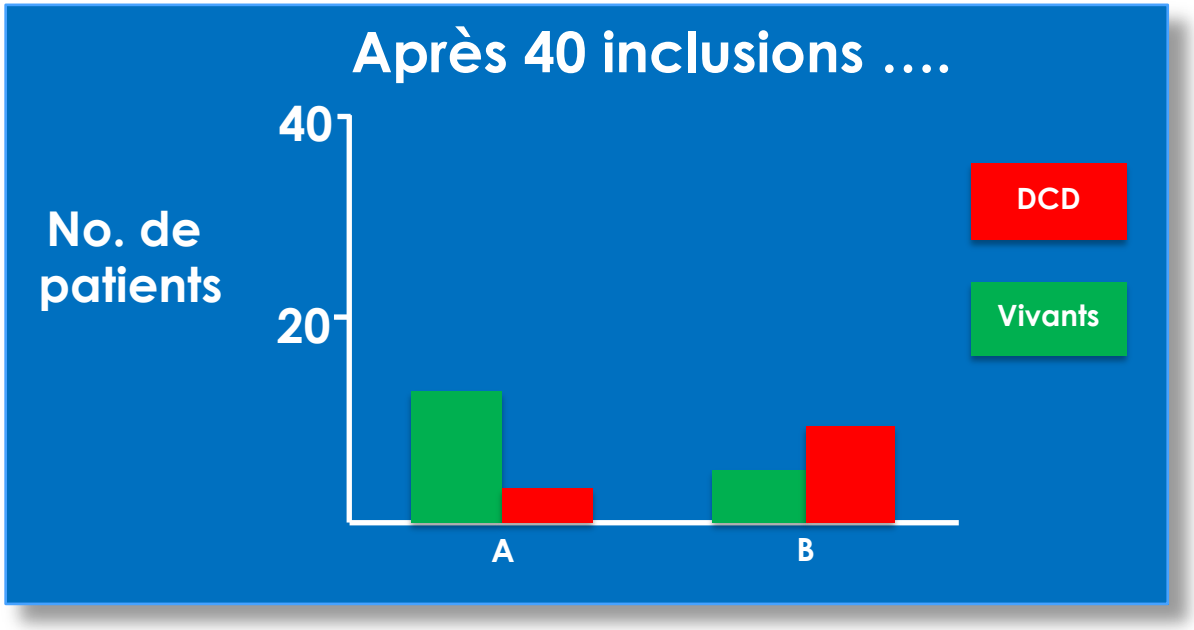
L'essai clinique traditionnel…



Arrêt de l'étude si on est 99% certain que A > B

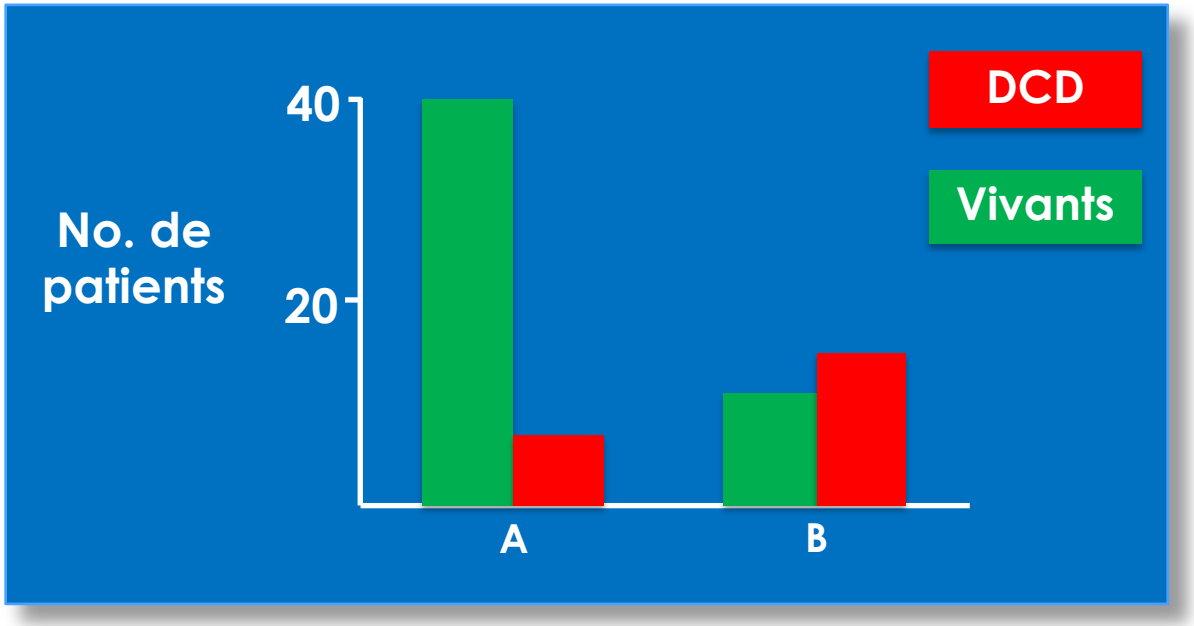
Et que se passe-t-il entre 50 et 99%?

Un essai A vs. B chez 400 patients



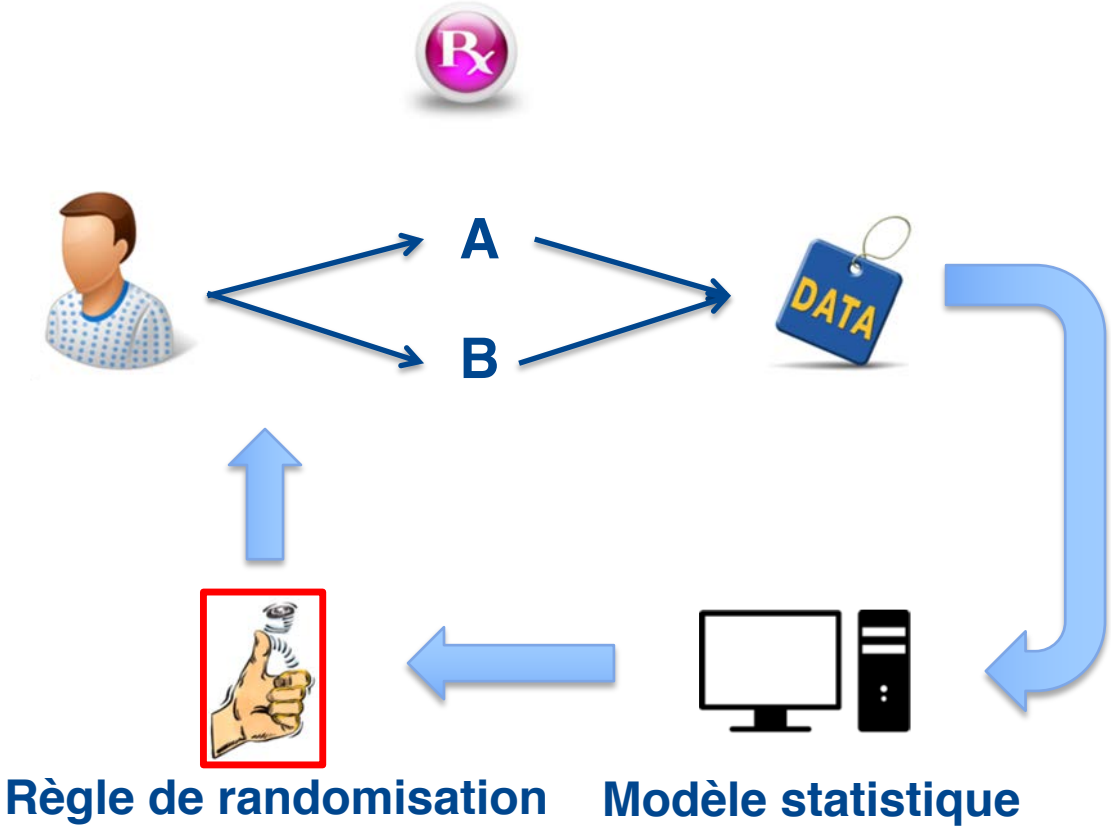
- La probabilité que A > B = 78%
- Randomisons PLUS de patients dans A que B …

Après 80 patients …

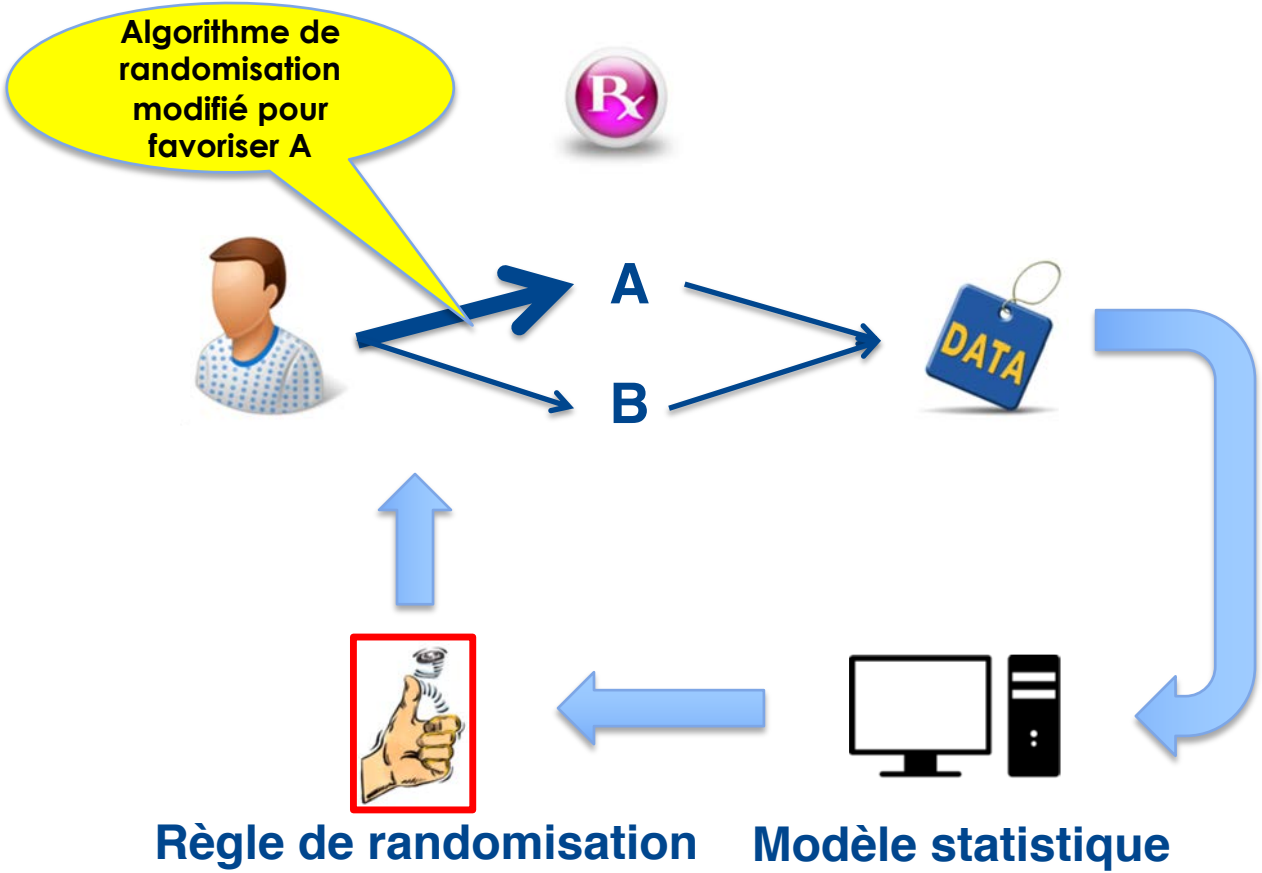


- La probabilité que A > B = 99.9%
- Arrêt de l'étude !

