COVID-19 Update 8/26/2020

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Proning 101

- Treatment strategy to improve oxygenation in severe ARDS
  - P:F ratio < 150
  - Refractory hypoxemia unresponsive to vent management

PaO_2 / FIO_2. Example for healthy person: 95/0.21= 452

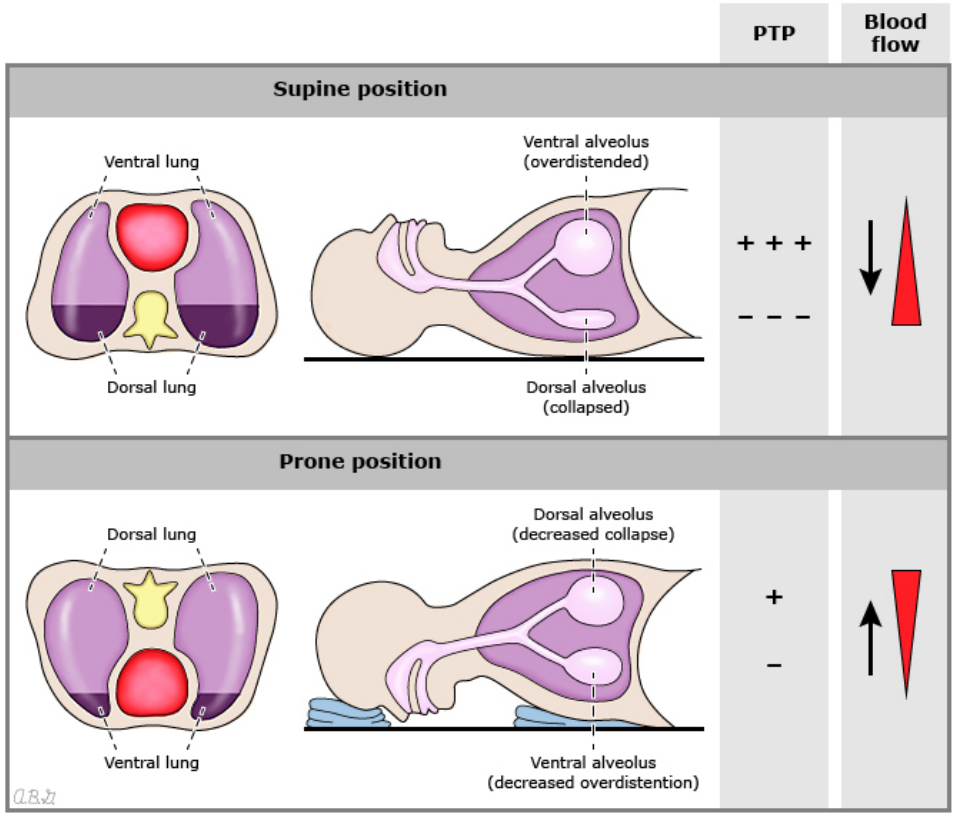
- Simple by definition
  - Requires team approach
  - Requires planning and attention to detail
- Methods
  - Bed to bed
  - Specialty beds

ARDS and

- PROSEVA trial (2013)
  - Prospective randomized control trial
  - Prone positioning improved both 28-day and 90-day mortality ▪
  - Similar complication rates in both groups

- APRONET trial (2018)
  - Prospective prevalence study
  - Prone positioning used in 32.9% of patients with severe ARDS
  - Low complication rate
  - Significant increase in oxygenation
  - Significant decrease in driving pressures

Physiology of prone positioning in acute respiratory distress syndrome



Shown in this figure are axial (left) and sagittal views (right) of the thoracic cage representing the changes that occur as a consequence of prone positioning compared with supine positioning. Distending pressure of lung is determined by the transpulmonary pressure (PTP). When an individual is supine, the ventral PTP (+++) significantly exceeds the dorsal PTP (---) resulting in greater expansion of the ventral alveoli than the dorsal alveoli; this effect is exaggerated in acute respiratory distress syndrome (ARDS) such that ventral alveoli become overdistended and dorsal alveoli become atelectatic (dark purple). Prone positioning reduces the difference between the dorsal and ventral PTP, making ventilation more homogeneous, leading to a decrease in dorsal alveolar overinflation and ventral alveolar collapse and recruitment of alveoli that had collapsed during the supine ventilation. In ARDS, there is substantial ventilation-perfusion mismatch in the supine position, since blood flow and alveolar collapse are both greatest in the dependent portions of the lung. When prone, ventilation/perfusion matching improves since the previously dependent lung continues to receive the majority of the blood flow as alveoli reopen, while the newly dependent lung continues to receive the minority of the blood flow as alveoli begin to collapse. NOTE: The terms dorsal and ventral are anatomy based, rather than gravity based.

Proning and COVID-19 ARDS

Face down, sats up...

dkbmed

COVID-19
KEEPING UP WITH A MOVING TARGET

Proning Bed

Advice on the use of masks for children in the community in the context of COVID-19

