La sfida della conduzione di studi interventistici in epoca pandemica: the rolling review trials

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Disclosures

- **No conflicts to disclose for this presentation**

- Director of the ANMCO Research Center that receives public grants of research from Oxford University, NIH, Canadian Government, PHRI, SID and private grants of research from Bayer, Sanofi-Aventis, Amgen, AstraZeneca, Menarini, Boehringer Ingelheim, DalCor.
- Scientific Coordinator of ESC EurObservational Research supported by unrestricted grants from Abbott Vascular, Bayer AG, Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Menarini, Novartis, Sanofi-Aventis, Servier, Amgen, Boston Scientific, MSD.
- Member of Trial Committees (SC, EC, CEC, DSMB) sponsored by Novartis, Cardiorentis, AstraZeneca, Bayer, Sanofi-Aventis.

Agenda

- What is a rolling review?
- Some examples
- Problems in the conduction and interpretation of trials
- Observational *versus* randomized studies: the example of remdesivir

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What is a rolling review?

- A rolling review is a regulatory tool that EMA uses to speed up the assessment of a promising medicine or vaccine during a public health emergency.
- Normally, all data on a medicine's effectiveness, safety and quality and all required documents must be submitted at the start of the evaluation in a formal application for marketing authorisation.
- In a rolling review, EMA's human medicines committee (CHMP) reviews data as they become available from ongoing studies, before a formal application is submitted.
- Once the CHMP decides that sufficient data are available, the formal application can be submitted by the company.
- By reviewing the data as they become available, the CHMP can reach its opinion sooner on whether or not the medicine or vaccine can be authorised.

What is a rolling review?

- During the rolling review, and throughout the pandemic, EMA and its scientific committees are supported by the COVID-19 EMA pandemic task force (COVID-ETF).

- This group brings together experts from across the European medicines regulatory network to advise on the development, authorisation and safety monitoring of medicines and vaccines for COVID-19 and facilitate quick and coordinated regulatory action.

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- **Some examples**
- Problems in the conduction and interpretations of trials
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Some examples: vaccines

- **EMA** starts **first rolling review** of a COVID-19 vaccine in the EUShare News **October 01, 2020**. EMA's human medicines committee (CHMP) has started the first 'rolling review' of a COVID-19 vaccine, which is being developed by the company **AstraZeneca** in collaboration with the University of Oxford.
- **BIONTECH AND PFIZER** INITIATE ROLLING SUBMISSION TO EUROPEAN MEDICINES AGENCY FOR SARS-COV-2 VACCINE CANDIDATE BNT162B2 Tuesday, **October 06, 2020** - 07:00am EDT
- European Medicines Agency Begins Rolling Review of **Moderna's mRNA Vaccine** Candidate Against COVID-19 (mRNA-1273) **November 17, 2020.**

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Quando la realtà supera la fantasia = FDA la caduta di un mito ?

- **Eric Topol** (Editor in Chief of Medscape) **to the FDA Commissioner Hahn** (Aug 31,2020)
  - I'm writing because **I'm gravely concerned about your leadership of the FDA**. Not only has your credibility been diminished but so has that of the FDA, its 15,000-plus staff members, and, most importantly, your ability to oversee the health interests of the American people.
  - Immediately after President Trump widely and aggressively promoted **hydroxychloroquine** as a "miracle drug," on **March 30, 2020**, you granted an Emergency Use Authorization for this drug without any sufficient or meaningful supportive evidence.
  - On **August 23, 2020** when you participated in a press conference with President Trump, a major advance in the treatment of patients with **convalescent plasma** was announced. This statement was based on a retrospective, observational study of over 35,000 patients who received convalescent plasma, without any controls for comparison. The claim of reduction of mortality is totally unsubstantiated. That was based on improved survival in a subgroup of a subgroup of a subgroup from about 1000 patients.
  - **August 28, 2020** broadening the **remdesivir** approval for any patient hospitalized with moderate COVID-19 on the basis of insufficient data to support this approval, as it is based on small, open-label studies with subjective endpoints.
  - These repeated breaches demonstrate **your willingness to ignore the lack of scientific evidence**, and to be complicit with the Trump Administration's politicization of America's healthcare institutions.

Quando la realtà supera la fantasia = FDA la caduta di un mito ?

- **The Pharmaceutical Industry Stands In For A Politically Impaired FDA** (Sept 8, 2020. *https://www.statnews.com/2020/09/10/hell-has-frozen-over-pharmaceutical-industry-stands-in-for-politically-impaired-fda/*)
  - Nine leading pharmaceutical and biotechnology companies issued a joint statement this week to assure the public they will not distribute their vaccines for Covid-19 before their safety and effectiveness have been firmly established.
  - There's no question that the FDA is politically impaired. Administration make a public display of its pressure on FDA leaders to approve a vaccine before the November elections. The FDA's leaders have done little to convince the public they will not capitulate to pressure from the Trump administration.
  - Without a functioning FDA, pharmaceutical manufacturers can lose this important guardrail.
  - Authors have a combined eight decades of experience in health care. We have seen a lot during that time. But we never would have expected to see the pharmaceutical industry feel compelled to step into the role FDA is mandated to fill. It is ironic and tragic at the same time.