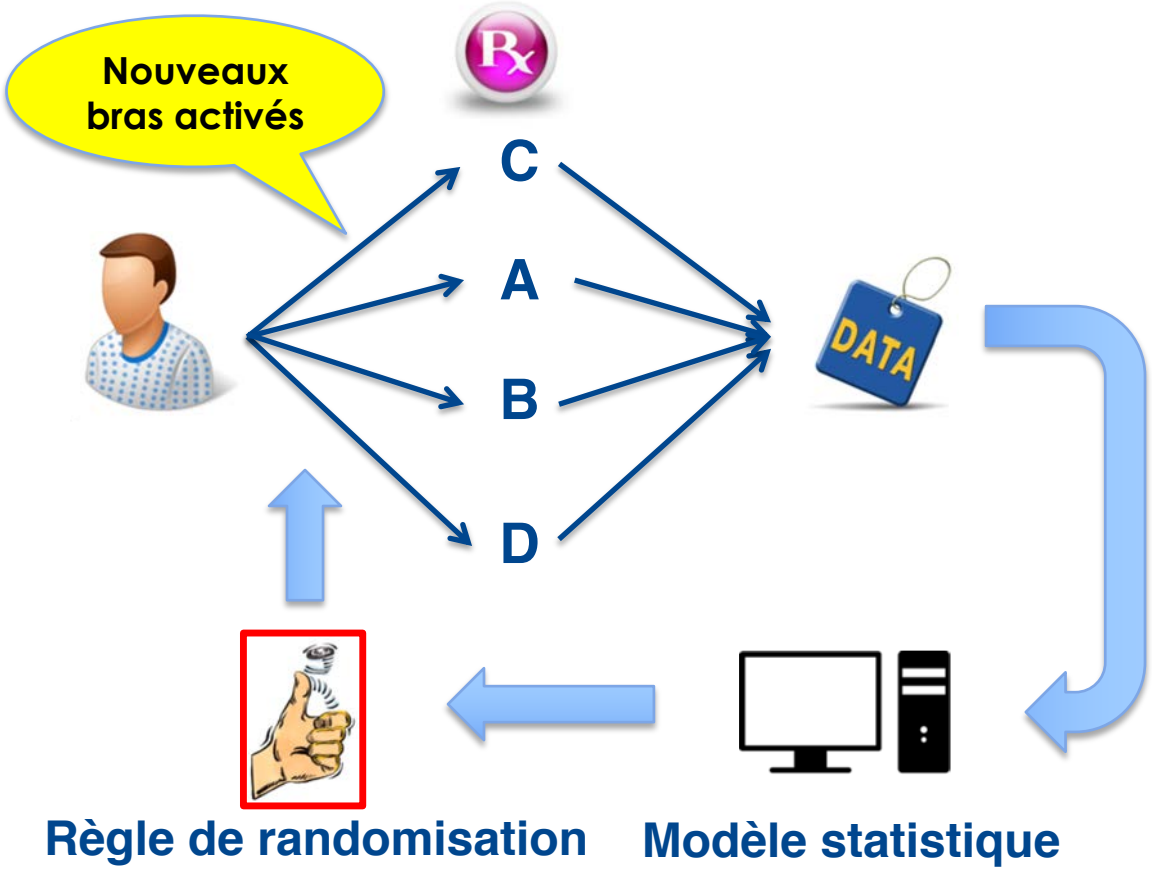
Randomisation 'response-adaptive'



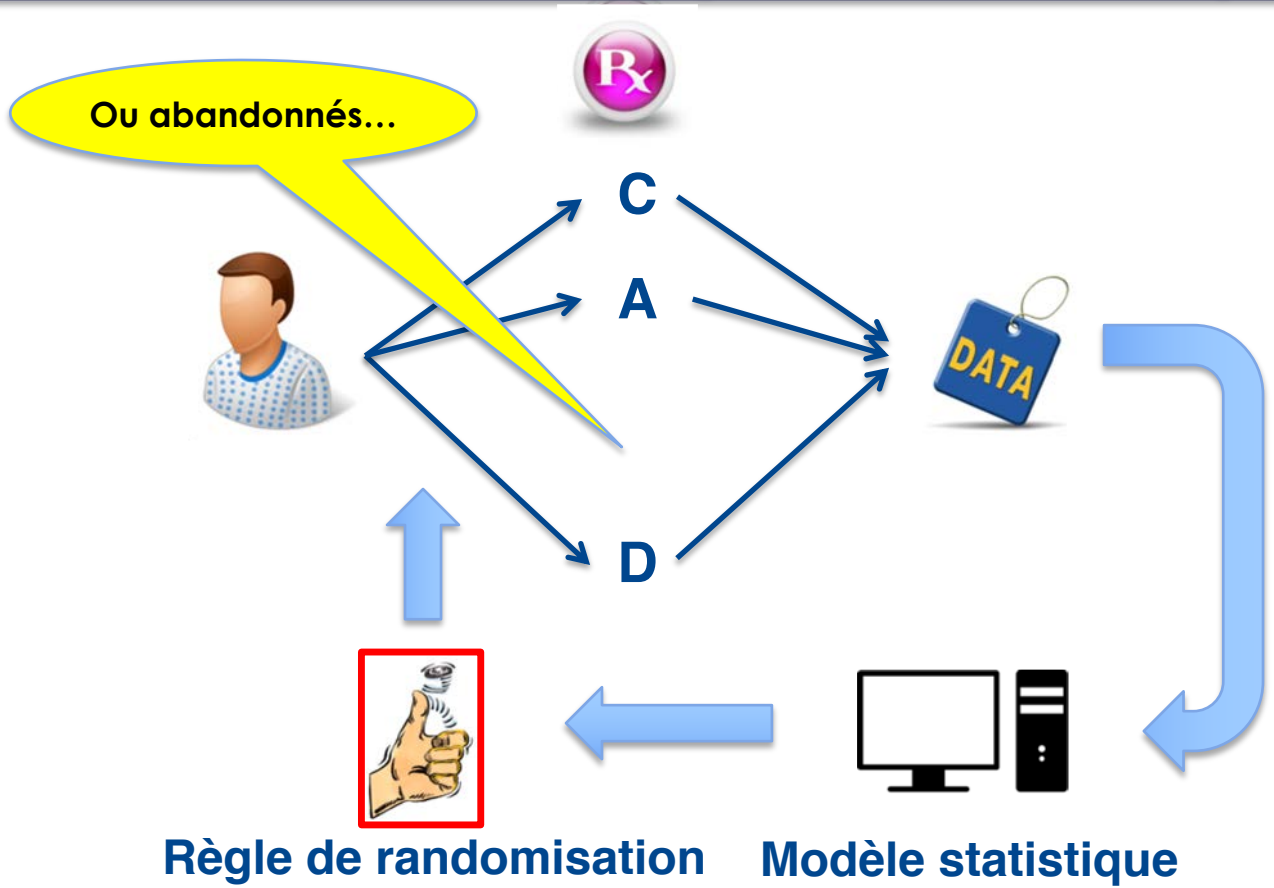
Randomisation 'response-adaptive'



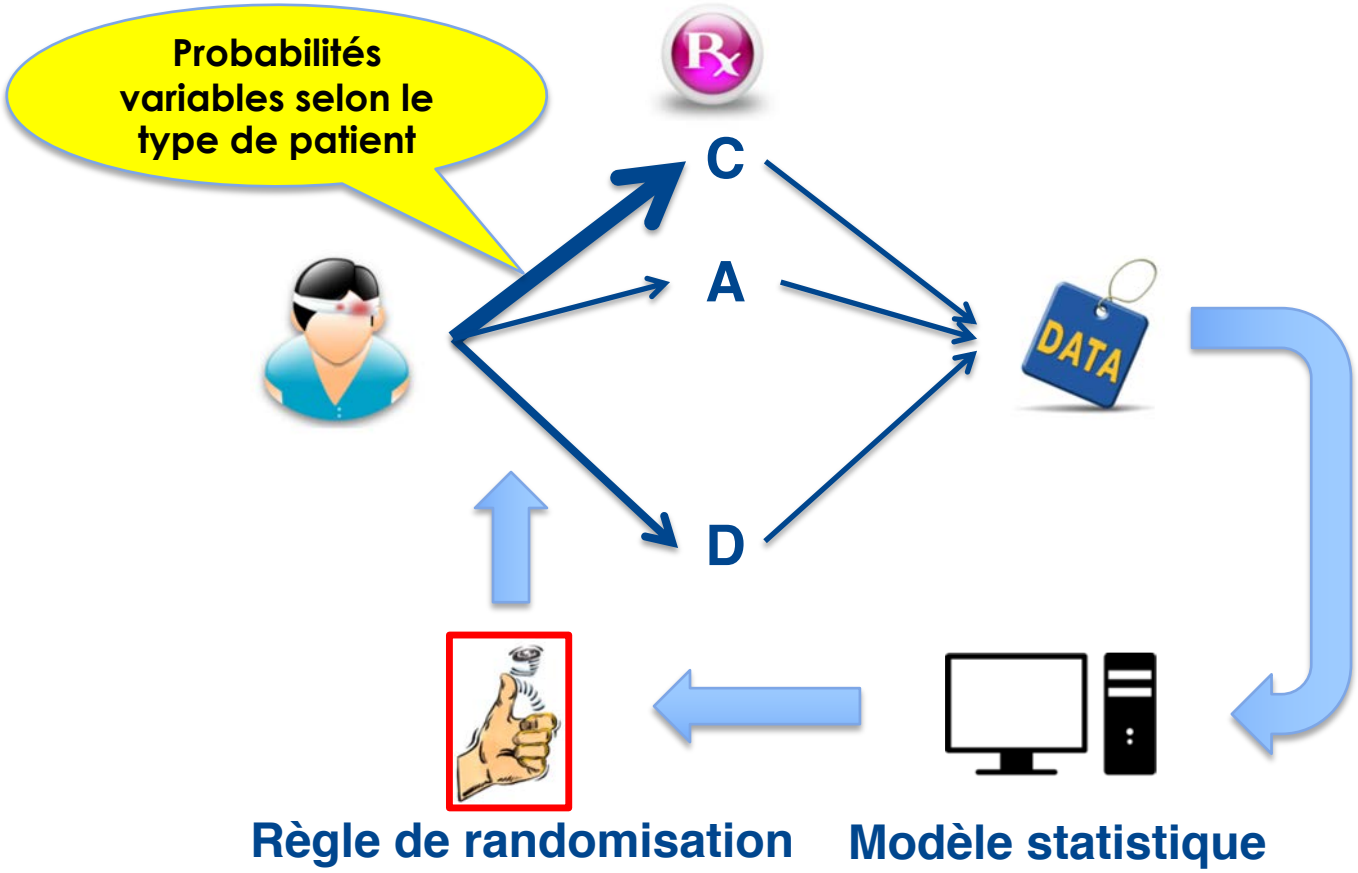
Randomisation 'response-adaptive'



Randomisation 'response-adaptive'



Randomisation 'response-adaptive'



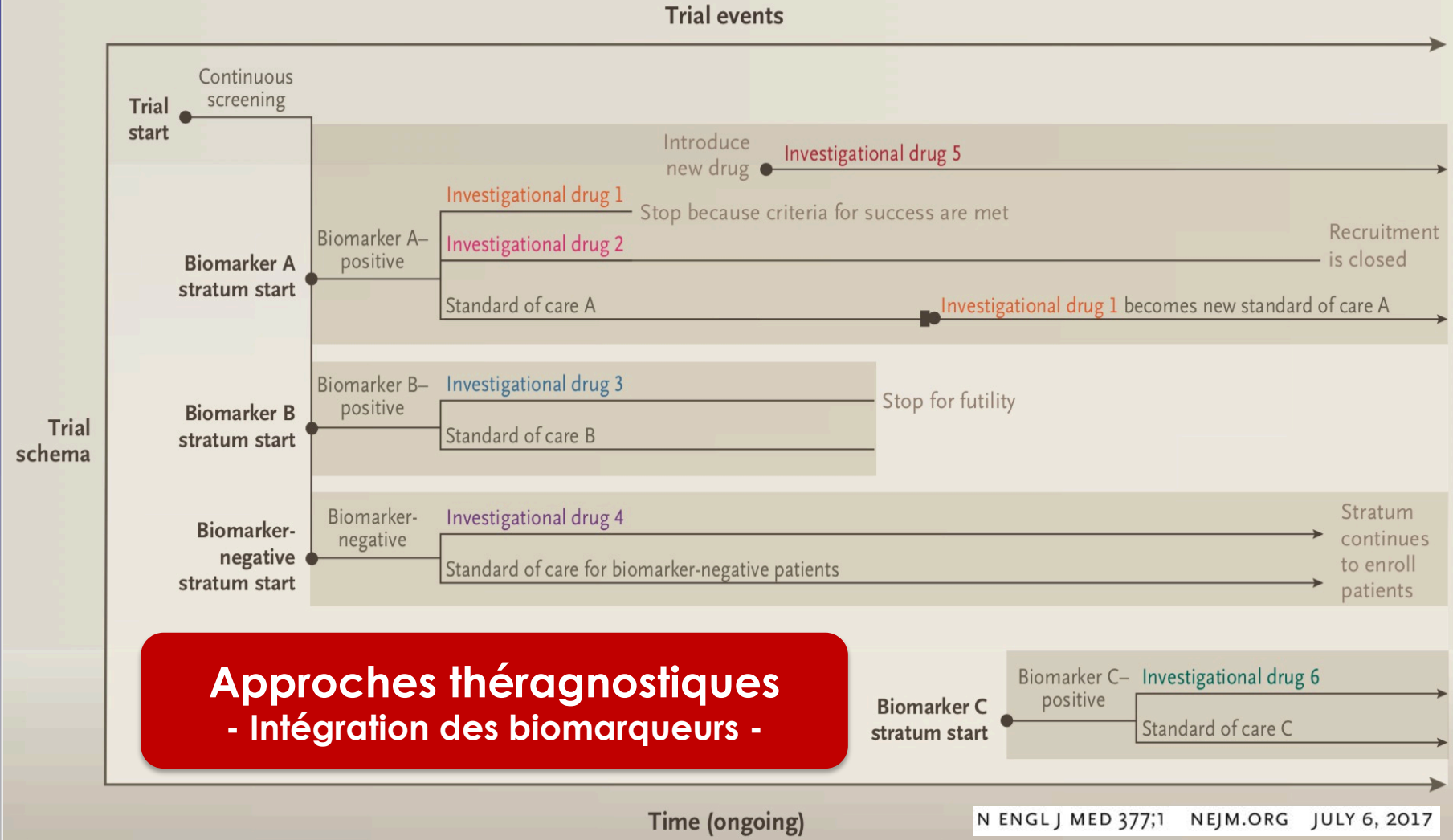
MASTER PROTOCOL: WHAT IS IT AND WHY ARE WE TALKING ABOUT IT?