Annex to the Advice on the use of masks in the context of COVID-19

21 August 2020

unicef

World Health Organization

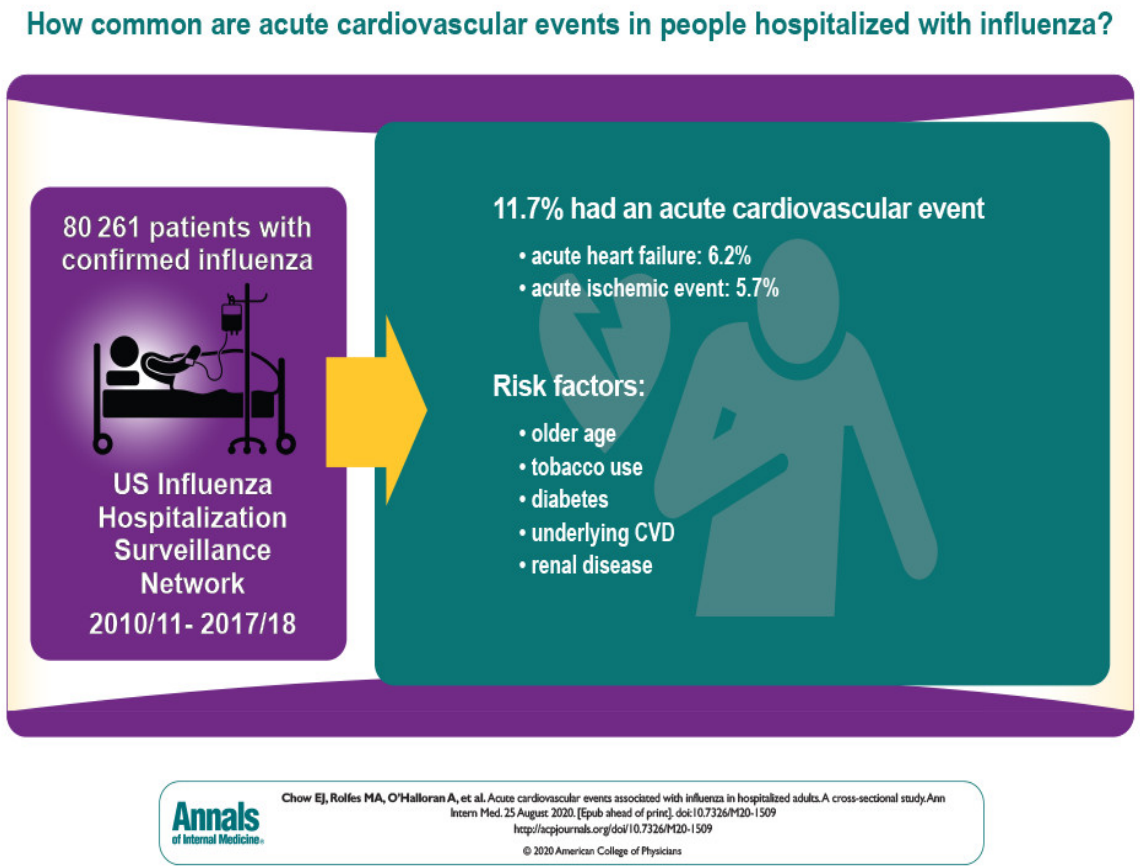
WHO Recommends Against Face Masks for Kids in Community Settings Under Age 5

- The World Health Organization recommends that children in the community setting under age 5 not wear masks as a preventive measure against COVID-19 in recent guidance on mask use.
- The decision was based on expert opinion on childhood developmental milestones, challenges with mask compliance, and the autonomy required to wear a mask properly.
- If countries use a 2- or 3-year age cutoff for recommending masks, then children should be directly supervised
- For youths aged 6 to 11 years, a risk-based approach should consider intensity of local transmission, a child's ability to comply, whether they live with at-risk adults, and other factors.

WHO Recommends Against Face Masks for Kids in Community Settings Under Age 5

- Adolescents aged 12 years and older should follow mask guidance for adults.
- Mask use should not be required for any child with developmental disorders, disabilities, or other health conditions that could interfere with wearing a mask.
- The WHO also notes that face shields only provide eye protection "and should not be considered as an equivalent to masks with respect to respiratory droplet protection and/or source control."

Acute Cardiovascular Events Associated with Influenza Hospitalization

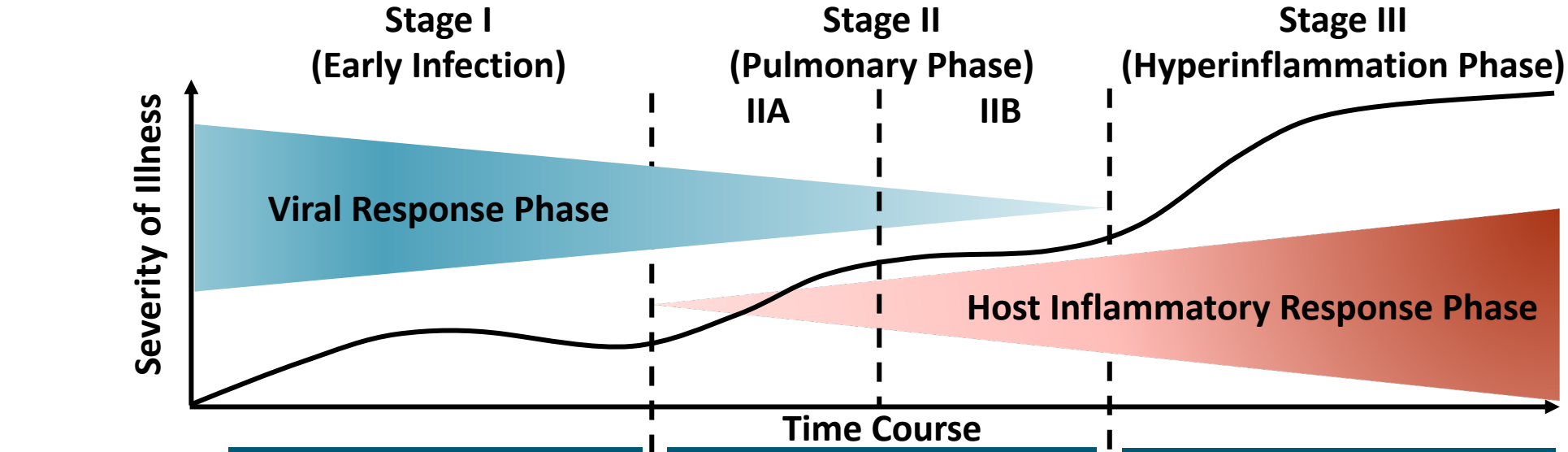


Influenza Vaccine: Routine Secondary Prevention for Patients With Cardiovascular Disease?

- The efficacy of influenza vaccines for secondary prevention of cardiovascular events is 15% to 45%
- Like that of statins, antihypertensive agents, and smoking cessation.
- We accept the important role of the latter interventions in secondary prevention of cardiovascular disease, but influenza vaccination continues to be overlooked.
- It is time to recognize the significant and preventable cardiovascular morbidity and mortality associated with influenza and to view influenza vaccination as a routine secondary preventive measure for cardiovascular events.

Chandini R. MacIntyre. Ann Int Med Aug 2020

COVID-19 Therapies Predicted to Provide Benefit at Different Stages



	Stage I (Early Infection)	Stage II (Pulmonary Phase) IIA	Stage II (Pulmonary Phase) IIB	Stage III (Hyperinflammation Phase)
Clinical symptoms	Mild constitutional symptoms Fever > 99.6°F Dry cough	Shortness of breath without (IIA) and with hypoxia (IIB) (PaO_2/FiO_2 ≤ 300 mm Hg)		ARDS SIRS/shock Cardiac failure
Clinical signs	Lymphopenia	Abnormal chest imaging Transaminitis Low-normal procalcitonin		Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation

Benefit demonstrated

Benefit unclear

Remdesivir

Dexamethasone

Oxygen

Convalescent Plasma

Slide credit:
clinicaloptions.com

Siddiqi. J Heart Lung Transplant. 2020;39:405.

