Management of Severe COVID-19 in Adults: Antivirals and Beyond

Benjamin Albrecht, PharmD, BCIDP
Clinical Pharmacy Specialist in Infectious Disease
Emory University Hospital
benjamin.albrecht@emoryhealthcare.org

EMORY UNIVERSITY SCHOOL OF MEDICINE

Serious Communicable Diseases Program

Project ECHO

Disclosures

I have nothing to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation.

Definitions

- **Authorization vs. Approval**
  - Emergency Use Authorization (EUA)
    - Used for national emergencies to help address the need to bypass the legal obstacles and time constraints associated with formal FDA approval
    - Anthrax, H1N1 2009, etc.
  - Does not equal FDA approval status
    - Use can only be within criteria specifically defined in EUA letter of authorization
    - **No "off-label" use**

- **Severe Illness:** Individuals who have SpO2 ≤94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.

- **Critical Illness:** Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

FDA= US Food and Drug Administration

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [5/24/2022].
Infectious Disease Society of America. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. IDSA. Available at https://www.idsociety.org/COVID19guidelines#. Accessed [5/24/2022].

Remdesivir (Veklury)

- MOA: Nucleotide analogue pro-drug → binds to RNA-dependent, RNA-polymerase, terminating viral RNA transcription and viral replication

- FDA approved in ≥12 years and ≥40 kg
  - 3-day course in mild-moderate, high risk, symptomatic, non-hospitalized patients w/in 7 days of SO
  - 5-10 day course in severe, hospitalized patients

- Monitoring: nausea(3-7%), prolonged prothrombin time (9%), Increased alanine aminotransferase (ALT)/aspirate aminotransferase(AST), hypersensitivity reactions
  - Consider holding therapy if ALT ≥10x upper limit of normal

MOA= mechanism of action; RNA= ribonucleic acid; SO= symptom onset

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Remdesivir (Veklury)

- Each 100 mg dose has 3-6g of sulfobutylether beta-cyclodextrin sodium (SBECD)
  - Eliminated renally → accumulation can lead to acute kidney and liver toxicity
  - Present in IV voriconazole, IV posaconazole, IM apripiprazole, IV amiodarone, and IV ziprasidone
  - Animal studies show **no renal toxicity at doses of >160 mg/kg/day** for an extended duration (1-6 months) → **37.5 kg patient at most**

- Two observational, case/cohort studies showing no dif. in adverse effects
  - Compared patients on remdesivir with CrCl <30 mL/min. vs. CrCl ≥30 mL/min.

- FDA approval language: For CrCl <30 mL/min., use only if benefit outweighs risk