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

Table 1. Types of Master Protocols.

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm



Approches théragnostiques
- Intégration des biomarqueurs -

I-SPY 2 TRIAL

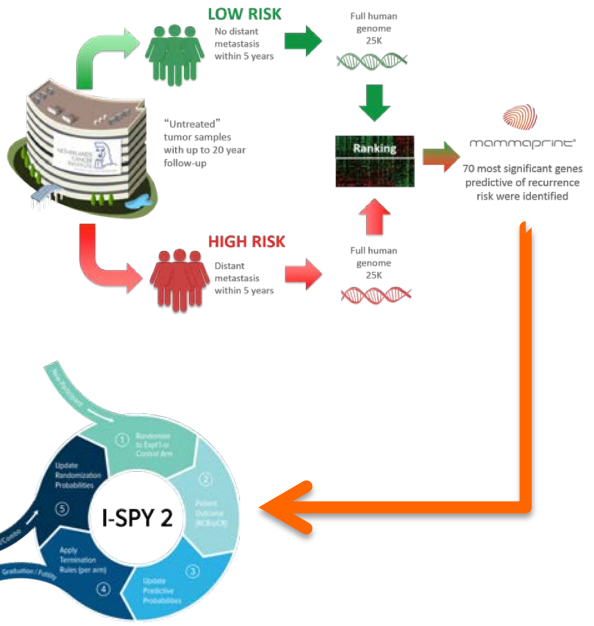
Home | About | Participants | Advocates | News

Trial Identifies Breast Cancer Patients Likely to Benefit from Experimental Drug

New Breast Cancer Results Illustrate Promise and Potential of I-SPY 2 Trial

Physicians

I-SPY 2 is a collaborative research effort that uses genetic and biological markers from individual patient's tumors to screen several promising new treatments simultaneously and allows doctors to quickly measure the effectiveness of the treatment prior to removing the tumor.



I-SPY 2 is an **Innovative** public-private collaboration that combines **Personalized Medicine** & **Novel Trial Design** to develop new cancer treatments much faster and for much less cost

Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer

H.S. Rugo, O.I. Olopade, A. DeMichele, C. Yau, L.J. van 't Veer, M.B. Buxton, M. Hogarth, N.M. Hylton, M. Paoloni, J. Perlmutter, W.F. Symmans, D. Yee, A.J. Chien, A.M. Wallace, H.G. Kaplan, J.C. Boughey, T.C. Haddad, K.S. Albain, M.C. Liu, C. Isaacs, Q.J. Khan, J.E. Lang, R.K. Viscusi, L. Pusztai, S.L. Moulder, S.Y. Chui, K.A. Kemmer, A.D. Elias, K.K. Edmiston, D.M. Euhus, B.B. Haley, R. Nanda, D.W. Northfelt, D. Tripathy, W.C. Wood, C. Ewing, R. Schwab, J. Lyandres, S.E. Davis, G.L. Hirst, A. Sanil, D.A. Berry, and L.J. Esserman, for the I-SPY 2 Investigators*

THE NEW ENGLAND JOURNAL OF MEDICINE 1812 1823 1828 1928

Adaptive Randomization of Neratinib in Early Breast Cancer

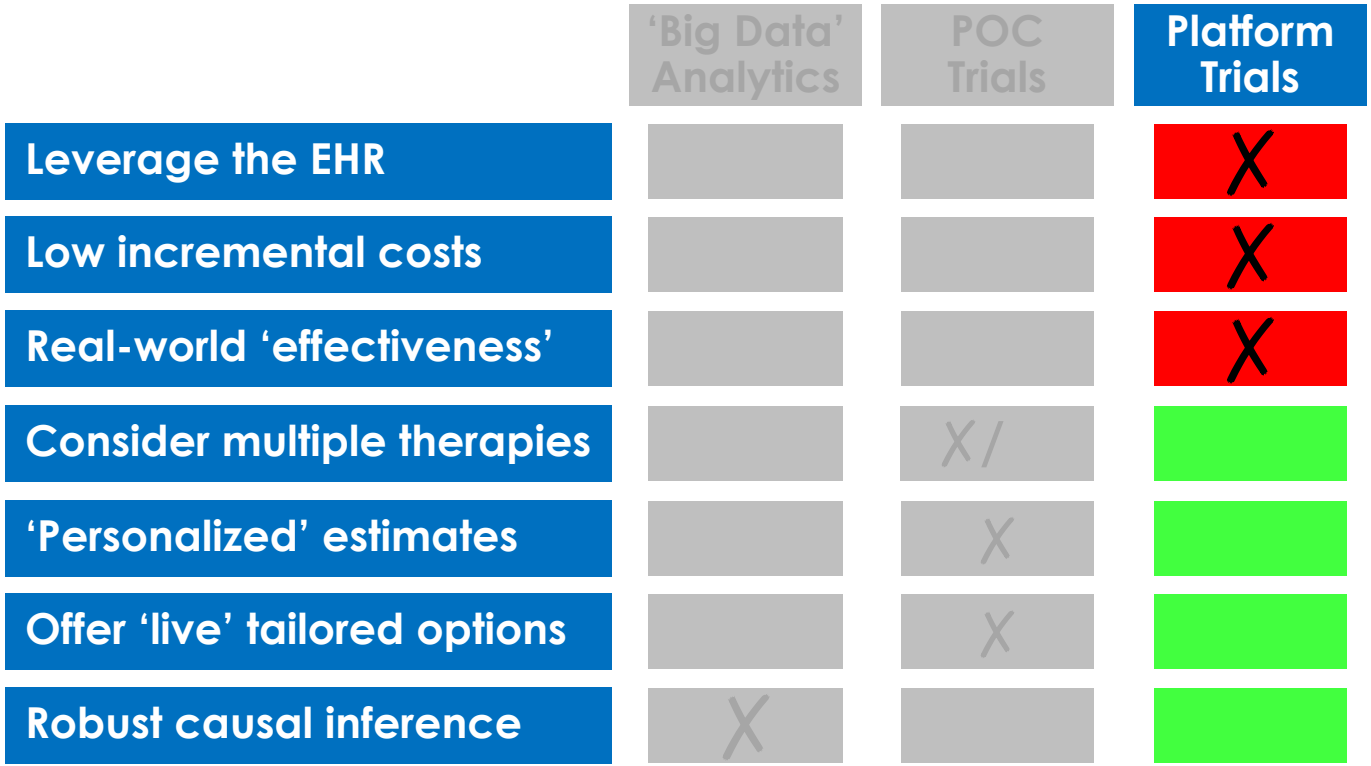
J.W. Park, M.C. Liu, D. Yee, C. Yau, L.J. van 't Veer, W.F. Symmans, M. Paoloni, J. Perlmutter, N.M. Hylton, M. Hogarth, A. DeMichele, M.B. Buxton, A.J. Chien, A.M. Wallace, J.C. Boughey, T.C. Haddad, S.Y. Chui, K.A. Kemmer, H.G. Kaplan, C. Isaacs, R. Nanda, D. Tripathy, K.S. Albain, K.K. Edmiston, A.D. Elias, D.W. Northfelt, L. Pusztai, S.L. Moulder, J.E. Lang, R.K. Viscusi, D.M. Euhus, B.B. Haley, Q.J. Khan, W.C. Wood, M. Melisko, R. Schwab, T. Helsten, J. Lyandres, S.E. Davis, G.L. Hirst, A. Sanil, L.J. Esserman, and D.A. Berry, for the I-SPY 2 Investigators*

VIEWPOINT

Derek C. Angus, MD, MPH

Fusing Randomized Trials With Big Data

The Key to Self-learning Health Care Systems?



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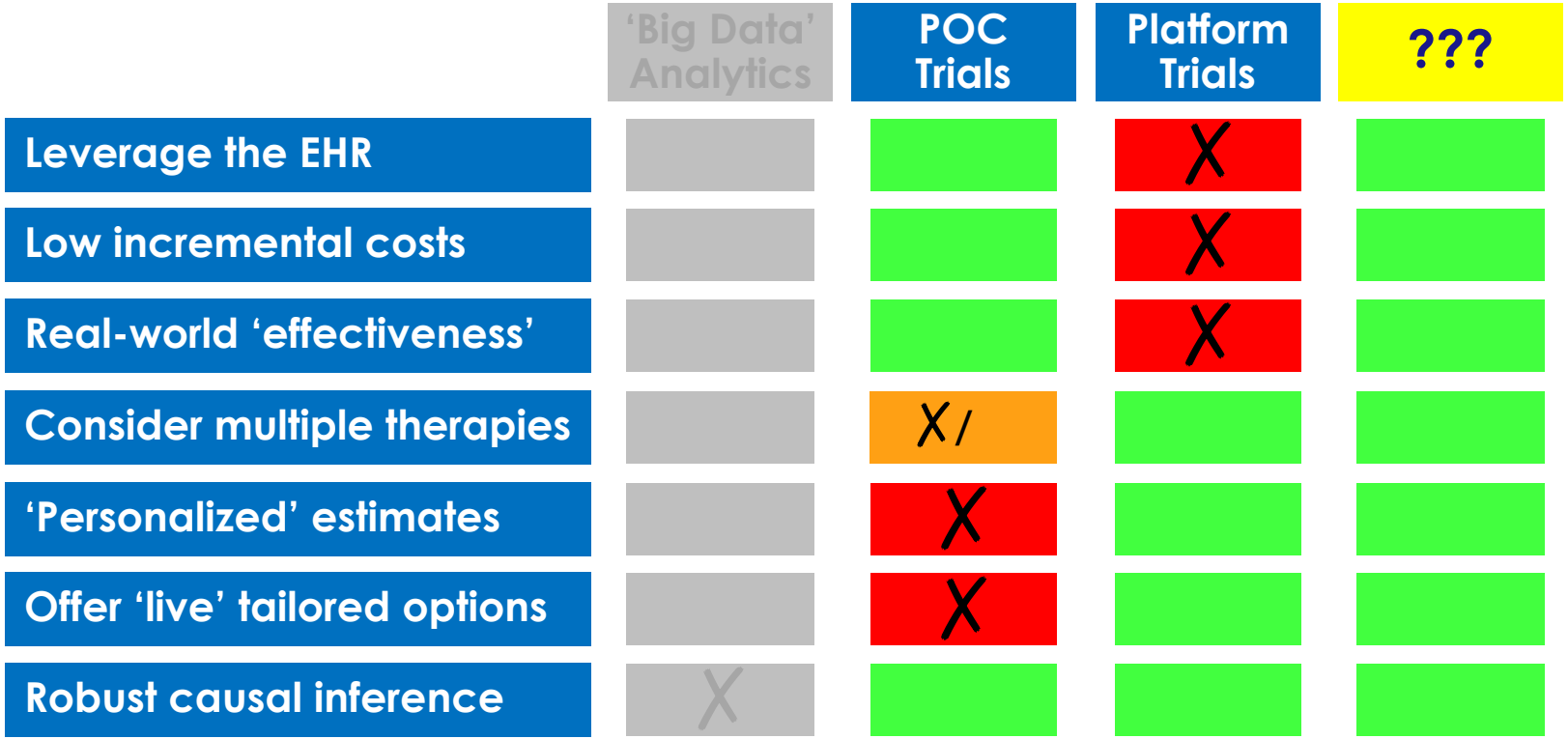
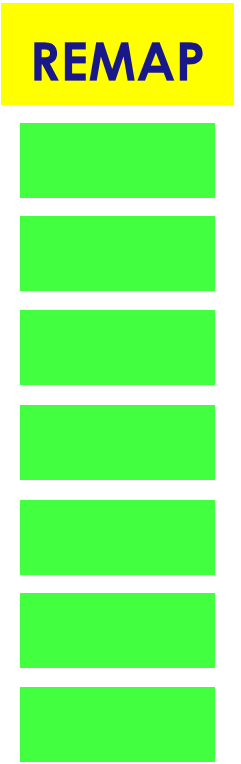
The Key to Self-learning Health Care Systems?