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L'esempio italiano

Commentary

COVID-19 trials in Italy: A call for simplicity, top standards and global pooling

Aldo P. Maggioni [a,*], Felicita Andreotti [b,1], Cristina Gervasoni [c], Giuseppe Di Pasquale [d]

- Note positive:
  - Celere approvazione da parte della autorità competente (AIFA)
  - Un solo Comitato Etico per tutte le sperimentazioni sui farmaci per il trattamento/prevenzione COVID-19
- 35 studi approvati e analizzati a fine Maggio 2020
  - 29 (83%) randomizzati, 6 osservazionali senza gruppo di controllo
    - 22 open label con end point suscettibili di valutazioni soggettive
    - 19 di piccola dimensione giustificati solo da assunzioni iper-ottimistiche di beneficio
    - Solo 5 (14%) di dimensioni adeguate a rispondere alla domanda del protocollo
- Conclusione: *While waiting for an effective vaccine, the crucial question is: will current trial results produce sufficiently reliable evidence on effective and safe preventive/ therapeutic approaches to face, potentially next autumn, a relapse of the infection? The answer is hopefully yes, but only thanks to the currently few adequately designed large-scale randomised trials*

Qualche esempio positivo

- **RECOVERY, UK** (oltre 25,000 pazienti inclusi, end point primario mortalità totale)
  - HCQ nessun beneficio
  - Lopinavir/ritonavir nessun beneficio
  - Desametazone: Riduzione 30% della mortalità totale, effetto più evidente nei pazienti ventilati
  - Adaptive design: Azithromycin, Tocilizumab, Convalescent plasma, Low-dose Dexamethasone (children only), Aspirin, Colchicine etc

- **SOLIDARITY, WHO** (oltre 15,000 pazienti inclusi, end point primario mortalità totale)
  - HCQ nessun beneficio
  - Lopinavir/ritonavir nessun beneficio
  - Interferone nessun beneficio
  - Remdesivir nessun beneficio
  - Adaptive design: artesunate, imatinib and infliximab

- **ACTIV IV acute and outpatients, NIH**

  Antithrombotic treatments
  - Heparin: preventive *versus* therapeutic
  - Antiplatelets: ticagrelor or clopidogrel
  - Adaptive design: SGLT2 inhibitors

ESC European Society of Cardiology
European Heart Journal (2020) **0**, 1–2
doi:10.1093/eurheartj/ehaa322

Aldo P Maggioni, Claudio Rapezzi, Luigi Tavazzi, and Roberto Ferrari

EHJ, April 2020

Key words to be adopted for COVID-19 research

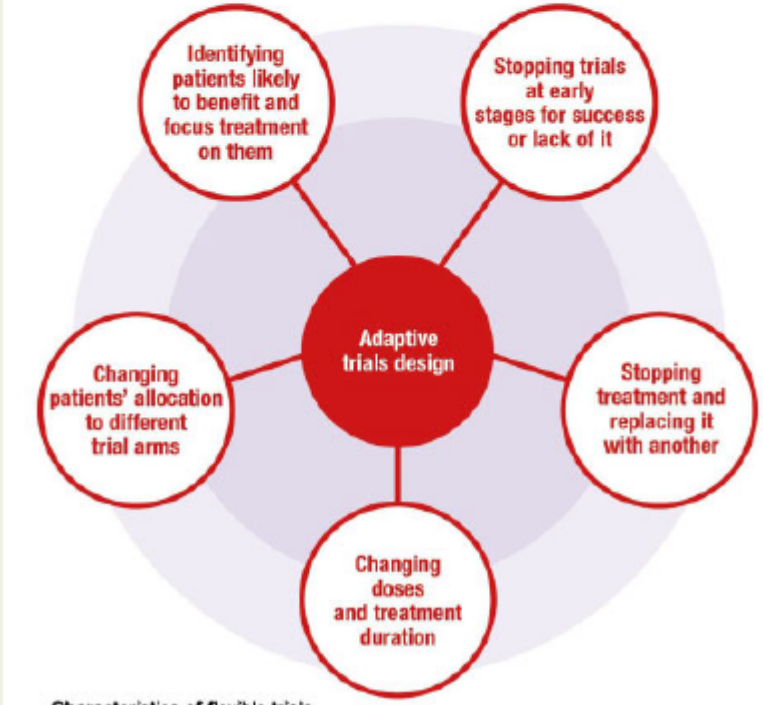
A return to simple, large, randomized trials

In 1984

An outstanding article was published by Salim Yusuf, one of the 'gurus' of clinical research.[1] The article set out the rules for cardiovascular research worldwide. A few years later, the trials for the treatment of acute myocardial infarction (MI) modified the treatment for this number one killer[2,3] and were followed by studies that contributed to the great success of cardiology.

Today

And this is a 'gift' from COVID-19, the lessons learnt seem to have been lost. A multitude of small, often uncontrolled clinical trials have started or are on the way, based on enthusiasm, but we risk wasting human and economic resources.