IV= intravenous; CrCl= creatinine clearance

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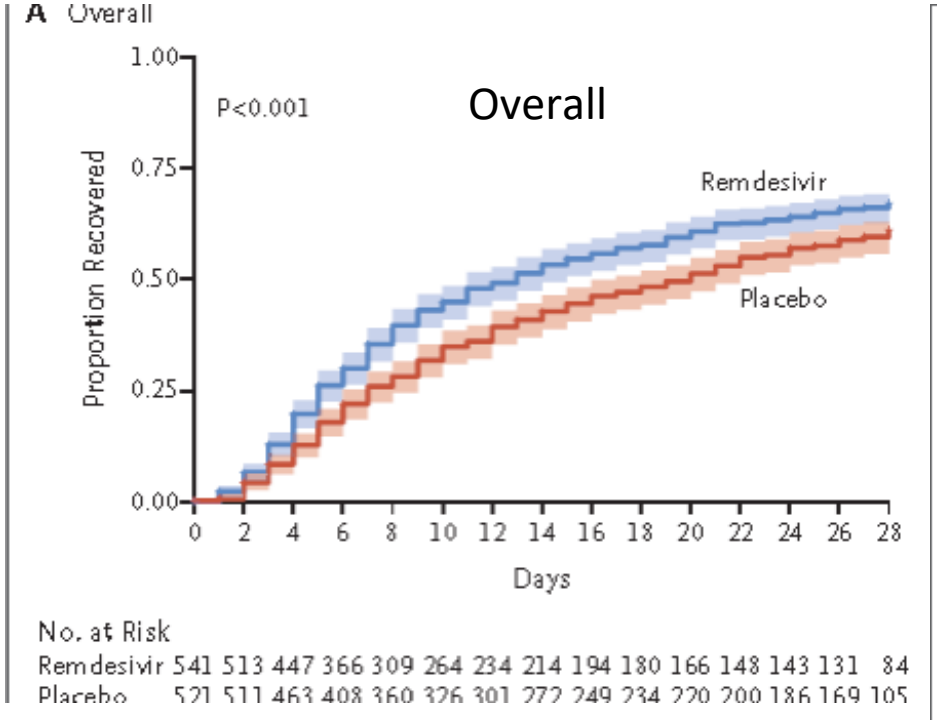
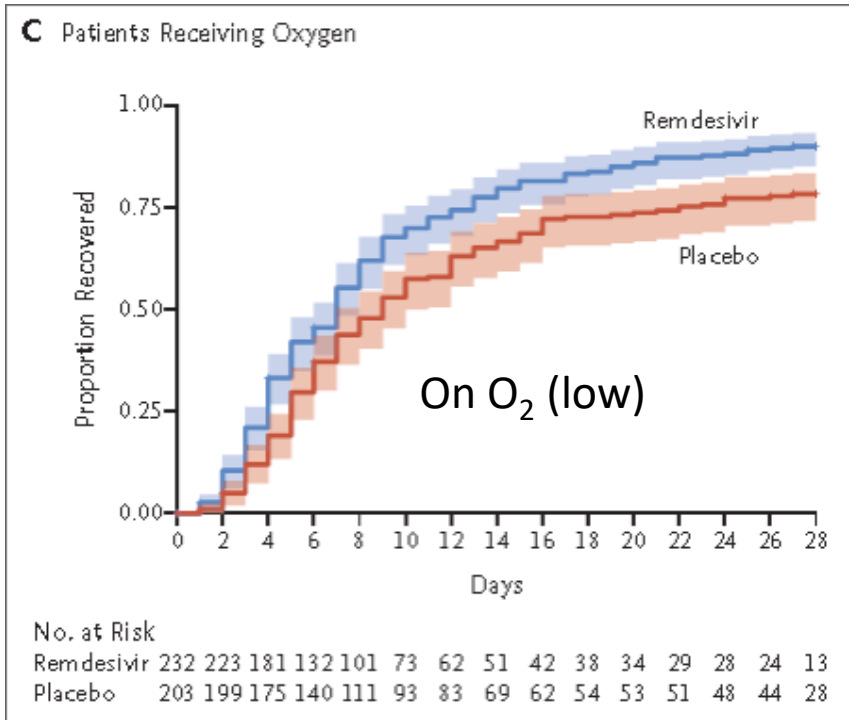
Infectious Disease Society of America. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. IDSA. Available at https://www.idsociety.org/COVID19guidelines#. Accessed [5/24/2022].
Butt, B., Hussain, T., Jarrar, M. T., Khalid, K., Albaker, W., Ambreen, A., & Waheed, Y. (2022). Efficacy and Safety of Remdesivir in COVID-19 Positive Dialysis Patients. Antibiotics, 11(2), 156.

ACTT-1 Trial

- Remdesivir 10-day course (541) vs. placebo (521)
- **Time to recovery: 10 vs. 15 days** (1.29; 95% CI 1.12-1.49; *P* <0.001)
- **Improved clinical status at day 15** (OR 1.5; 95% CI, 1.2-1.9; *P* <0.001)