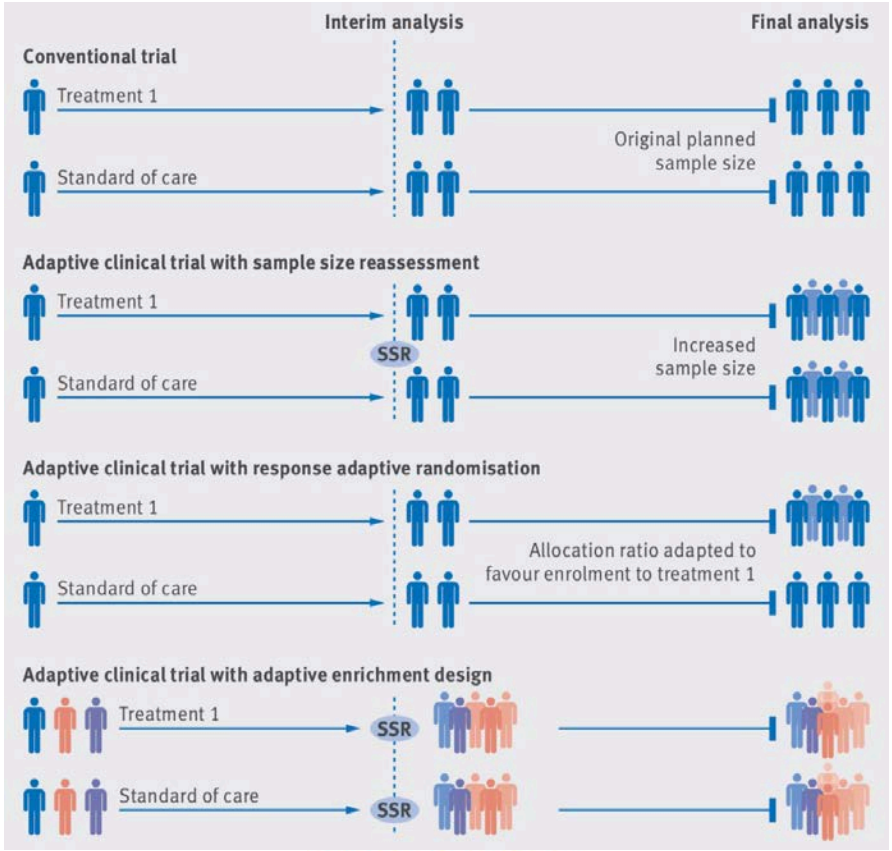


A l'interface entre l'essai 'POC' & l'essai "Platform"

- **REMAP**
  - **R**andomized
  - **E**mbedded
  - **M**ultifactorial
  - **A**daptive
  - **P**latform trial



Soins intensifs: prêts pour l'aventure?



BMJ 2018;360:k698

Rationale and Design of an Adaptive Phase 2b/3 Clinical Trial of Selepressin for Adults in Septic Shock

Selepressin Evaluation Programme for Sepsis-induced Shock—Adaptive Clinical Trial

Roger J. Lewis[1,2,3,4], Derek C. Angus[5,6], Pierre-François Laterre[7], Anne Louise Kjølbye[8], Egbert van der Meulen[8], Allan Blemings[8], Todd Graves[4], James A. Russell[9], Jan E. Carlsen[10], Karsten Jacobsen[8], Donald M. Yealy[11], Steven M. Opal[12], Nis A. Windeløv[8], Bruno François[13], Anders Perner[14], Peter Pickkers[15], and Scott M. Berry[4]

Ann Am Thorac Soc Vol 15, No 2, pp 250–257, Feb 2018

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney Injury

A Randomized Clinical Trial

JAMA. 2018;320(19):1998-2009.

Peter Pickkers, MD, PhD; Ravindra L. Mehta, MD; Patrick T. Murray, MD; Michael Joannidis, MD; Bruce A. Molitoris, MD; John A. Kellum, MD; Mirjam Bachler, PhD; Eric A. J. Hoste, MD, PhD; Oscar Hoiting, MD; Kenneth Krell, MD; Marlies Ostermann, MD, PhD; Wim Rozendaal, MD; Miia Valkonen, MD, PhD; David Brealey, MD, PhD; Albertus Beishuizen, MD, PhD; Ferhat Meziani, MD, PhD; Raghavan Murugan, MD, MS, FRCP; Hilde de Geus, MD, PhD; Didier Payen, MD, PhD; Erik van den Berg, MSc; Jacques Arend, MD; for the STOP-AKI Investigators

Original Investigation | Critical Care Medicine

Effect of Levocarnitine vs Placebo as an Adjunctive Treatment for Septic Shock

The Rapid Administration of Carnitine in Sepsis (RACE) Randomized Clinical Trial

JAMA Network Open. 2018;1(8):e186076.

Alan E. Jones, MD; Michael A. Puskarich, MD, MS; Nathan I. Shapiro, MD, MPH; Faheem W. Guirgis, MD; Michael Runyon, MD, MPH; Jason Y. Adams, MD; Robert Sherwin, MD; Ryan Arnold, MD; Brian W. Roberts, MD, MSc; Michael C. Kurz, MD, MS; Henry E. Wang, MD, MS; Jeffrey A. Kline, MD; D. Mark Courtney, MD; Stephen Trzeciak, MD, MPH; Sarah A. Sterling, MD; Utsav Nandi, MD; Deepti Patki, MS; Kert Viele, PhD

WP 5/Practice C
REMAP-CAP study

WP leaders: Marc Bonten & Jean-Daniel Chiche

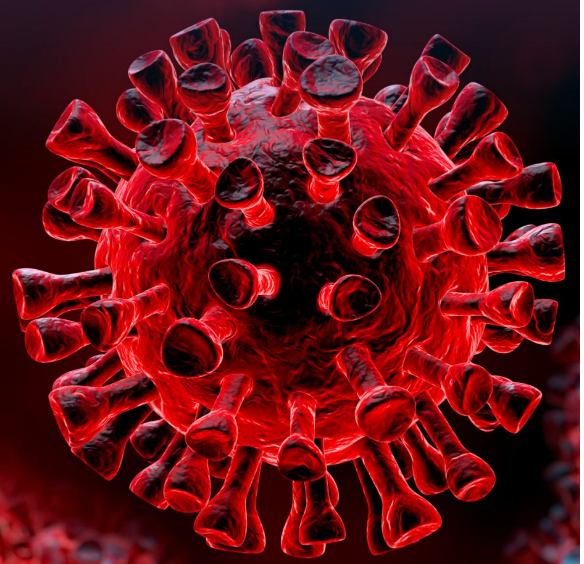
PREPARE is funded by the European Commission under grant number 602525

Design full study (REMAP-CAP)

- Perpetual trial -> Research platform
- Start with 3 selected interventions:
  - Antibiotics, steroids & ventilatory strategy
    - High equipoise
    - Low ethical barriers
    - Low costs (incl. no additional diagnostics)
- Response adaptive randomization (RAR)
- Future options: selection of new suitable treatments:
  - Diagnostics
  - Antivirals

Preuve de concept

Pandémie COVID-19



The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study

Rationale and Design

Derek C. Angus[1], Scott Berry[2], Roger J. Lewis[2,3,4], Farah Al-Beidh[5], Yaseen Arabi[6], Wilma van Bentum-Puijk[7], Zahra Bhimani[8], Marc Bonten[7,9], Kristine Broglio[2], Frank Brunkhorst[10], Allen C. Cheng[11,12], Jean-Daniel Chiche[13], Menno De Jong[14], Michelle Detry[2], Herman Goossens[15], Anthony Gordon[5], Cameron Green[12], Alisa M. Higgins[12], Sebastiaan J. Hullegie[7], Peter Kruger[16], Francois Lamontagne[17], Edward Litton[18], John Marshall[8,19], Anna McGlothlin[2], Shay McGuinness[12,20,21], Paul Mouncey[22], Srinivas Murthy[23], Alistair Nichol[12,24,25], Genevieve K. O'Neill[12], Rachael Parke[20,21,26], Jane Parker[12], Gernot Rohde[27,28], Kathryn Rowan[22], Anne Turner[21], Paul Young[21,29], Lennie Derde[7,30], Colin McArthur[21,31], and Steven A. Webb[12,18,32]

Ann Am Thorac Soc Vol 17, No 7, pp 879–891, Jul 2020

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

The Writing Committee for the REMAP-CAP Investigators

JAMA. 2020;324(13):1317-1329. doi:10.1001/jama.2020.17022

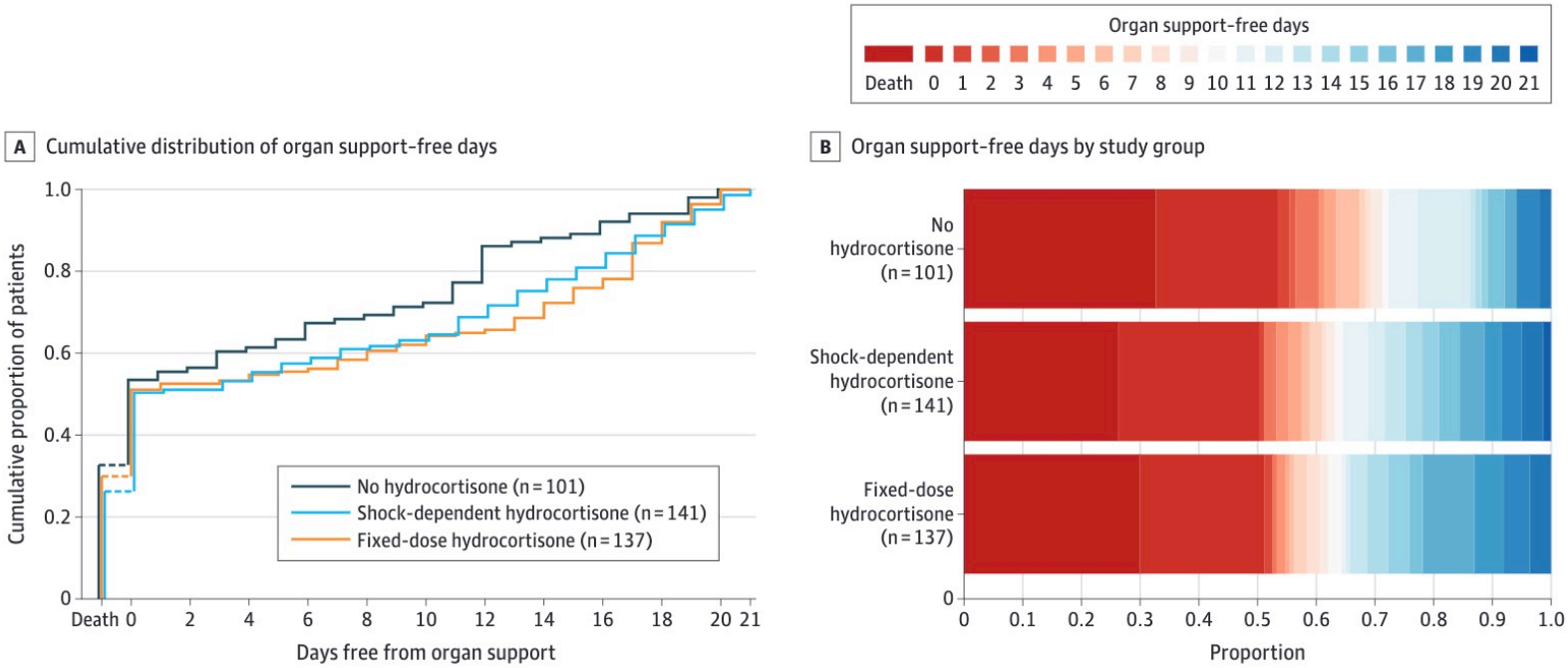
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