Characteristics of flexible trials

Problems in the conduction of non-COVID trials

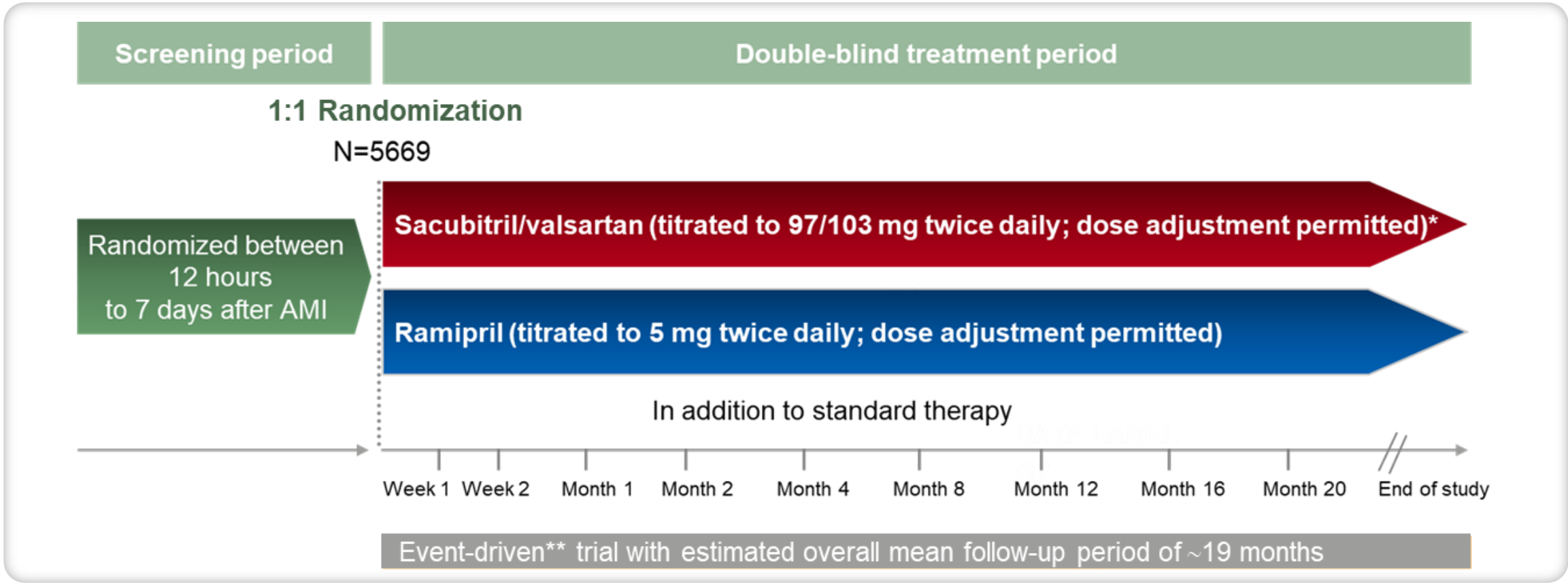
Problems:

- Difficult/impossible follow-up visits.
- Scarce documentation of events for central adjudication.
- Increased number of undefined causes of death/hospitalizations.

Consequences:

- Lower event rate than expected.
- Reduced power of the study.
- Neutral results with the clear perception of a favorable effect.

PARADISE-MI: Study design



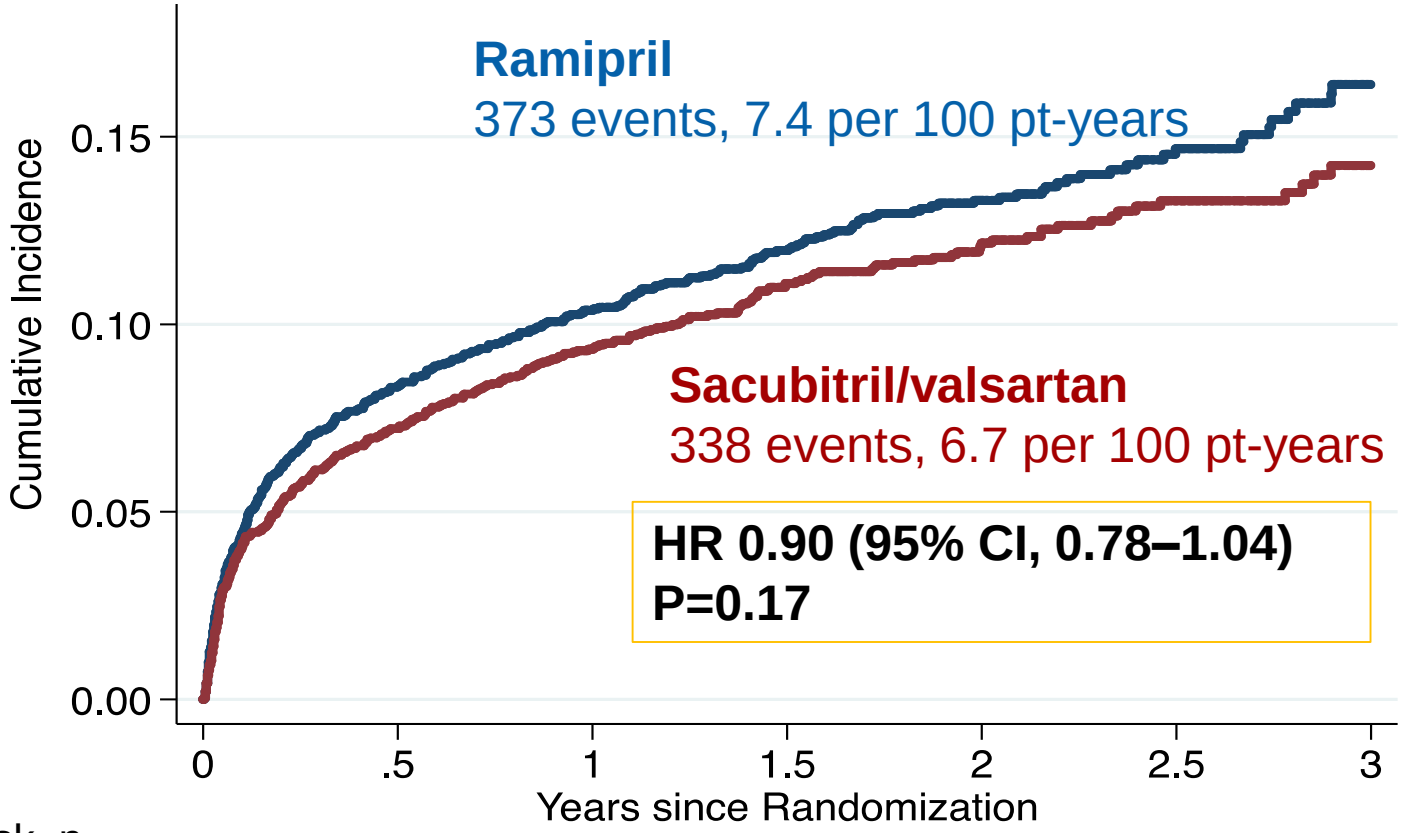
*Blinded treatment with two doses of valsartan 40 or 80 mg twice daily required before starting the study medication for patients who were randomized to sacubitril/valsartan and previously treated with ACEis

**Event-driven study (approx. 43 months): at least 708 first primary composite endpoint events and 592 first CV death or HF hospitalization events

1. Jering KS, et al. Eur J Heart Fail. 2021. doi: 10.1002/ejhf.2191. Online ahead of print;
2. ClinicalTrials.gov Identifier: NCT02924727. Accessed on 7 August 2020.