IDSA Recommendations on Treatment and Management of Patients With COVID-19

- Overarching goal: recruit patients into ongoing trials to provide needed evidence regarding efficacy and safety of potential therapies

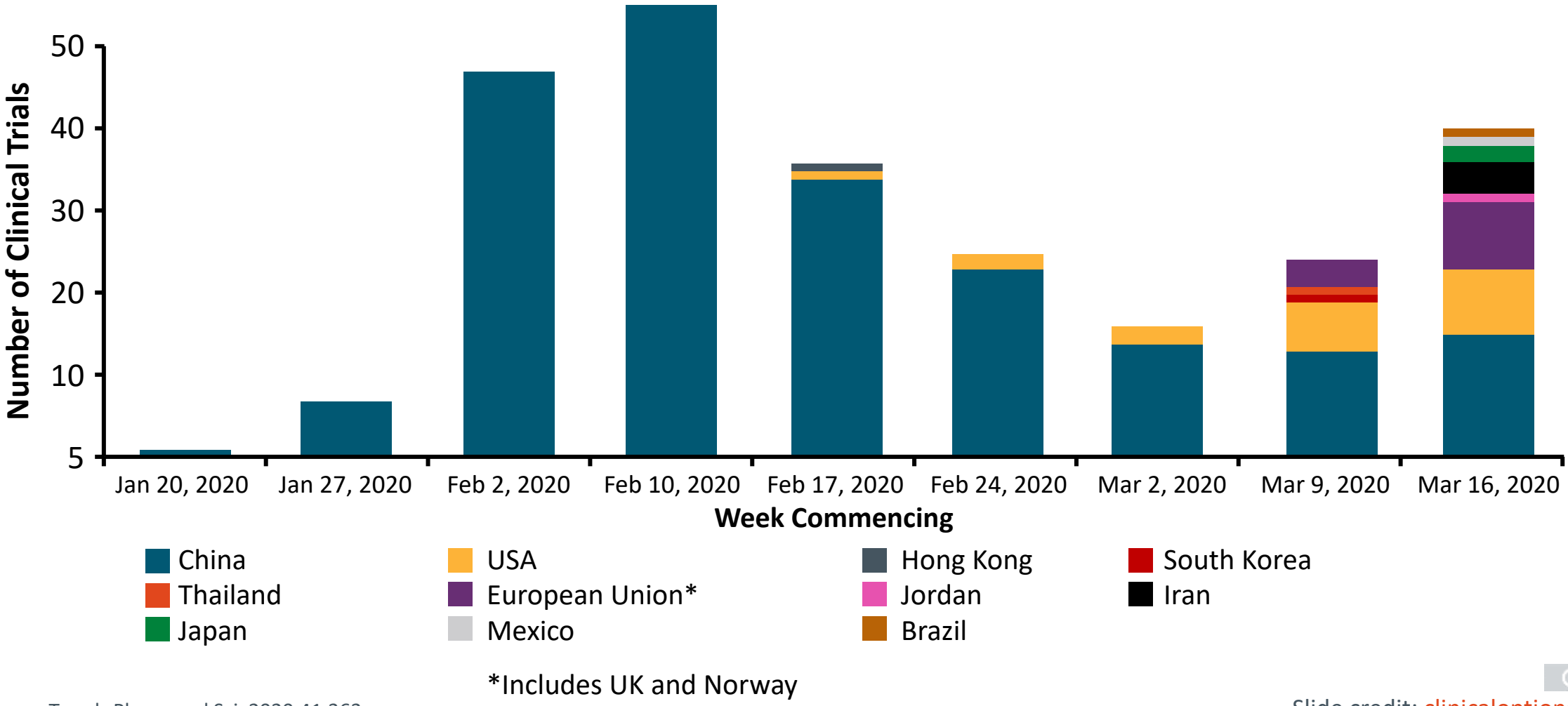
IDSA Guidance	Patient Population	Treatment
Suggests	▪ Hospitalized with severe* COVID-19 ▪ Hospitalized with severe* COVID-19	▪ Remdesivir† ▪ Glucocorticoids
Recommended only in context of a clinical trial	▪ COVID-19 ▪ Hospitalized with COVID-19 ▪ Hospitalized with COVID-19 ▪ Hospitalized with COVID-19	▪ (Hydroxy)chloroquine ▪ Lopinavir/ritonavir ▪ Tocilizumab ▪ Convalescent plasma
Suggests against outside context of a clinical trial	▪ Hospitalized with severe* COVID-19 ▪ COVID-19	▪ Famotidine ▪ (Hydroxy)chloroquine + azithromycin

Note: Among patients hospitalized with COVID-19 without hypoxemia requiring supplemental oxygen, the panel suggests against glucocorticoids.
*Severe illness defined as SpO2 ≤ 94% on room air, and those who require supplemental oxygen, mechanical ventilation or ECMO.
†For patients with severe COVID-19 on supplemental oxygen, 5 days suggested; for patients on mechanical ventilation or ECMO, 10 days.

IDSA. COVID-19 Guideline, Part 1: Treatment and Management. Version 2.1.0.

Slide credit: clinicaloptions.com

Geographic Distribution of Ongoing Clinical Trials for COVID-19



*Includes UK and Norway

Lythgoe. Trends Pharmacol Sci. 2020;41:363.