ACTT= Adaptive COVID-19 Treatment Trial

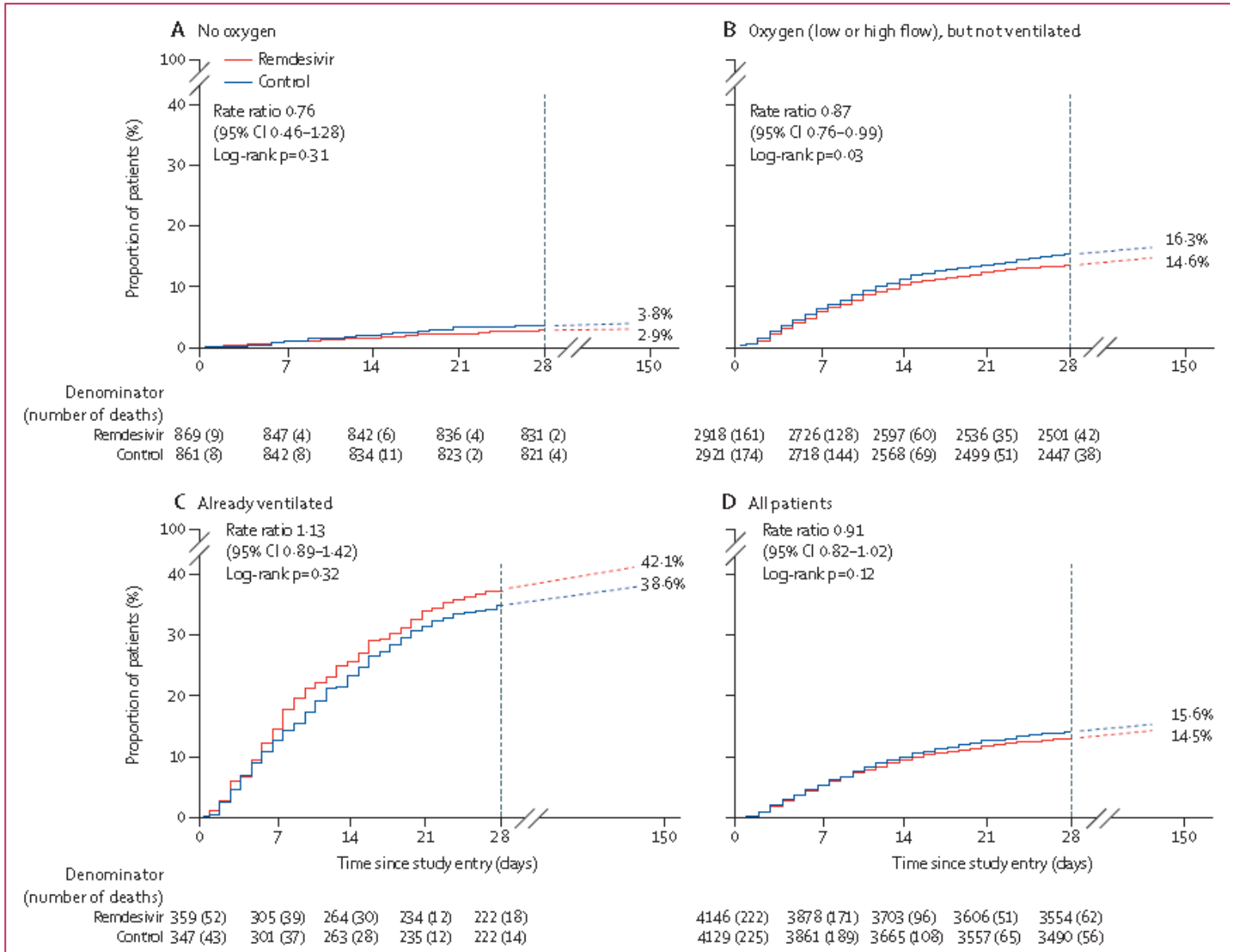
Beigel, J. H., Tomashek, K. M., Dodd, L. E., Mehta, A. K., Zingman, B. S., Kalil, A. C., ... & Lane, H. C. (2020). Remdesivir for the treatment of Covid-19. New England Journal of Medicine, 383(19), 1813-1826.

WHO Solidarity Trial

- 4146 pts on remdesivir 10-day course vs. 4129 pts on SOC
- Final results; **28-day mortality**:
  - Overall no significant reduction
  - **Significant reduction seen in patients on low O_2**
- Meta-analysis
  - Significant but modest reduction
    - Mortality
    - Progression to MV

GS-US-540-5773: multinational, open-label, randomized controlled trial **w/ 5 vs. 10-day remdesivir** vs. SOC for hospitalized patients

- **No difference in clinical status on day 14** (adjusting for baseline status)



WHO= World Health Organization; SOC= standard of care; MV= mechanical ventilation