PARADISE-MI: Primary outcome

CV death, first HF hospitalization or outpatient HF



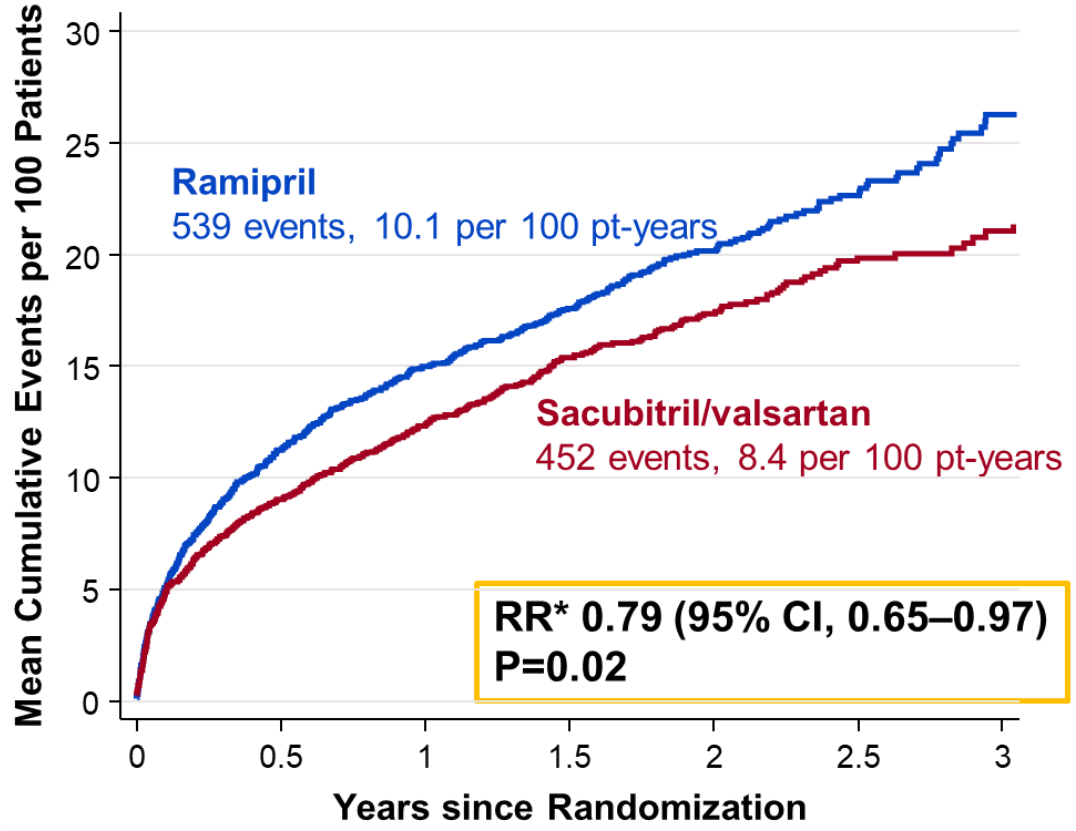
Patients at risk, n

Ramipril	2831	2577	2318	1725	1091	570	278
Sacubitril/valsartan	2830	2614	2342	1732	1101	567	280

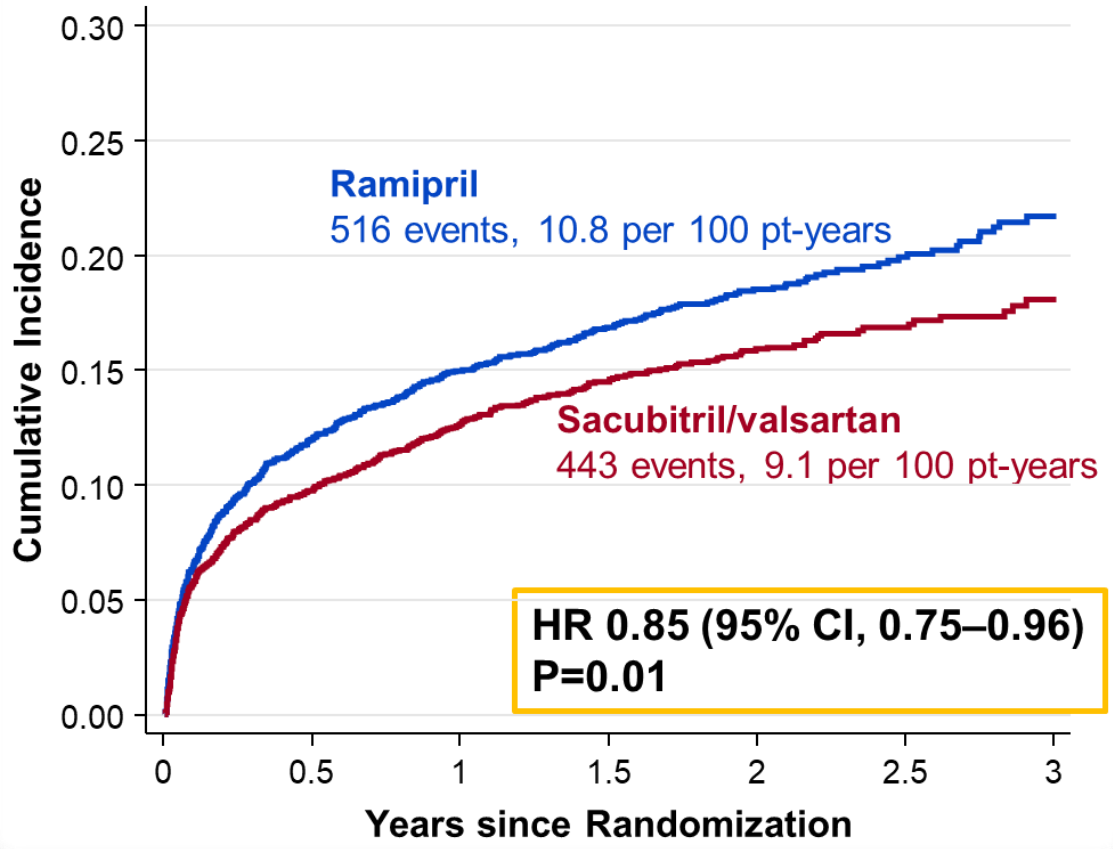
Pfeffer MA. Late-breaking clinical trials. Presentation # 402-08 ACC2021 (May 15, 2021)