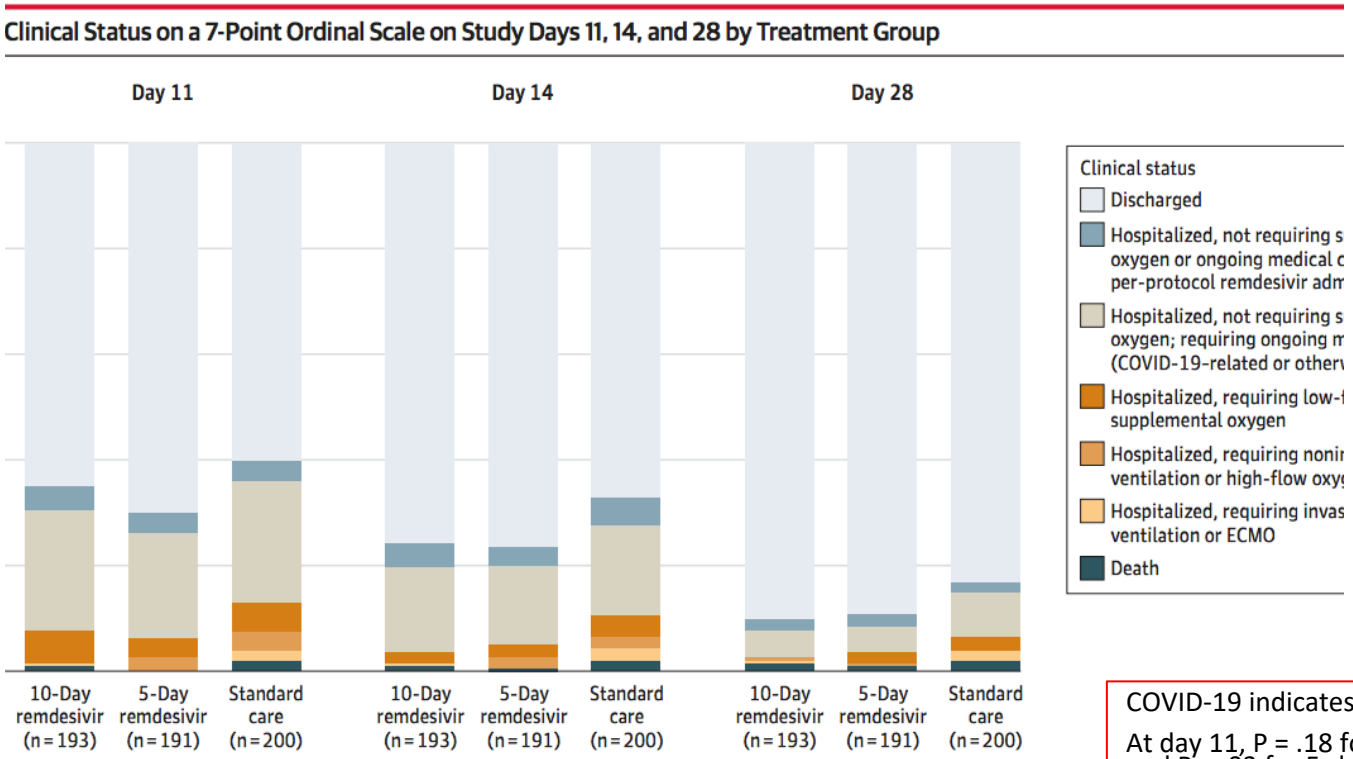
Slide credit: clinicaloptions.com

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19

- **OBJECTIVE**
  - To determine the efficacy of 5 or 10 days of remdesivir treatment compared with SOC standard care on clinical status on day 11 after initiation of treatment.
- **DESIGN, SETTING, AND PARTICIPANTS**
  - Randomized, open-label trial of hospitalized patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation >94%) enrolled from March 15 through April 18, 2020, at 105 hospitals in the United States, Europe, and Asia. The date of final follow-up was May 20, 2020.
- **INTERVENTIONS**
  - Patients were randomized in a 1:1:1 ratio to receive a 10-day course of remdesivir (n = 197), a 5-day course of remdesivir (n = 199), or standard care (n = 200).
- **MAIN OUTCOMES AND MEASURES**
  - The primary end point was clinical status on day 11 on a 7-point ordinal scale ranging from death (category 1) to discharged (category 7).

Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA.* Published online August 21, 2020. doi:10.1001/jama.2020.16349

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19



- Patients with moderate COVID-19 randomized to a 10-day course of remdesivir did not have a statistically significant difference in clinical status compared with SOC at day 11
- Patients randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard care, **but the difference was of uncertain clinical importance.**

COVID-19 indicates coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation.

At day 11, P = .18 for comparison of the distribution of the 10-day remdesivir group vs standard care and P = .02 for 5-day remdesivir vs standard care .

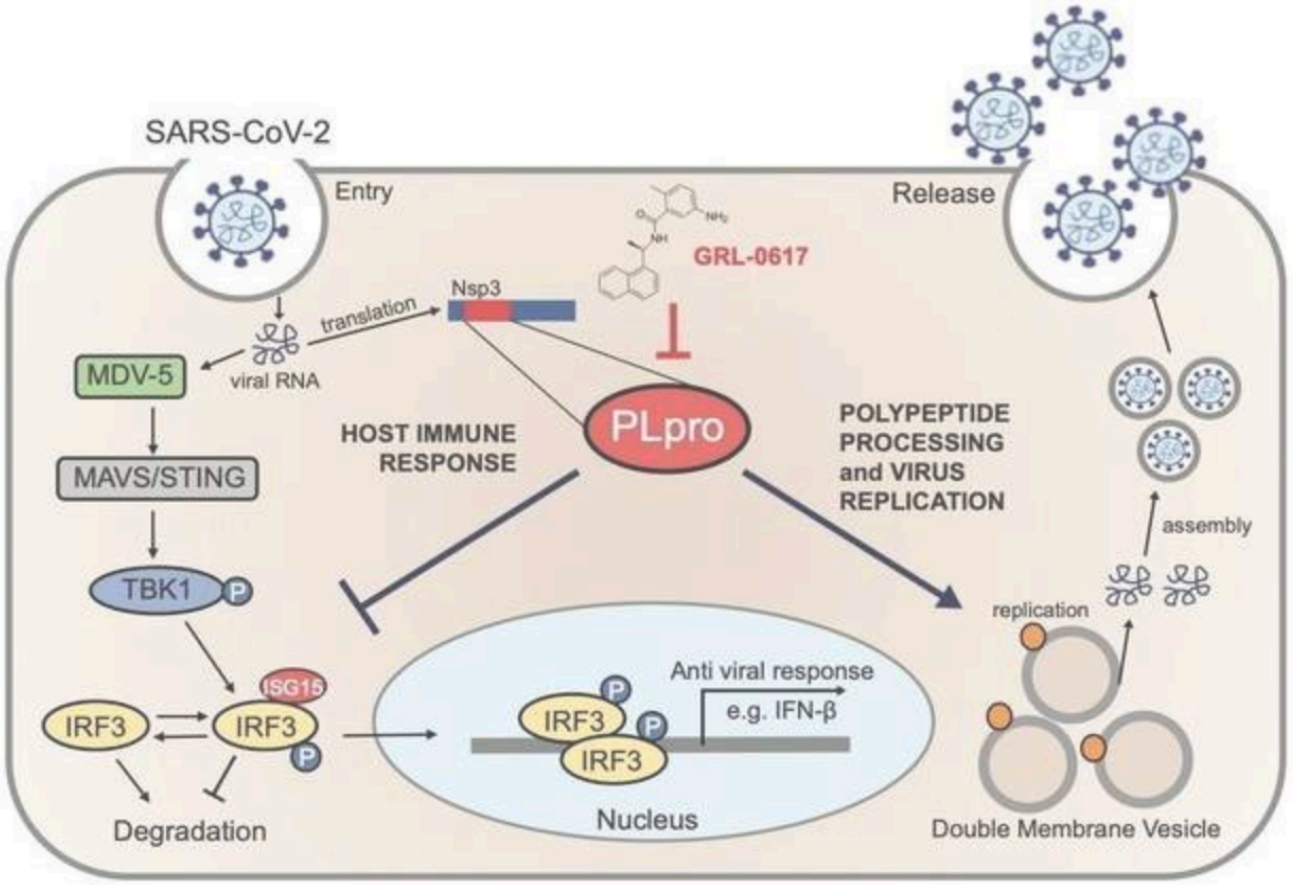
At day 14, P = .03 for comparisons of both the 5-day and 10-day remdesivir groups vs standard care.