The Writing Committee for the REMAP-CAP Investigators

Figure 2. Organ Support–Free Days

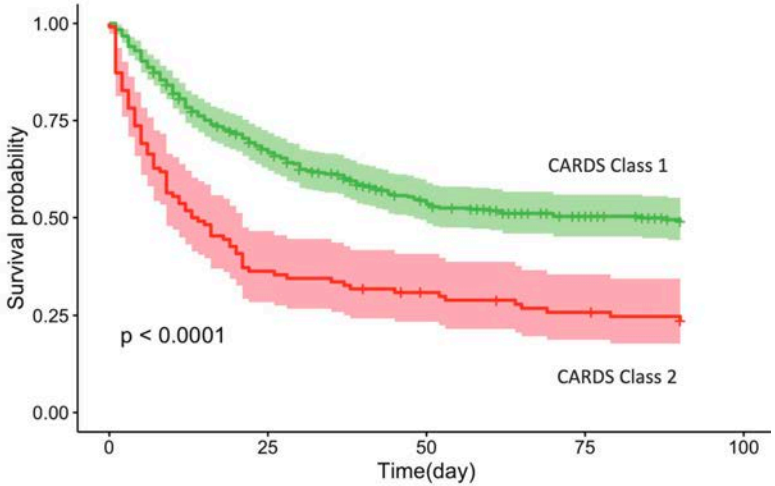


JAMA. 2020;324(13):1317-1329. doi:10.1001/jama.2020.17022

Latent Class Analysis Reveals COVID-19-related ARDS Subgroups with Differential Responses to Corticosteroids

Pratik Sinha ; David Furfaro , Matthew J Cummings , Darryl Abrams , Kevin Delucchi , Manoj V. Maddali , June He , Alison Thompson , Michael Murn , John Fountain , Amanda Rosen , Shelief Y. Robbins-Juarez , Matthew A Adan , Tejus Satish , Mahesh Madhavan , Aakriti Gupta , Alexander K Lyashchenko , Cara Agerstrand , Natalie H Yip , Kristin M. Burkart , Jeremy R Beitler ; Matthew R Baldwin , Carolyn S Calfee , Daniel Brodie , and Max R. O'Donnell ; ... Show less

- **483 patients avec SDRA COVID-19**
- **Latent class analysis (LCA) & classification phénotypes hypo/ hyperinflammatoires**



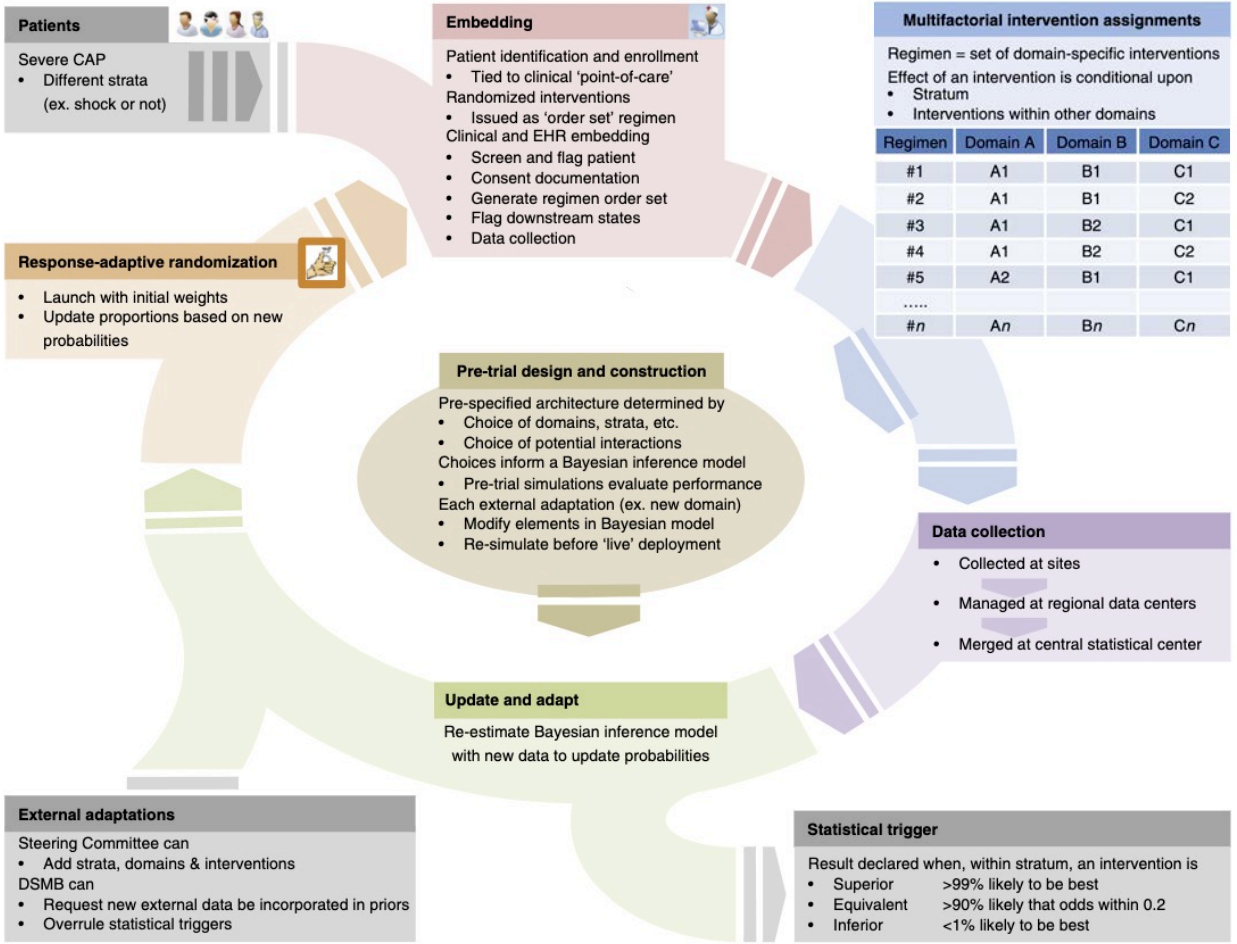
SEULS LES PATIENTS DE PHÉNOTYPE HYPERINFLAMMATOIRE (CLASS 2) BÉNÉFICIENT DE LA CORTICOTHÉRAPIE

Corticosteroid use	COVID-19-related ARDS Class		P-value
	Class 1	Class 2	
Yes	120/244 (49%)	52/76 (68%)	0.0273
No	58/127 (46%)	30/34 (88%)	


Autres domaines? cibles thérapeutiques?
COVID-19
Cytokine Storm
IL-6
MCP-1
IL-1β
IFN-β
IL-9
IFN-γ
IL-1
IL-8
IFN-α
TNF-α
IL-10
IL-12

The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study

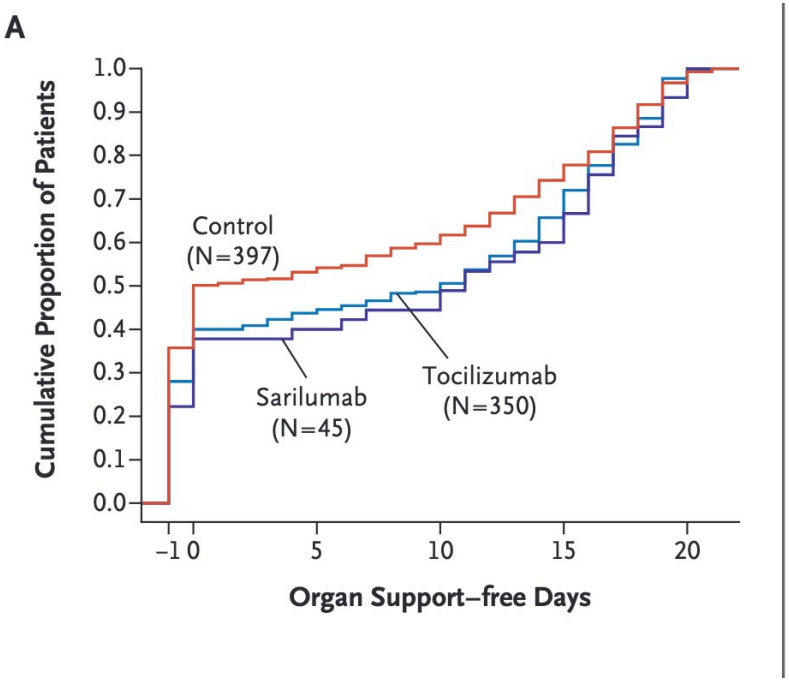
Rationale and Design

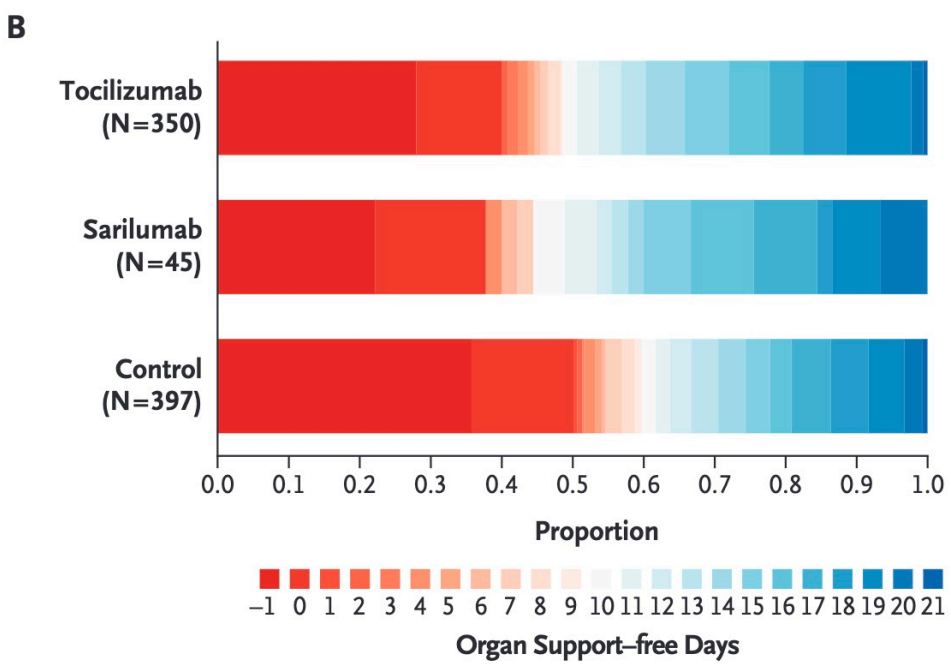


Ann Am Thorac Soc Vol 17, No 7, pp 879–891, Jul 2020

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

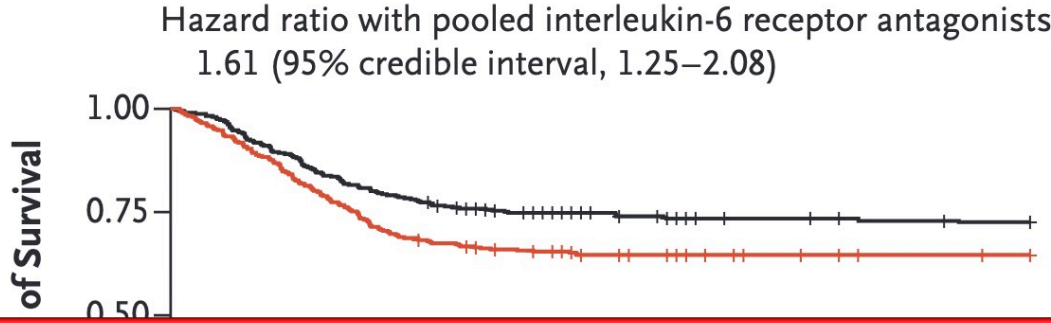




N Engl J Med 2021;384:1491-502.