PARADISE-MI: Cumulative incidence of 'total CEC-adjudicated' and 'investigator-reported' primary outcomes

Total (first and recurrent) CEC-adjudicated primary events



Investigator-reported primary endpoint



*Negative binomial regression with Weibull baseline intensity function

Pfeffer MA. Late-breaking clinical trials. Presentation # 402-08 ACC2021 (May 15, 2021)

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- **Observational *versus* randomized studies: the example of remdesivir**

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med. 2003 Feb 13;348(7):645-50

SOUNDING BOARD

Understanding the Divergent Data on Postmenopausal Hormone Therapy

Francine Grodstein, Sc.D., Thomas B. Clarkson, D.V.M., and JoAnn E. Manson, M.D., Dr.P.H.

Table 2. Results from Observational Studies of Combined Hormone Therapy and from the Women's Health Initiative and the Heart and Estrogen/Progestin Replacement Study.*

Disease	Women's Health Initiative	Heart and Estrogen/ Progestin Replacement Study	Observational Studies of Estrogen with Progestin
		relative risk (95% confidence interval)	
Breast cancer	1.26 (1.00–1.59)	1.30 (0.77–2.19)	
<5 yr			1.15[7]
≥5 yr			1.53[7]
Colorectal cancer	0.63 (0.43–0.92)	NA	0.66 (0.59–0.74)[8]†
Hip fracture	0.66 (0.45–0.98)	1.10 (0.49–2.50)	0.75 (0.68–0.84)[9]†
Stroke	1.41 (1.07–1.85)	1.2 (1.0–1.4)‡	1.45 (1.10–1.92)[10]
Pulmonary embolism	2.13 (1.39–3.25)	2.8 (0.9–8.7)	2.1 (1.2–3.8)[11]†
Coronary heart disease	1.29 (1.02–1.63)	0.99 (0.80–1.22)	0.61 (0.45–0.82)[12]

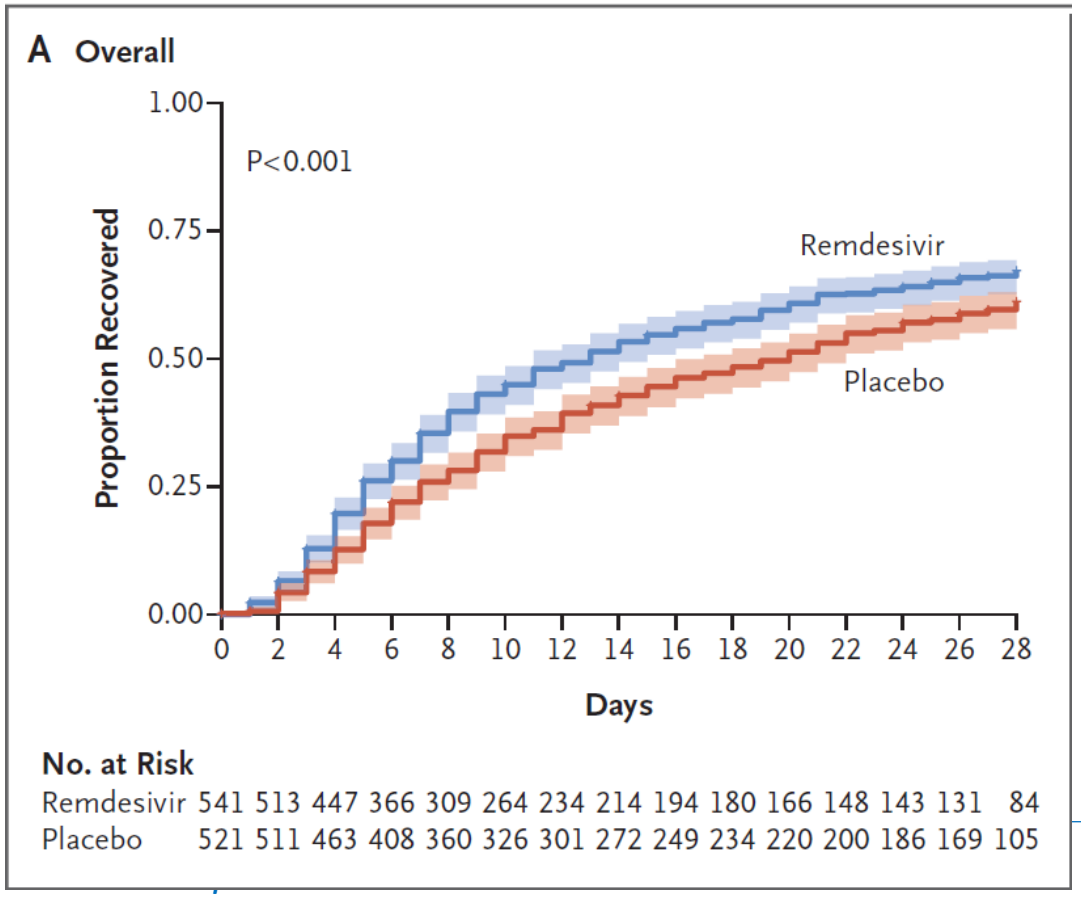
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

This article was published on October 8, 2020, at NEJM.org.