At day 28, P = .03 for comparison of the 10-day remdesivir group vs standard care and P = .08 for 5-day remdesivir vs standard care .

Spinner CD, Gottlieb RL, Criner GJ, et al.. *JAMA.* Published online August 21, 2020. doi:10.1001/jama.2020.16349

COVID-19: Anti-viral strategy with double effect

by Brigitte Holfelder, Max planck Society. Med Press 2020



- When the SARS-CoV-2 virus penetrates human cells, it lets the human host cell produce proteins for it.
- One of these viral proteins, called PLpro, is essential for the replication and rapid spread of the virus
- The pharmacological inhibition of this viral enzyme not only blocks virus replication but also strengthens the anti-viral immune response at the same time.

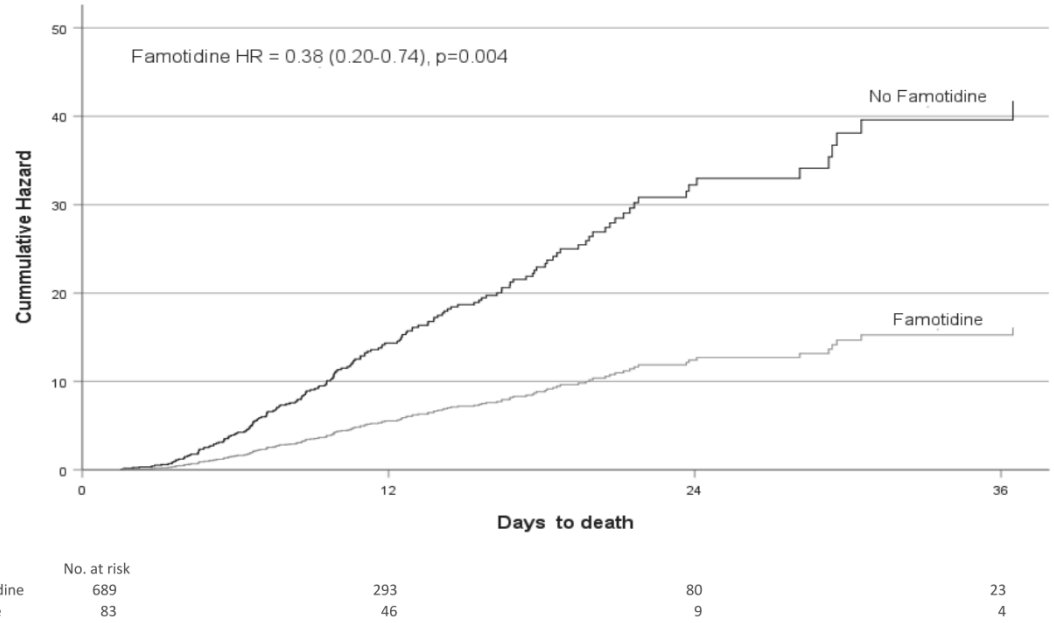
PLPRO: Papain-Like Protease

COVID-19 and Famotidine

- Plpro (Papain-like protease) is an early acting protease responsible for initial processing of the SARS CoV2 polyprotein into active subunits and is implicated in early infection phase inhibition of innate (interferon) immune responses which otherwise would suppress viral replication.
- A ranked list of licensed compounds with predicted binding activity in the Plpro catalytic site was computationally generated and Famotidine an over the counter histamine H2 antagonist scored among the highest of the compounds
- Samples of famotidine have been submitted for in vitro testing in COVID-19 cultures.
- Retrospective observational study suggest clinical benefits associated with administration of famotidine in hospitalized patients with COVID-19
- Randomized study comparing famotidine to placebo is ongoing (ClinicalTrials.gov Identifier: NCT04370262)

Impact of Famotidine on Clinical Outcomes of Hospitalized COVID-19 patients

- Objective
  - Outcomes in patients hospitalized with COVID-19 receiving Famotidine vs No Famotidine
- Methods
  - Retrospective, propensity-matched observational study of consecutive COVID-19 positive patients between February 24, 2020 to May 13, 2020.
- Results
  - 83/878 (9.5%) on Famotidine
    - Patients on Famotidine were younger
    - Comorbidities and other demographics were similar
  - Hospital Mortality of patients on famotidine was lower compared to those not on Famotidine OR 0.37 (95% CI 0.16-0.86 p=0.2)
  - Inflammatory markers also lower on Famotidine group
  - Propensity score matching to adjust for age difference did not alter the results



American Journal of Gastroenterology 2020

Key RCT Data For Other Investigational Agents

Agent	N	Population	Comparator	Primary Outcome
Lopinavir/ritonavir[1]	199	Adults, severe	SOC alone	▪ No difference in time to clinical improvement
Lopinavir/ritonavir[2]	86	Adults, mild-to-moderate	Umifenovir or no antiviral	▪ No difference in rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid
Lopinavir/ritonavir + ribavirin + IFNβ1b[3]	86	Adults, hospitalized	LPV/RTV	▪ Significantly shorter median time from start of study treatment to negative nasopharyngeal swab for combination treatment
Lopinavir/ritonavir*[4]	1596	Hospitalized	SOC alone	▪ No difference in 28-day mortality
Favipiravir*[5]	240	Adults, pneumonia	Umifenovir	▪ No difference in clinical recovery rate of Day 7
Hydroxychloroquine*[6]	150	Adults, mild-to-moderate	SOC alone	▪ No difference in negative conversion of SARS-CoV-2 by Day 28
Hydroxychloroquine*[7]	1542	Hospitalized	SOC alone	▪ No difference in 28-day mortality

*Published as a preprint or by press release only; not yet peer-reviewed.