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*



CONCLUSIONS

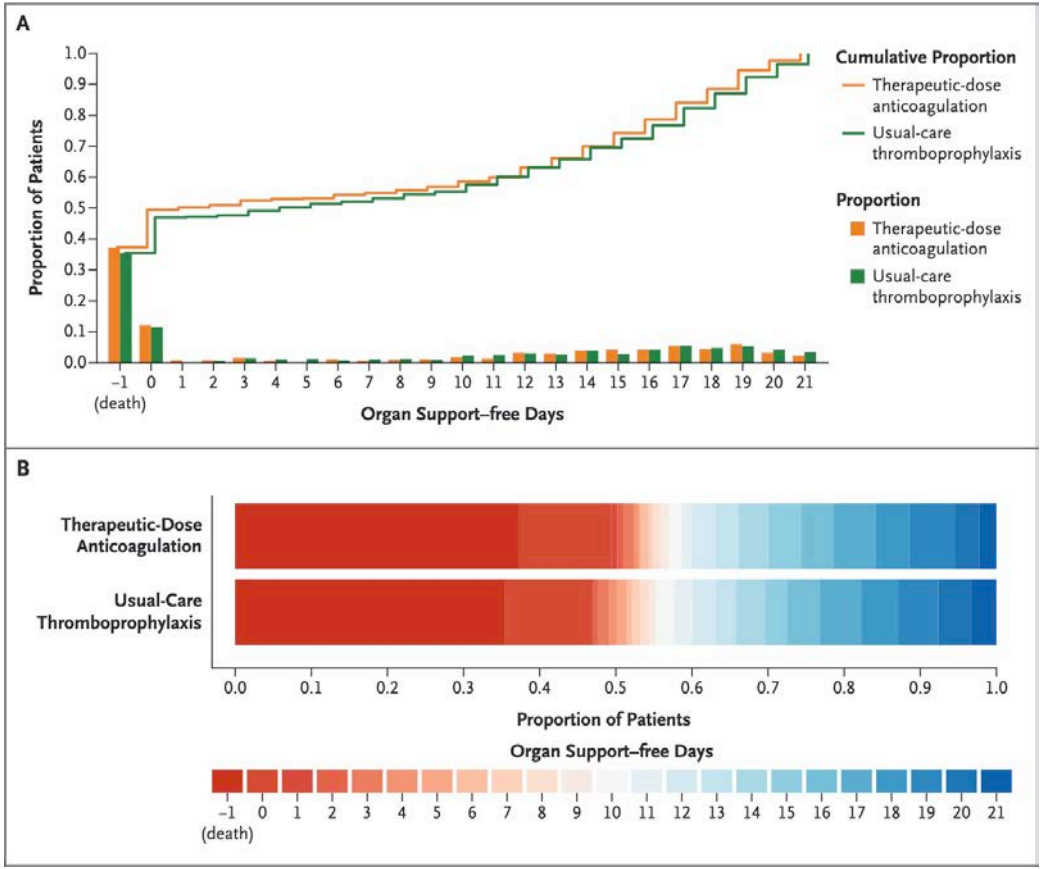
In critically ill patients with Covid-19 receiving organ support in ICUs, treatment with the interleukin-6 receptor antagonists tocilizumab and sarilumab improved outcomes, including survival. (REMAP-CAP ClinicalTrials.gov number, NCT02735707.)

93% des patients inclus après la publication des résultats sur la dexamethasone ont reçu des corticostéroides!

N Engl J Med 2021;384:1491-502.

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*



Chez les patients Covid-19 de soins intensifs, une stratégie initiale d'anticoagulation à dose thérapeutique n'améliore ni la survie hospitalière ni la résolution des défaillances cardio-vasculaire ou respiratoire par rapport à une thrombo-prophylaxie standard.

N Engl J Med 2021;385:777-89.

COVID-19 must catalyse changes to clinical development

Rod MacKenzie✉, Peter Honig, Judy Sewards, Robert Goodwin and Marie-Pierre Hellio

The response to the COVID-19 pandemic has shown that exceptional efforts can dramatically accelerate the clinical development of vaccines. We propose that it is time to also take immediate actions to improve clinical trials in other areas to better serve all patients.

Vers une plateforme d'essais 'SDRA' ?

COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome

Luciano Gattinoni, M.D.*
Medical University of Göttingen
Göttingen, Germany

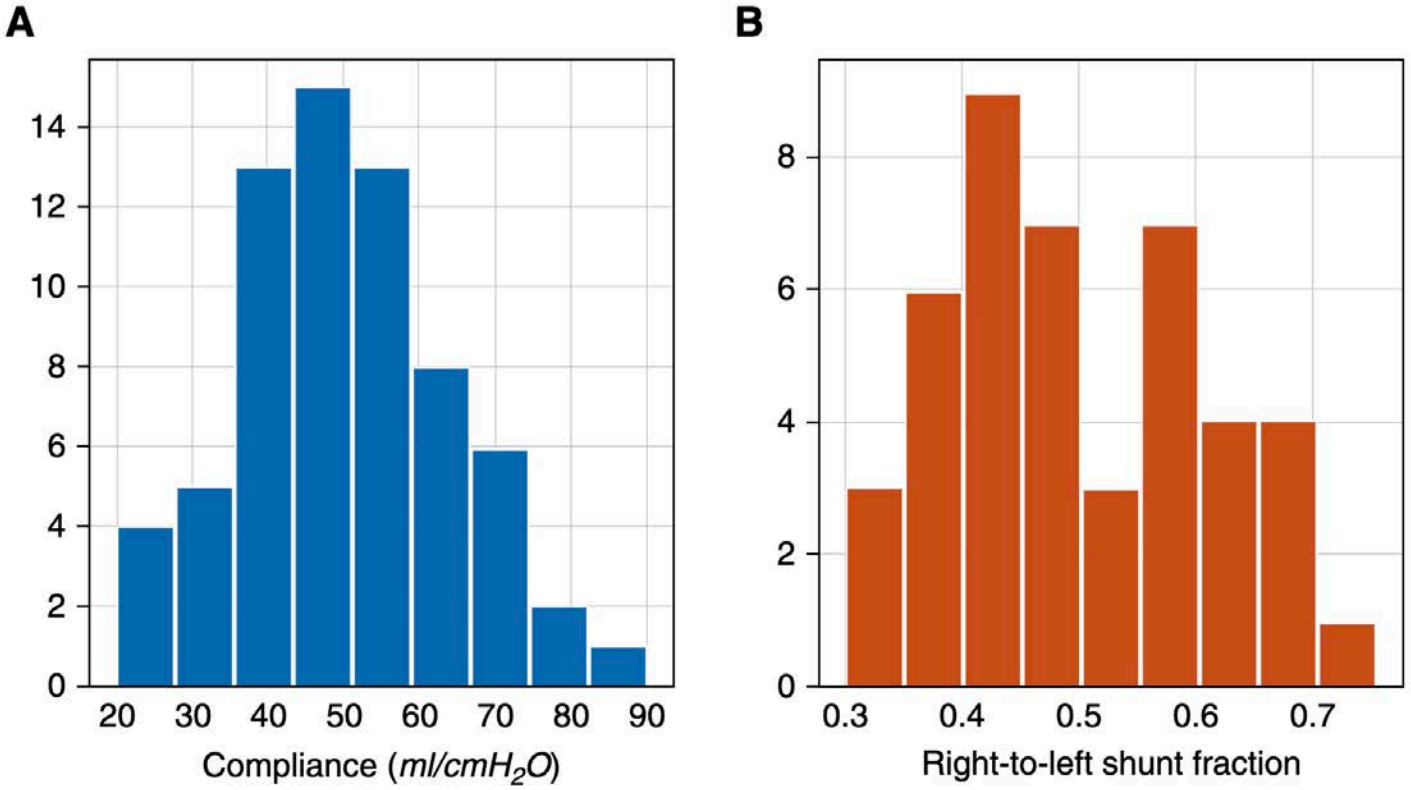
Silvia Coppola, M.D.
University of Milan
Milan, Italy

Massimo Cressoni, M.D.
University of Milan-Bicocca
Milan, Italy

Mattia Busana, M.D.
Medical University of Göttingen
Göttingen, Germany

Sandra Rossi, M.D.
University Hospital Parma
Parma, Italy

Davide Chiumello, M.D.
University of Milan
Milan, Italy



American Journal of Respiratory and Critical Care Medicine Volume 201 Number 10 | May 15 2020

COVID-19 pneumonia: different respiratory treatments for different phenotypes?

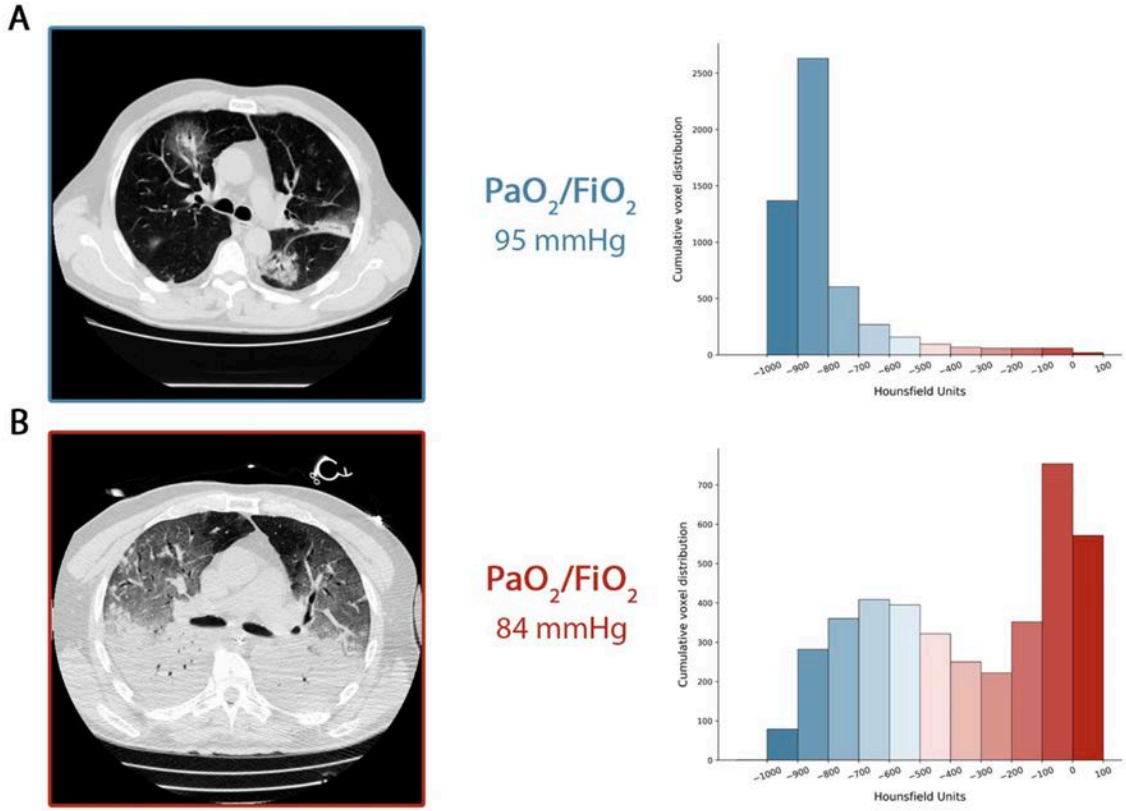
Luciano Gattinoni[1*], Davide Chiumello[2], Pietro Caironi[3,4], Mattia Busana[1], Federica Romitti[1], Luca Brazzi[5] and Luigi Camporota[6]

Type L

- Low elastance
- Low V_A/Q ratio
- Low lung weight
- Low lung recruitability

Type H

- High elastance.
- High right-to-left shunt
- High lung weight
- High lung recruitability