	Overall	
	Remdesivir (N=541)	Placebo (N=521)
Recovery		
No. of recoveries	399	352
Median time to recovery (95% CI) — days	10 (9–11)	15 (13–18)
Rate ratio (95% CI)†	1.29 (1.12–1.49 [P<0.001])	
Mortality over entire study period‡		
Hazard ratio (95% CI)	0.73 (0.52–1.03)	
No. of deaths by day 29	59	77
Kaplan–Meier estimate of mortality by day 29 — % (95% CI)	11.4 (9.0–14.5)	15.2 (12.3–18.6)

Comparative Effectiveness Of Remdesivir Treatment In Patients Hospitalized With Covid-19

A. P. Chokkalingam et al *(World Microbe Forum June 2021)*

Table. All-cause mortality hazard ratios (HRs) overall and stratified by baseline oxygen support level

	Overall		Room/Ambient Air		Low-flow Oxygen		High-flow oxygen/NIV		IMV/ECMO	
	Referent	RDV	Referent	RDV	Referent	RDV	Referent	RDV	Referent	RDV
N $_{patients}$	9271	9271	5015	5015	2814	2814	1036	1036	182	182
PY follow-up	148	204	71	98	42	60	26	32	6	8
N $_{events}$	1275	1428	420	512	314	359	398	395	105	100
Event rate (per PY)	8.62	7.00	5.95	5.20	7.50	6.00	15.28	12.38	17.96	13.27
HR (95% CI)*	0.79 (0.73, 0.85)		0.85 (0.74, 0.96)		0.74 (0.63, 0.86)		0.81 (0.70, 0.93)		0.74 (0.56, 0.97)	

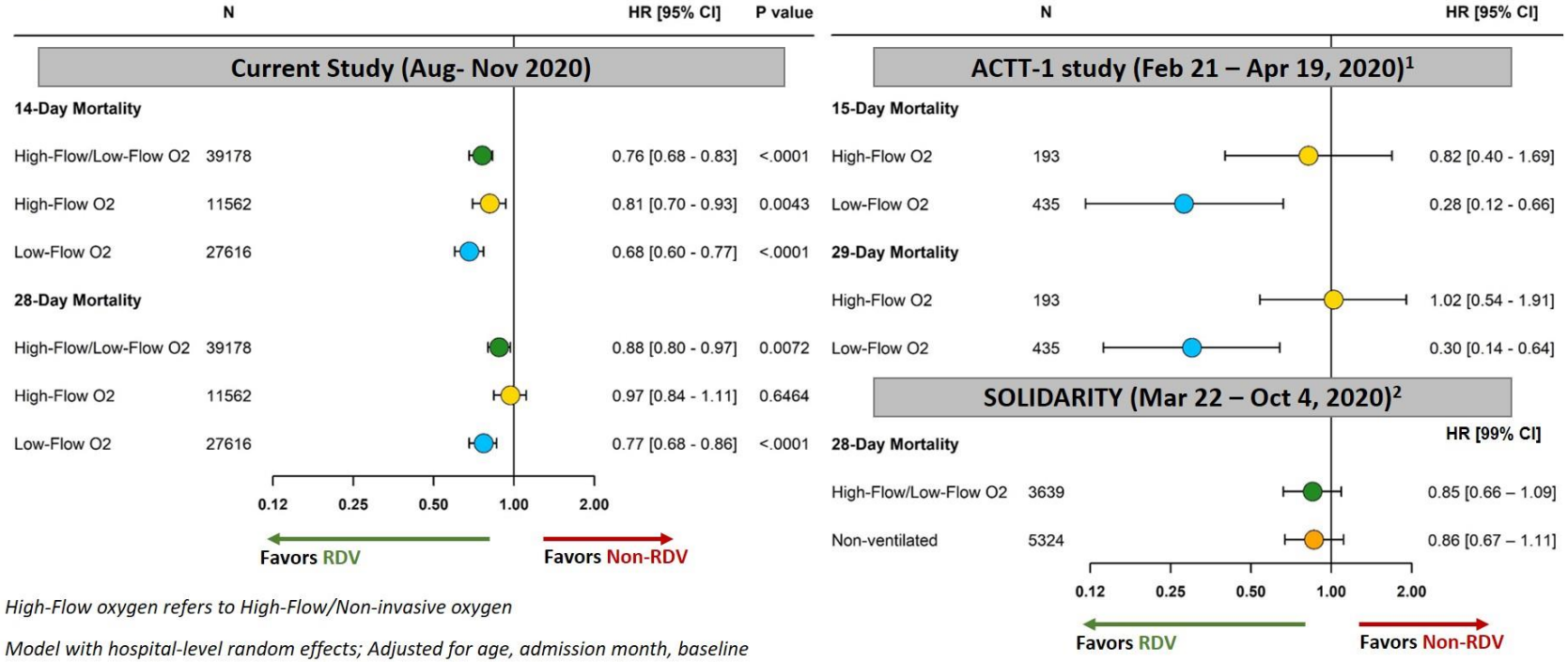
*Adjusted for baseline demographic and clinical characteristics, comorbidities, and concomitant medications

HR: hazard ratio; IMV/ECMO: invasive mechanical ventilation/extracorporeal membrane oxygenation; N: number; NIV: non-invasive ventilation; PY: person-years; RDV: remdesivir

Remdesivir Treatment is Associated with Improved Survival in Hospitalized Patients with COVID-19. E.