1. Cao. NEJM. 2020;382:1787. 2. Li. Med. 2020;[Epub]. 3. Hung. Lancet. 2020;395:1695.
4. https://www.recoverytrial.net/files/lopinavir-ritonavir-recovery-statement-29062020_final.pdf
5. Chen. https://doi.org/10.1101/2020.03.17.20037432 6. Tang. https://doi.org/10.1101/2020.04.10.20060558
7. https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf

Key RCT Data For Other Investigational Agents (Cont.)

Agent	N	Population	Comparator	Primary Outcome
Tocilizumab[1,2]	129	Moderate or severe pneumonia	Standard care alone	▪ Improvement in composite endpoint of death or need for ventilation at Day 14 with tocilizumab vs standard care
Sarilumab (200 or 400 mg)[3,4]	457	Severe or critical	Placebo	▪ CRP decline: 77% and 79% vs 21% ▪ IDMC recommended continuing phase III only in critical subgroup with 400 mg sarilumab vs placebo

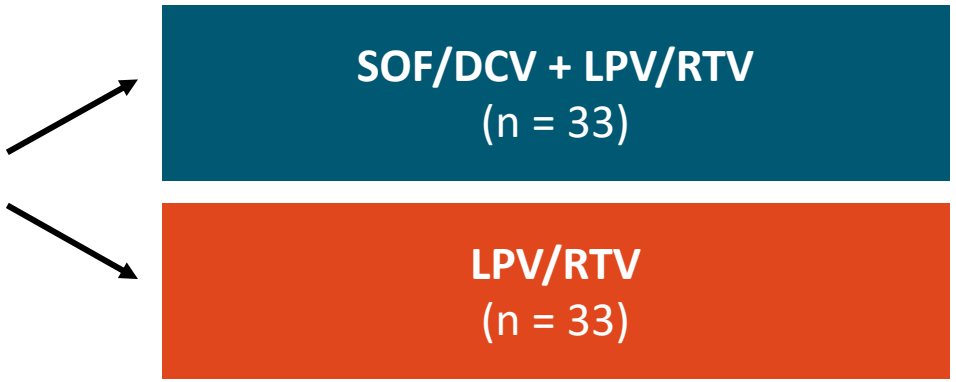
1. https://www.aphp.fr/contenu/tocilizumab-improves-significantly-clinical-outcomes-patients-moderate-or-severe-covid-19
2. NCT04331808. 3. NCT04315298. 4. https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-provide-update-us-phase-23-adaptive

Slide credit: clinicaloptions.com

DDRI: SOF/DCV + LPV/RTV vs LPV/RTV for Severe COVID-19

- Sofosbuvir and daclatasvir: anti-HCV direct-acting antivirals, with in vitro activity against SARS-CoV-2 cell lines; DCV EC50 estimates for SARS-CoV-2 within PK exposure levels at standard dosing[1]
- DDRI: open-label, randomized, controlled trial at 4 university hospitals in Iran[2]

Adults hospitalized with fever and ≥ 1 of: respiratory rate > 24/min, O_2 saturation < 94%, or PaO_2/FiO_2 ratio < 300; PCR confirmed SARS-CoV-2; and diagnostic chest CT scan
(N = 66)



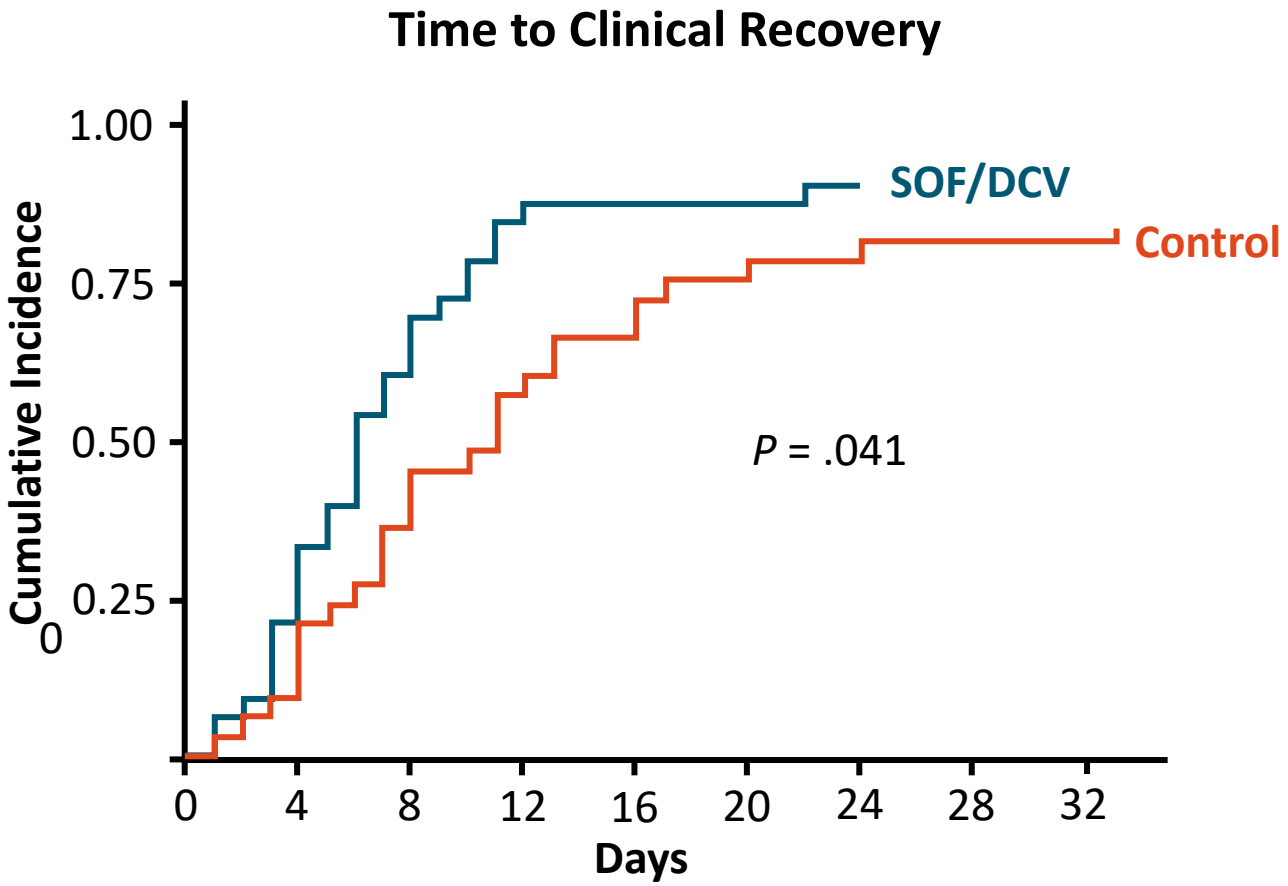
- Primary endpoint: clinical recovery (composite) within 14 days from study treatment initiation until: fever normalization, respiratory rate ≤ 24/min on room air, O_2 saturation ≥ 94% on room air sustained for ≥ 24 hrs