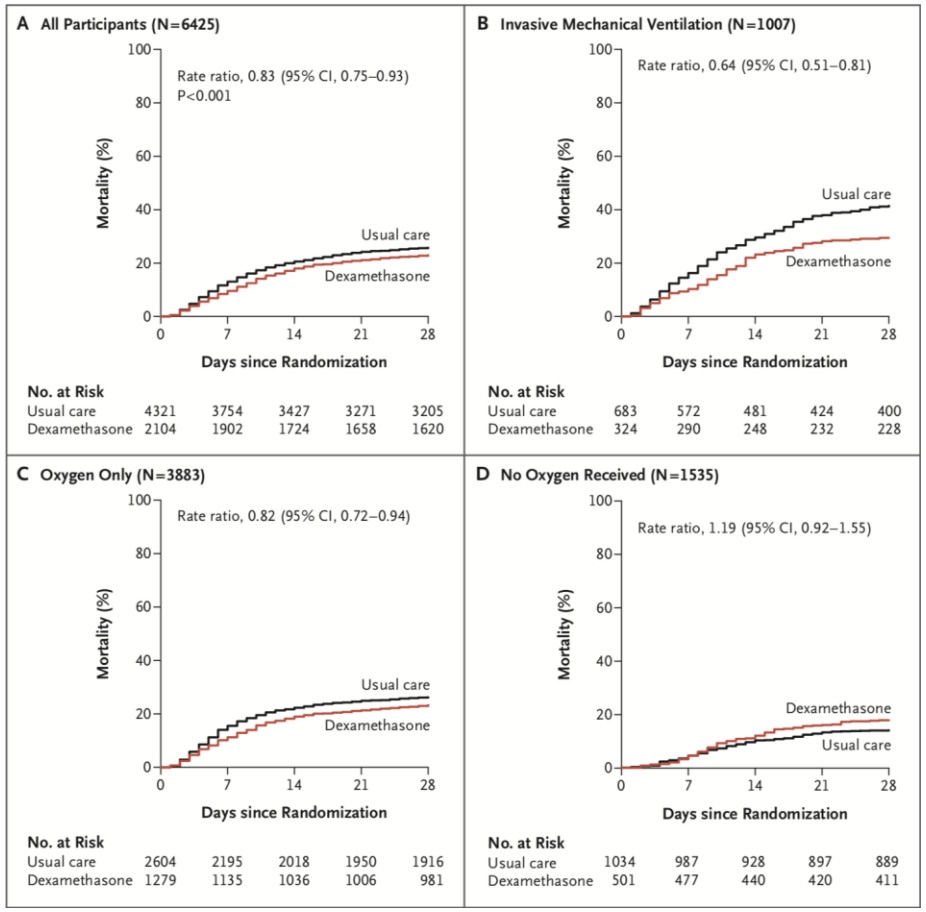
COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [5/24/2022].
WHO Solidarity Trial Consortium. (2022). Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. The Lancet.

COVID-19 Severity	Therapeutics
Severe and on O_2 but not yet HF	• Remdesivir IV 200 mg x1 day 1, then 100 mg IV Q24hr x 4 days (up to 9 days w/ progression)
Severe on escalating O_2 (HF, NIMV, etc.)	• Remdesivir IV 200 mg x1 day 1, then 100 mg IV Q24hr x 4 days (up to 9 days w/ progression)
Critical requiring MV or ECMO	

HF= high flow oxygen (>10L/min); NIMV= non-invasive mechanical ventilation;
ECMO= extracorporeal membrane oxygenation

RECOVERY: Dexamethasone

- Dexamethasone 6 mg Qday x 10 days or discharge (2104) vs. SOC (4321)
- Similar co-morbidities
- **Significant reduction in 28-day all-cause mortality (22.9% vs. 25.7%; 0.83 (0.75-0.93))**
  - <u>All besides non-hypoxic</u> (17.8% vs. 14%)
    - Trend toward **potential harm**
  - Most notable reductions in 7 days since SO
  - Reductions in need for RRT & MV by day 28
  - Median duration of 7 days



RRT= renal replacement therapy

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RECOVERY Collaborative Group. (2021). Dexamethasone in hospitalized patients with Covid-19. New England Journal of Medicine, 384(8), 693-704.