E. Mozaffari et al (World Microbe Forum June 2021)

Figure. Time to mortality results from three studies



High-Flow oxygen refers to High-Flow/Non-invasive oxygen

Model with hospital-level random effects; Adjusted for age, admission month, baseline treatments (anticoagulants, convalescent plasma, steroids, tocilizumab use), DVT/PE, ischemic stroke, ICU stay/Step-down/General ward at baseline

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final report. *N Engl J Med* 2020;383:1813-1826
2. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19—interim WHO SOLIDARITY trial results. *N Engl J Med* 2021;384:497-511.

Remdesivir Vs. Standard Of Care For Severe Covid-19

A.S. Go et al ((World Microbe Forum June 2021)

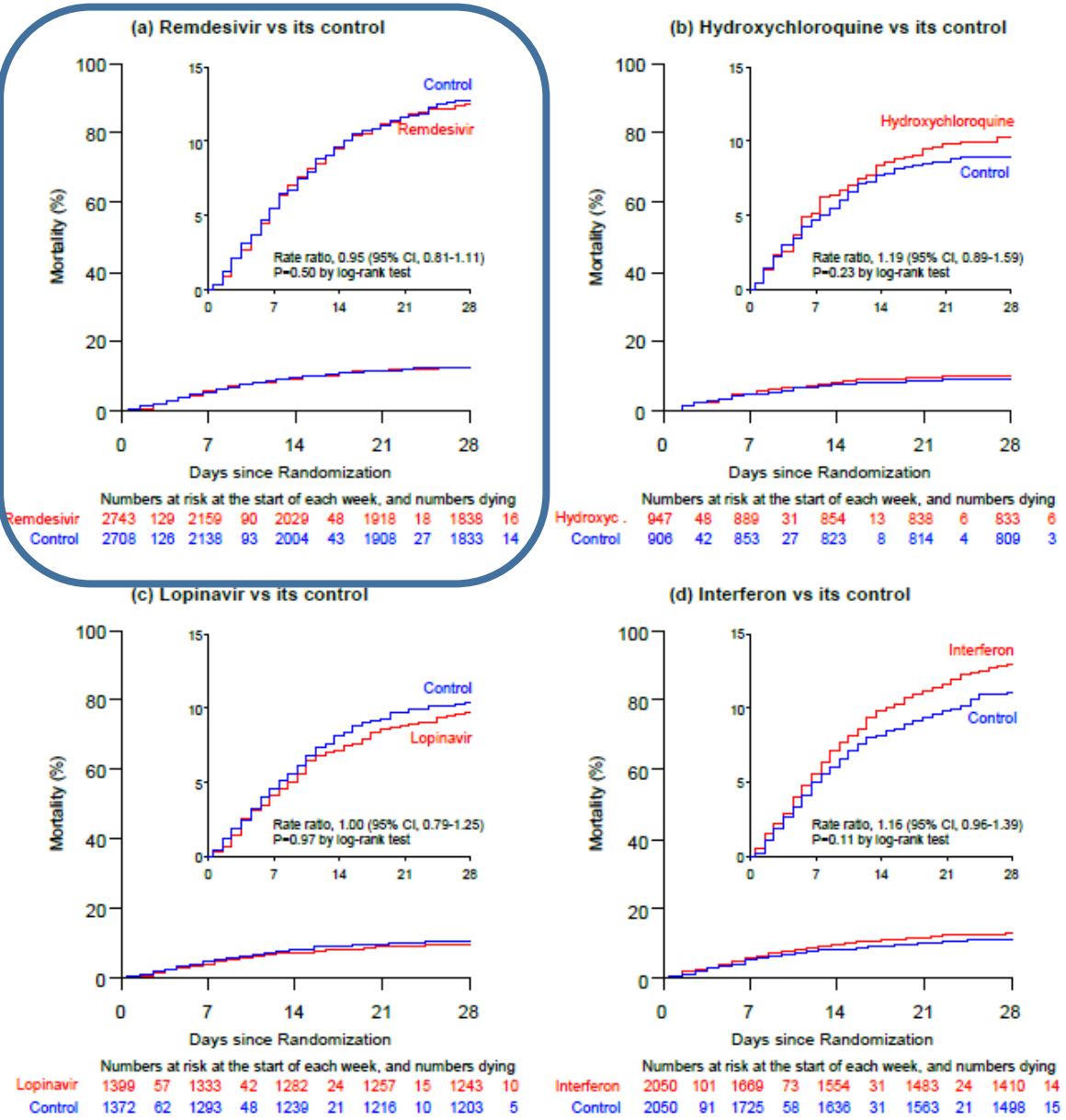
Table . All-cause mortality hazard ratios (HRs), overall and stratified by baseline oxygen support level

	Overall		IMV/ECMO		High-Flow/NIV		Low-Flow	
	N patients N events (%)	HR (95% CI) p-value	N patients N events (%)	HR (95% CI) p-value	N patients N events (%)	HR (95% CI) p-value	N patients N events (%)	HR (95% CI) p-value
RDV	1974 247 (12.5%)	**0.59 (0.49-0.70) P<0.0001**	342 79 (23.0%)	**0.51 (0.35-0.73) P=0.0003**	443 110 (24.8%)	**0.66 (0.50-0.86) P=0.0022**	1234 66 (5.3%)	**0.49 (0.36-0.68) P<0.0001**
SOC	1132 244 (21.5%)		104 43 (41.3%)		326 109 (33.4%)		714 96 (13.4%)	

Note: IMV/ECMO: invasive mechanical ventilation/extracorporeal membrane oxygenation; NIV: non-invasive ventilation; CI: confidence interval

Figure 2. Effects of (a) Remdesivir, (b) Hydroxychloroquine, (c) Lopinavir, and (d) Interferon on 28-day mortality

Kaplan-Meier graphs of in-hospital mortality. The inset shows the same data on an expanded y-axis.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