1. Sacramento. bioRxiv. 2020;[Preprint only]. Not yet peer reviewed. 2. Sadeghi. IAS COVID-19. Abstr. 11125.

Slide credit: clinicaloptions.com

DDRI: Time to Clinical Recovery

Outcome and Cotreatments	SOF/DCV (n = 33)	Control (n = 33)	*P* Value
Clinical recovery ≤ 14 days, n (%)	29 (88)	22 (67)	.076
Time to clinical recovery, median days (IQR)	6 (4-10)	11 (6-17)	.041
Invasive mechanical ventilation, n (%)	3 (9)	7 (21)	.303
Concomitant treatments, n (%)			
▪ LPV/RTV	11 (33)	21 (64)	.026
▪ Corticosteroids	12 (36)	8 (24)	.422
▪ Antibiotics	29 (88)	30 (91)	1.000

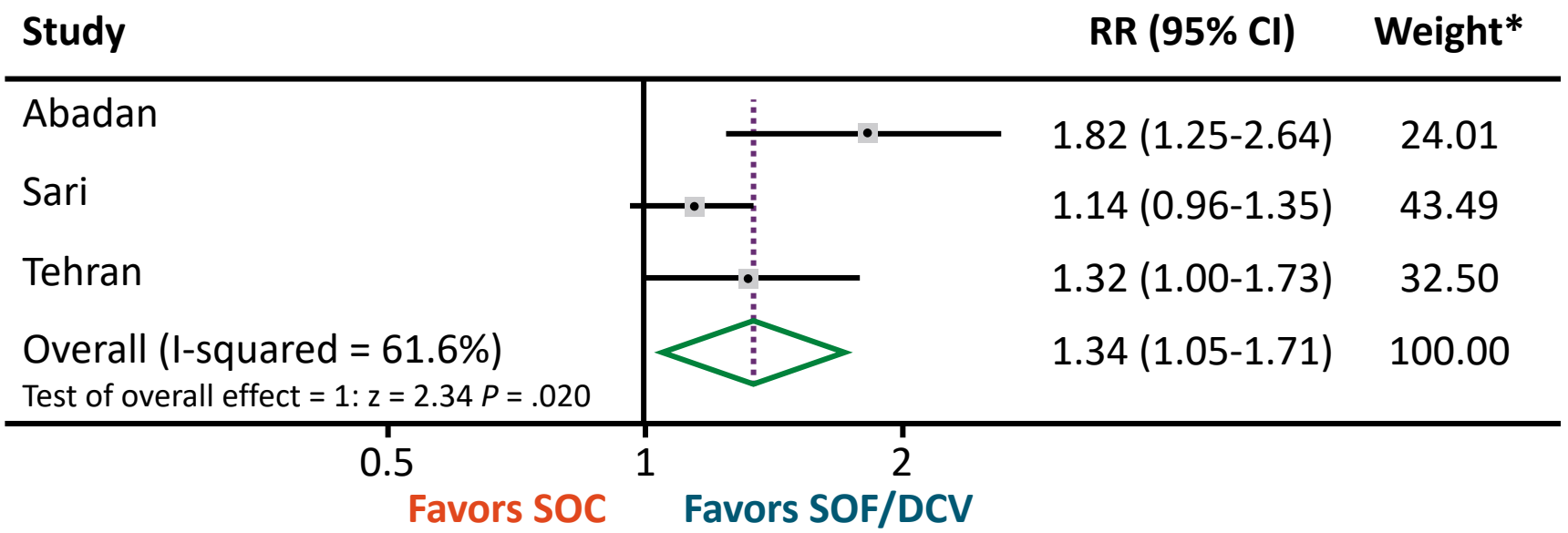


Sadeghi. IAS COVID-19. Abstr. 11125.

Slide credit: clinicaloptions.com

Meta-Analysis of 3 Trials in Iran Investigating SOF/DCV for COVID-19: Clinical Recovery < 14 Days

Trial	Treatment Arms	Endpoint
DDRI (Tehran), N = 66	SOF/DCV + LPV/RTV vs LPV/RTV	Time to clinical recovery within 14 days
Abadan, N = 62	SOF/DCV + HCQ vs LPV/RTV + HCQ + RBV	Time to hospital discharge
Sari, N = 48	SOF/DCV + RBV vs HCQ ± LPV/RTV	Duration of hospitalization



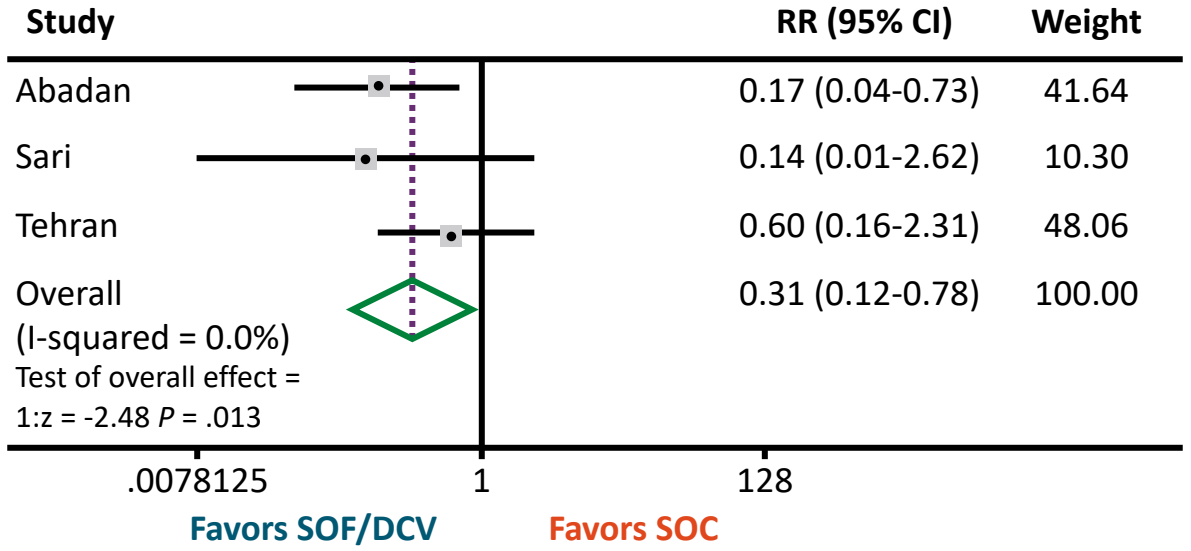
*Weights from random-effects model; continuity correction applied to studies with zero cells.