COVID-19 Severity	Therapeutics
Severe and on O_2 but not yet HF	• Remdesivir IV 200 mg x1 day 1, then 100 mg IV Q24hr x 4 days (up to 9 days w/ progression) • **Dexamethasone 6 mg IV/PO x 10 days or until discharge**
Severe on escalating O_2 (HF, NIMV, etc.)	• Remdesivir IV 200 mg x1 day 1, then 100 mg IV Q24hr x 4 days (up to 9 days w/ progression) • **Dexamethasone 6 mg IV/PO x 10 days or until discharge**
Critical requiring MV or ECMO	• **Dexamethasone 6 mg IV/PO x 10 days or until discharge**

Baricitinib (Olumiant)

- Selective inhibitor of Janus kinase (JAK) 1 & 2
  - Targeting dysregulated inflammatory response from SARS-CoV-2 infection
    - Inhibits cytokine response
  - Impairs AP2-associated kinase 1 in human cells, preventing viral cellular entry and assembly

- **Oral formulation only**

- Dose adjustments
  - Really adjusted by eGFR: 30-<60 mL/min. (2 mg Qday), 15-<30 mL/min. (1 mg Qday), **<15 mL/min./HD (No use)**
  - Lymphocytes <200 cells/mm3 **or** ANC <500 cells/mm3 (hold dose)

- **FDA-approved** for COVID-19
  - Also FDA-approved for rheumatoid arthritis (2mg Qday)

eGFR= estimated glomerular filtration rate; HD= hemodialysis; ANC= absolute neutrophil count
Qday= once daily

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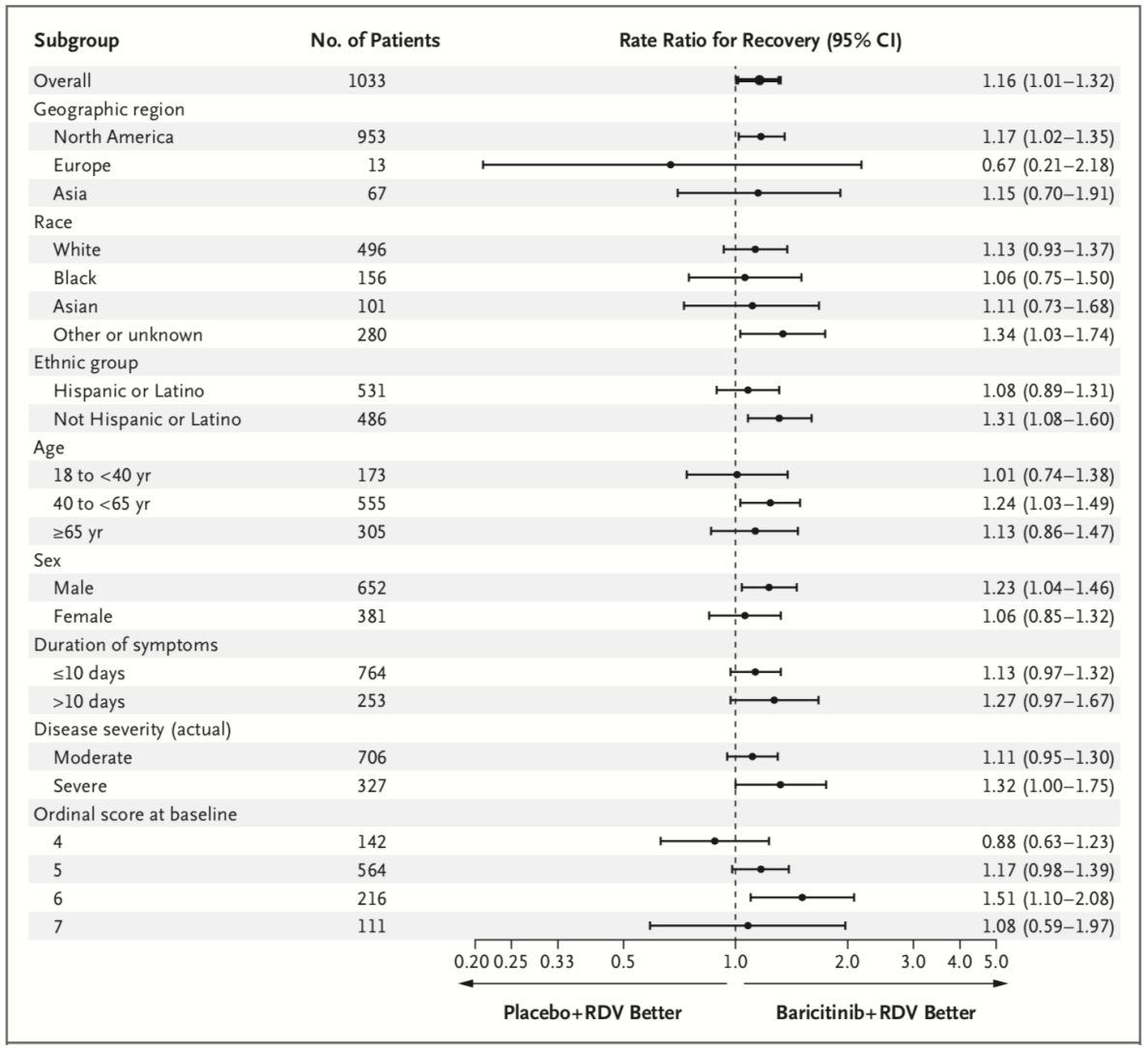
Kalil, A. C., Patterson, T. F., Mehta, A. K., Tomashek, K. M., Wolfe, C. R., Ghazaryan, V., ... & Beigel, J. H. (2021). Baricitinib plus remdesivir for hospitalized adults with Covid-19. New England Journal of Medicine, 384(9), 795-807.