	Deaths reported / Patients randomized in ITT analyses (28-day risk, K-M%)		Active-group deaths: log-rank statistics		Ratio of death rates (RR), & 99% CI (or 95% CI, for total)
	Active	Control	O-E	Variance	Active : Control
(a) Remdesivir					
Age at entry					
<50	61/961 (6.9)	59/952 (6.8)	2.3	29.8	1.08 [0.67-1.73]
50-69	154/1282 (13.8)	161/1287 (14.2)	-7.6	77.5	0.91 [0.68-1.21]
70+	86/500 (20.5)	83/469 (21.6)	-2.9	41.5	0.93 [0.63-1.39]
Respiratory support at entry					
Ventilated	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 [0.80-1.80]
Not ventilated	203/2489 (9.4)	232/2475 (10.6)	-15.8	108.0	0.86 [0.67-1.11]
Total	**301/2743 (12.5)**	**303/2708 (12.7)**	**-8.3**	**148.8**	**0.95 [0.81-1.11]**
Heterogeneity around total χ^2_3: 3.9					**2p = 0.50**

N Engl J Med. 2021 Feb 11;384(6):497-511

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01499-z

Check for updates

OPEN

Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial

Evdoxia Kyriazopoulou[1], Garyfallia Poulakou[2], Haralampos Milionis[3], Simeon Metallidis[4], Georgios Adamis[5], Konstantinos Tsiakos[6], Archontoula Fragkou[7], Aggeliki Rapti[6], Christina Damoulari[1], Massimo Fantoni[8], Ioannis Kalomenidis[9], Georgios Chrysos[10], Andrea Angheben[11], Ilias Kainis[12], Zoi Alexiou[13], Francesco Castelli[14], Francesco Saverio Serino[15], Maria Tsilika[1], Petros Bakakos[16], Emanuele Nicastri[17], Vassiliki Tzavara[18], Evangelos Kostis[19], Lorenzo Dagna[20], Panagiotis Koufargyris[1], Katerina Dimakou[21], Spyridon Savvanis[7], Glykeria Tzatzagou[22], Maria Chini[23], Giulio Cavalli[20], Matteo Bassetti[24], Konstantina Katrini[1], Vasileios Kotsis[25], George Tsoukalas[26], Carlo Selmi[27], Ioannis Bliziotis[28], Michael Samarkos[29], Michael Doumas[30], Sofia Ktena[1], Aikaterini Masgala[31], Ilias Papanikolaou[32], Maria Kosmidou[3], Dimitra-Melia Myrodia[2], Aikaterini Argyraki[33], Chiara Simona Cardellino[11], Katerina Koliakou[34], Eleni-Ioanna Katsigianni[34], Vassiliki Rapti[2], Efthymia Giannitsioti[10], Antonella Cingolani[8], Styliani Micha[34], Karolina Akinosoglou[35], Orestis Liatsis-Douvitsas[34], Styliani Symbardi[36], Nikolaos Gatselis[37], Maria Mouktaroudi[1,34], Giuseppe Ippolito[17], Eleni Florou[34], Antigone Kotsaki[1], Mihai G. Netea[38,39], Jesper Eugen-Olsen[40], Miltiades Kyprianou[34], Periklis Panagopoulos[41], George N. Dalekos[37] and Evangelos J. Giamarellos-Bourboulis[1,34] ✉

Early increase of soluble urokinase plasminogen activator receptor (suPAR) serum levels is indicative of increased risk of progression of coronavirus disease 2019 (COVID-19) to respiratory failure. The SAVE-MORE double-blind, randomized controlled trial evaluated the efficacy and safety of anakinra, an IL-1α/β inhibitor, in 594 patients with COVID-19 at risk of progressing to respiratory failure as identified by plasma suPAR ≥6 ng ml^{-1}, 85.9% ($n = 510$) of whom were receiving dexamethasone. At day 28, the adjusted proportional odds of having a worse clinical status (assessed by the 11-point World Health Organization Clinical Progression Scale (WHO-CPS)) with anakinra, as compared to placebo, was 0.36 (95% confidence interval 0.26–0.50). The median WHO-CPS decrease on day 28 from baseline in the placebo and anakinra groups was 3 and 4 points, respectively (odds ratio (OR) = 0.40, $P < 0.0001$); the respective median decrease of Sequential Organ Failure Assessment (SOFA) score on day 7 from baseline was 0 and 1 points (OR = 0.63, $P = 0.004$). Twenty-eight-day mortality decreased (hazard ratio = 0.45, $P = 0.045$), and hospital stay was shorter.

Conclusioni

- Il processo di Rolling review è stato necessario data l'emergenza, determinata dalla pandemia, di trovare rapidamente trattamenti preventivi/curativi.
- Per i vaccini questo processo ha funzionato efficamente.
- Salvo rari esempi di straordinaria efficacia (UK NHS, NIH, WHO), gli studi sui trattamenti hanno spesso privilegiato la necessità di apparire rispetto a un interesse più generale di salute pubblica.
- Per i trattamenti, la velocizzazione delle procedure regolatorie, anche dovuta alla emotività/necessità politiche del momento, ha qualche volta prodotto macroscopici errori valutativi.

Implicazioni pratiche

- **Dal punto di vista del regulator:** processi più snelli di valutazione del profilo di rischio/beneficio di nuovi approcci terapeutici sono sicuramente necessari.
- **Dal punto di vista del ricercatore:** la ricerca collaborativa dovrebbe prevalere sulla ricerca individuale.
- **Dal punto di vista del SSN:** finanziare una rete nazionale/internazionale di ricerca pronta a intervenire ogniqualvolta si presentino problemi di salute pubblica dovrebbe essere una scelta prioritaria.
- **Dal punto di vista del paziente:** comprendere che, di fronte a situazioni sanitarie mai o poco studiate in precedenza, la scienza non può fornire risposte immediate e che ogni approccio terapeutico, anche se chiaramente efficace, non può determinare risultati favorevoli nel 100% dei casi.