Intensive Care Med (2020) 46:1099–1102

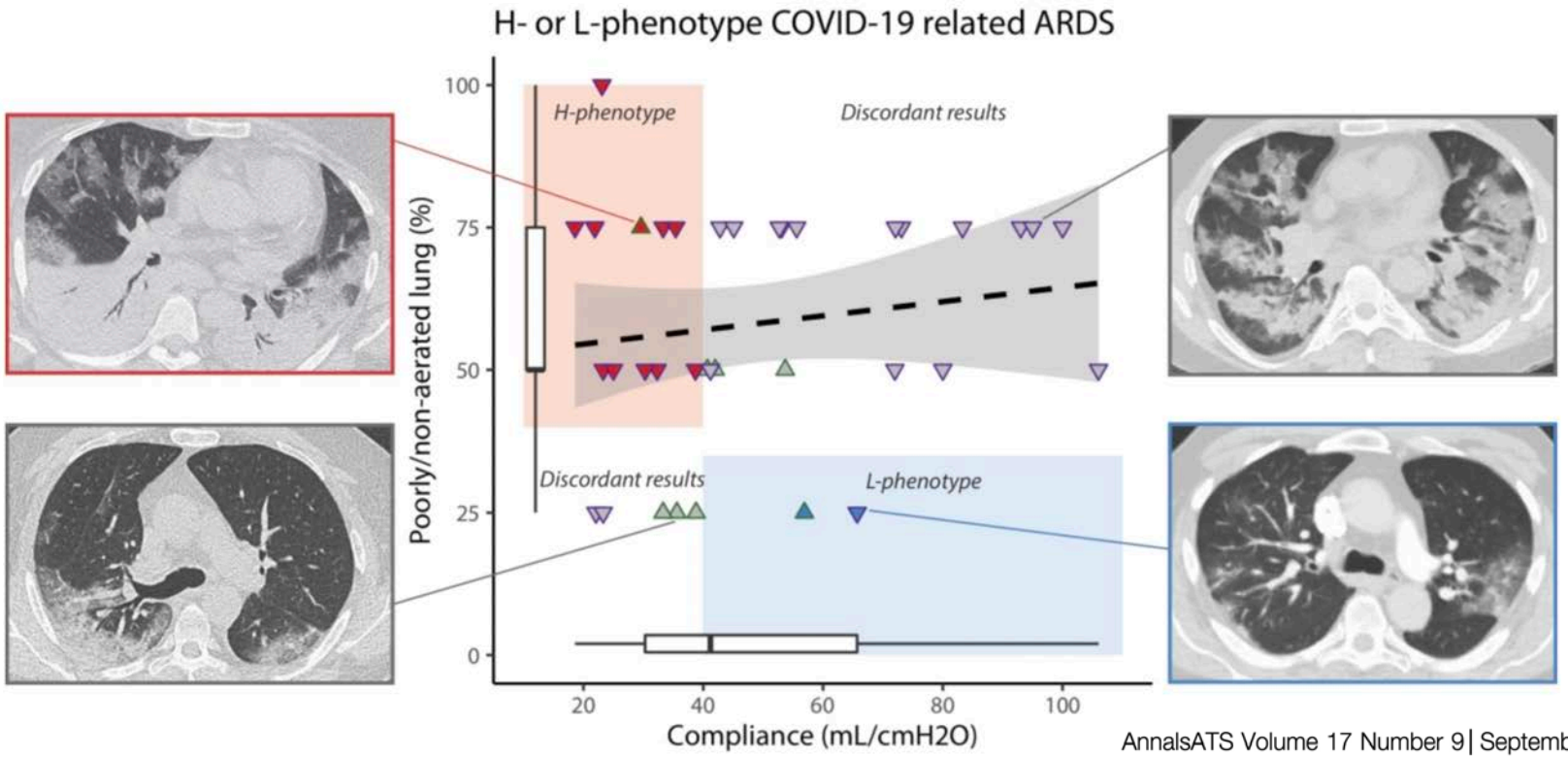
Annals of the American Thoracic Society

Subphenotyping ARDS in COVID-19 Patients: Consequences for Ventilator Management

Lieuwe DJ Bos , Frederique Paulus , Alexander P.J. Vlaar , Ludo F M Beenen , and Marcus J. Schultz
+ Author Information

https://doi.org/10.1513/AnnalsATS.202004-376RL PubMed: 32396457

Received: April 26, 2020 Accepted: May 12, 2020 Published Online: May 12, 2020



Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial

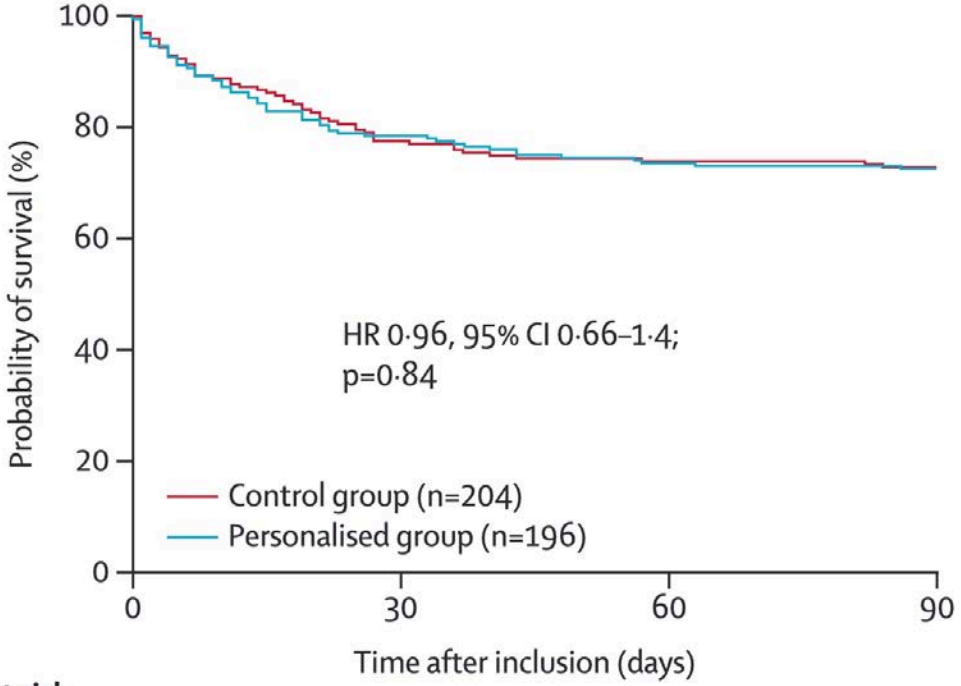
Lancet Respir Med 2019

*Jean-Michel Constantin, Matthieu Jabaudon, Jean-Yves Lefrant, Samir Jaber, Jean-Pierre Quenot, Olivier Langeron, Martine Ferrandière, Fabien Grelon, Philippe Seguin, Carole Ichai, Benoit Veber, Bertrand Souweine, Thomas Uberti, Sigismond Lasocki, François Legay, Marc Leone, Nathanael Eisenmann, Claire Dahyot-Fizelier, Hervé Dupont, Karim Asehnoune, Achille Sossou, Gérald Chanques, Laurent Muller, Jean-Etienne Bazin, Antoine Monsel, Lucile Borao, Jean-Marc Garcier, Jean-Jacques Rouby, Bruno Pereira, Emmanuel Futier, for the AZUREA Network**

	Control group (n=204)	Personalised group (n=196)	
		Focal lung morphology	Non-focal lung morphology
Mode of ventilation	Volume control	Volume control	Volume control
Tidal volume	6 mL/kg IBW	8 mL/kg IBW	6 mL/kg IBW
PEEP	PEEP/FiO_2	5–9 cm H_2O	To reach Pplat of 30 cm H_2O
PEEP-PSV	Free	5–9 cm H_2O	≥10 cm H_2O
Recruitment manoeuvre	Rescue	Rescue	Mandatory
Prone position	Encouraged	Mandatory	Rescue

Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial

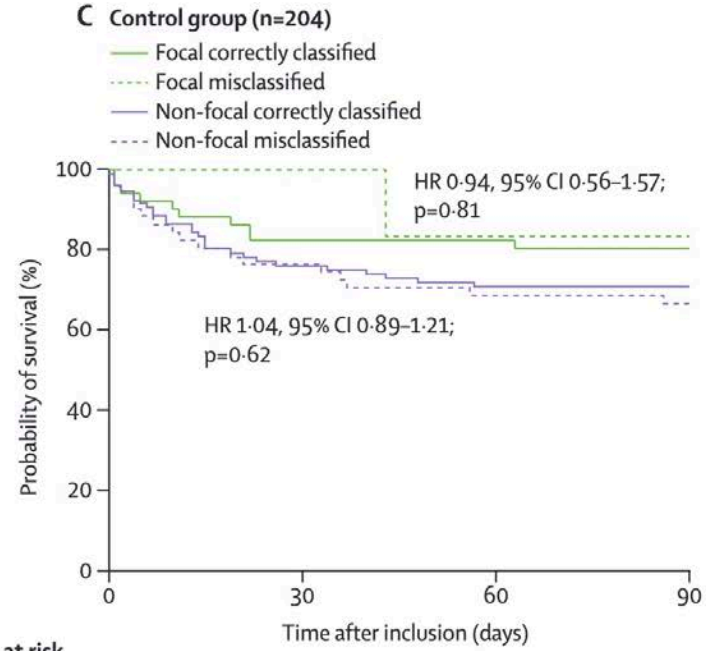
Lancet Respir Med 2019

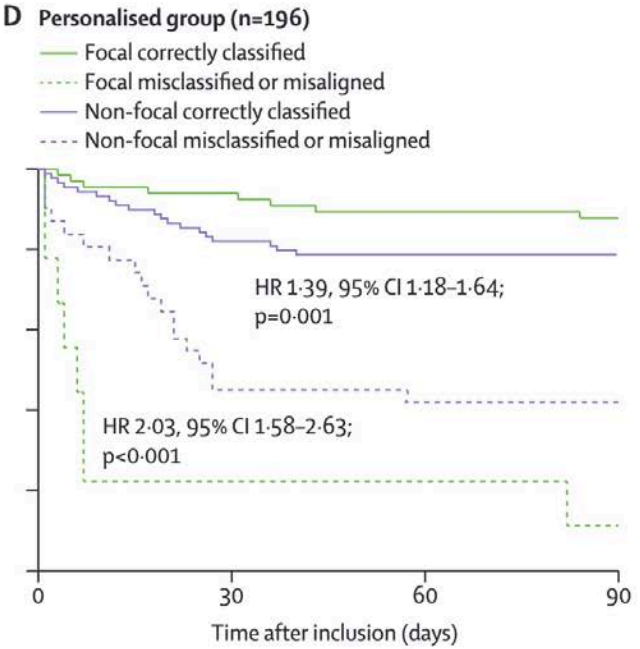


Number at risk				
Personalised group	196	151	144	141
Control group	204	160	150	146

Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial

Lancet Respir Med 2019





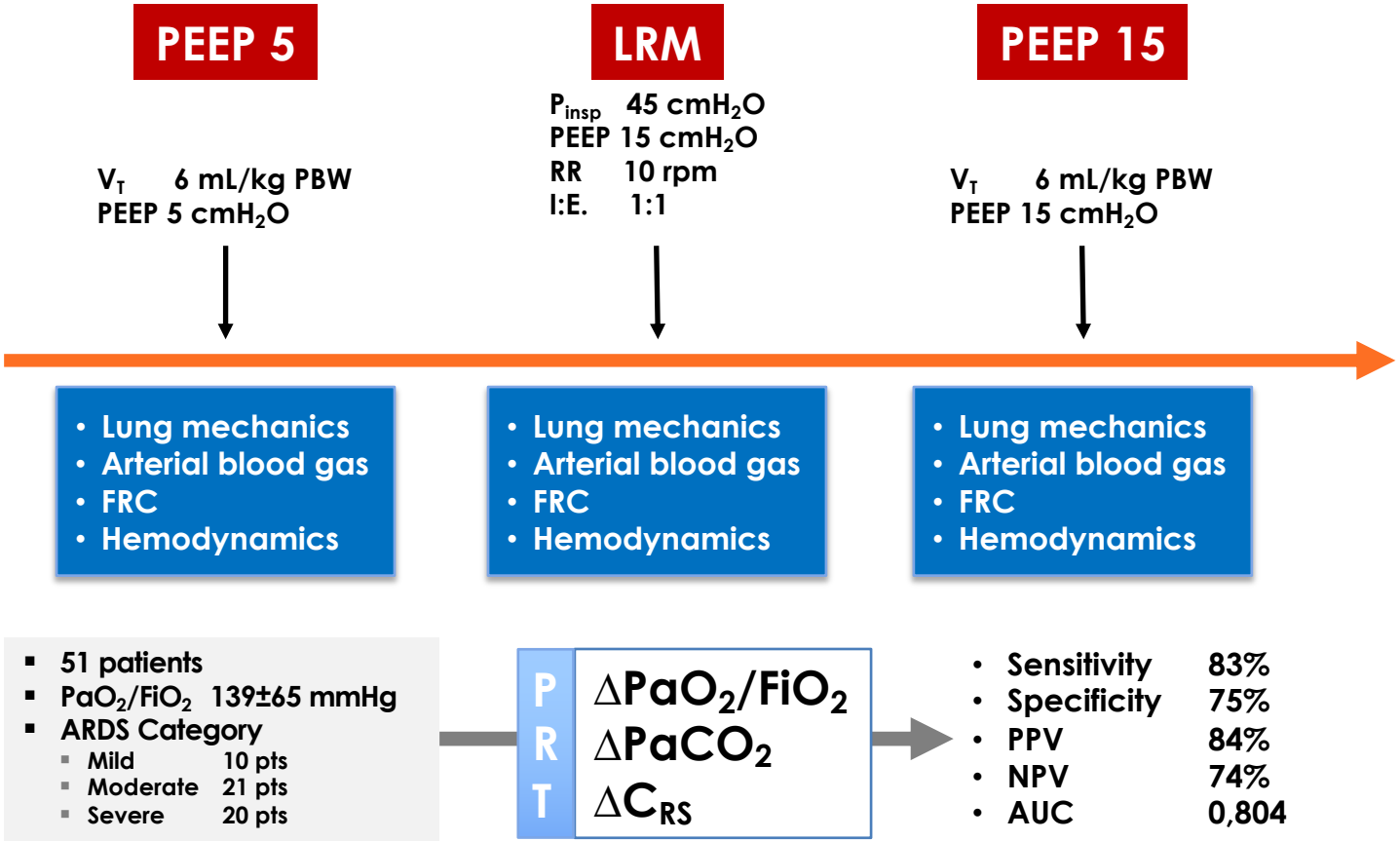
Number at risk								
Focal correctly classified	51	42	42	41	67	61	58	56
Focal misclassified	6	6	5	2	9	2	2	1
Non-focal correctly classified	96	73	68	68	89	74	71	71
Non-focal misclassified	51	39	35	32	31	14	13	13

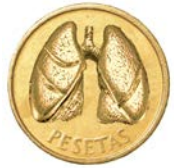
PESETAS – PEEP Selection Test in ARDS

PEEP-selection test in ARDS - assessment of PEEP responsiveness to titrate end-expiratory pressure in patients with moderate and severe acute respiratory distress syndrome. A prospective randomised trial with Bayesian response adaptive randomisation design.