Sadeghi. IAS COVID-19. Abstr. 11125.

Slide credit: clinicaloptions.com

Meta-Analysis of 3 Trials in Iran Investigating SOF/DCV for COVID-19: Survival

Death, n/N	SOF/DCV	Control
DDRI (Tehran)	3/33	5/33
Abadan	2/35	9/27
Sari	0/24	3/24
Total (*P* = .005)	**5/92 (5.4%)**	**17/84 (20%)**



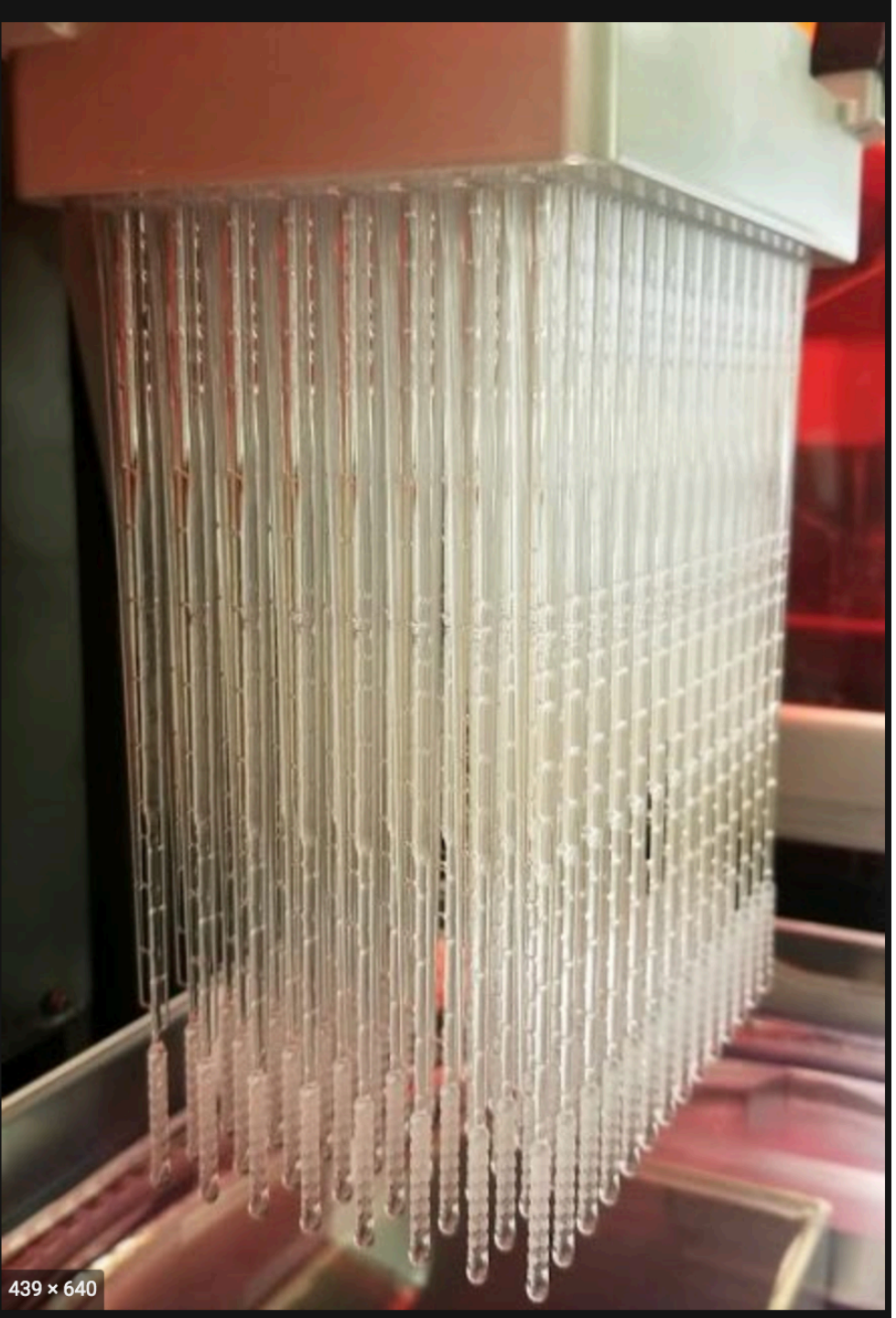
- DISCOVER in Iran (N = 600): double-blind, placebo-controlled trial comparing LPV/RTV + SOF/DCV vs LPV/RTV in moderate or severe COVID-19 infection
  - Currently recruiting; results anticipated Sept 2020

Sadeghi. IAS COVID-19. Abstr. 11125.

Slide credit: clinicaloptions.com

3-D-PRINTED NASOPHARYNGEAL SWAB FOR THE DIAGNOSIS OF SARS-COV-2

- 3D-printed polyester-tipped swabs shown to be effective for use in nasopharyngeal sample collection and diagnosis of COVID-19
- Overall concordance between the prototype and control swabs 81%, with most discordant results resulting from prototype-positive, control-negative results
- Prototype had higher sensitivity than the control swabs (91% vs. 81%)



3-D-PRINTED NASOPHARYNGEAL SWAB FOR THE DIAGNOSIS OF SARS-COV-2

Materials required to make these swabs are

Safe	Readily available	Durable

Total cost of production for each swab is estimated at around $ 0.05

Alghounaim M et al. Low-Cost Polyester-Tipped 3-Dimensionally-Printed Nasopharyngeal Swab for the Diagnosis of Severe Acute Respiratory Syndrome-Related Coronavirus 2 (SARS-CoV-2) *Journal of Clinical Microbiology* Aug 12, 2020