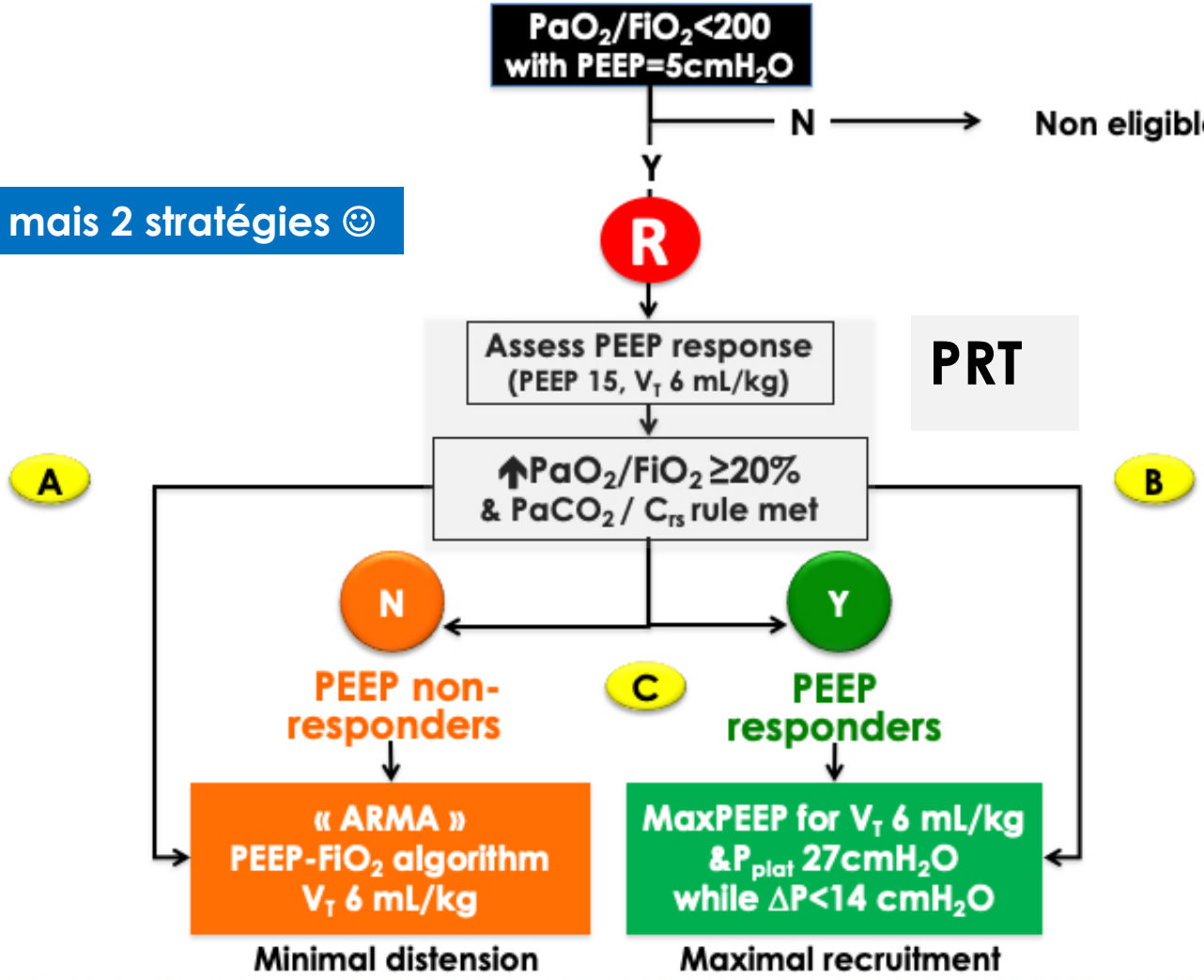
- **Hypothesis**
  - ***Patients with greater amounts of recruitable lung may benefit from higher PEEP levels, provided that attention is paid to maintain ΔP below 14 cmH_2O***
  - ***Setting PEEP based on results of a PEEP-responsiveness test (PRT) improves survival as compared to low- and high-PEEP strategies applied independently of the patient response.***

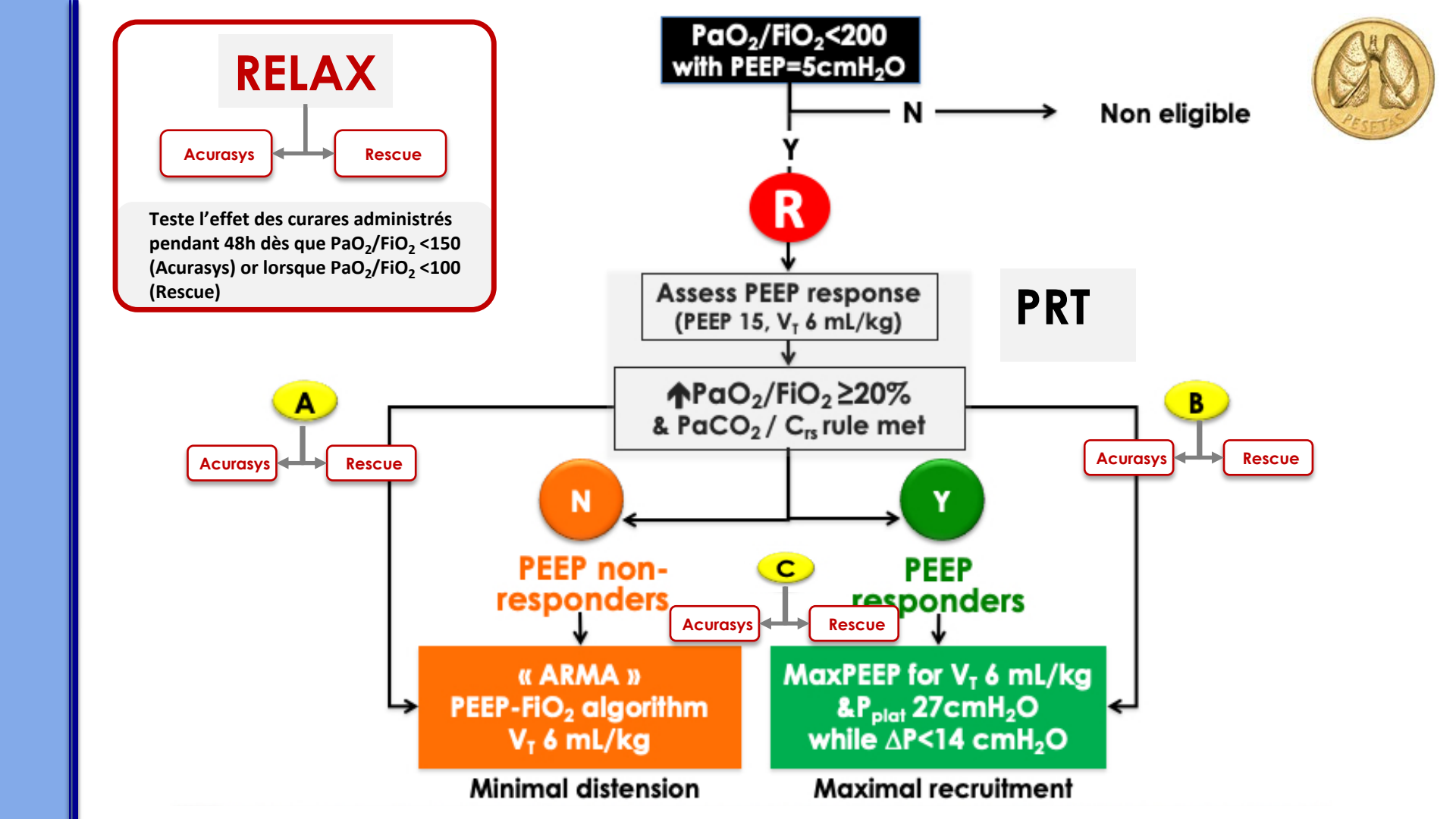
A PEEP-responsiveness test to identify lung recruitment





3 bras, mais 2 stratégies ☺




RELAX
Acurasys
Rescue
Teste l'effet des curares administrés pendant 48h dès que PaO2/FiO2 <150 (Acurasys) or lorsque PaO2/FiO2 <100 (Rescue)
PaO2/FiO2<200 with PEEP=5cmH2O
N
Non eligible
Y
R
Assess PEEP response (PEEP 15, VT 6 mL/kg)
PRT
↑PaO2/FiO2 ≥20% & PaCO2 / Crs rule met
A
Acurasys
Rescue
B
Acurasys
Rescue
N
Y
PEEP non-responders
C
Acurasys
Rescue
PEEP responders
« ARMA » PEEP-FiO2 algorithm VT 6 mL/kg
MaxPEEP for VT 6 mL/kg &Pplat 27cmH2O while ΔP<14 cmH2O
Minimal distension
Maximal recruitment

Multifactorial intervention assignments

Regimen = set of domain-specific interventions

Effect of an intervention is conditional upon

- Stratum
- Interventions within other domains

Regimen	PESETAS	RELAX	STRIVE
#1	A1	B1	C1
#2	A1	B1	C2
#3	A1	B2	C1
#4	A1	B2	C2
#5	A2	B1	C1
…..			
#*n*	A*n*	B*n*	C*n*

Ann Am Thorac Soc Vol 17, No 7, pp 879–891, Jul 2020

Self-learning healthcare is …

fused care and research

"Of all forms of inequality, injustice in health care is the most shocking and most inhumane." — Martin Luther King, Jr.


thank you
danke
謝謝
рахмат
ngiyabonga
teşekkür ederim
gracias
merci
obrigado
bedankt
спасибо
Баярлалаа
dziękuje
go raibh maith agat
mochchakkeram
tapadh leat
sukriya
kop khun krap
terima kasih
감사합니다
ευχαριστώ
arigatô
dakujem
takk
grazie
мерси
taiku
sagolun
mauruuru
hvala
dank je
mersi
kia ora
barka
welalin
tack
spas
misaotra
matondo
paldies
grazzi
mahalo
хвала
asante
manana
obrigada
murakoze
tenki
djiere dieuf
tau
дякую
mamnun
chokrane
faafetai lava
vinaka
спасибі
blagodaram
kiitos
dankie
dhanyavad
nanni
nandri
köszönöm
bayarlalaa
gràçie
enkosi
dankon
aĉiū
akun
chnorakaloutioun
gratias ago
gràcies
sulpáy
sobodi
dĕkuji
mèsi
didi madloba
najis tuke
kam sah hamnida
rahmat
ありがとう
tanemirt
rahmet
diolch
xièxie
dhanyavadagalu
shukriya
mercê
trugarez
তোমাকে ধন্যবাদ