ACTT-2

- International, randomized, double blind, controlled trial
- Remdesivir (10 days) + baricitinib (14 days) (515) vs. remdesivir + placebo (518)
- Outcomes:
  - Combo patients recovered median 1 day faster than remdesivir alone (7 vs. 8, 1.16; 95% CI, 1.01-1.32; *P*=0.03)
  - Greatest difference seen in patients on HF O2 or NIMV
  - Fewer adverse events in combo arm



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ACTT-4

- International, randomized, double-blind, double placebo-controlled trial

- Hospitalized adults w/ COVID-19 requiring respiratory support
  - LF (</=15 L/min), HF (>15 L/min), NIMV
  - Rem + dex + placebo (494) vs. rem + bari +placebo (516)

- Outcomes
  - **No significant dif. In efficacy**
    - Small % on HF or NIMV —> subgroup analysis not possible
  - **Significantly less adverse events seen with bari combo vs. dex combo (30% vs. 37%, 7.5%; 95% CI, 1.6-13.3)**
    - **Significantly less treatment-related events and severe adverse events**

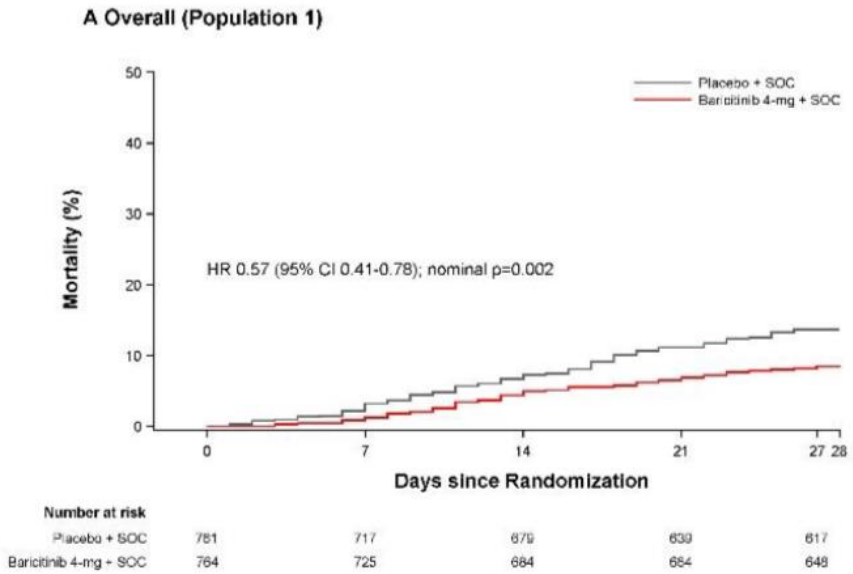
COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [5/24/2022].
Wolfe, Cameron R., et al. "Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial." The Lancet Respiratory Medicine (2022).

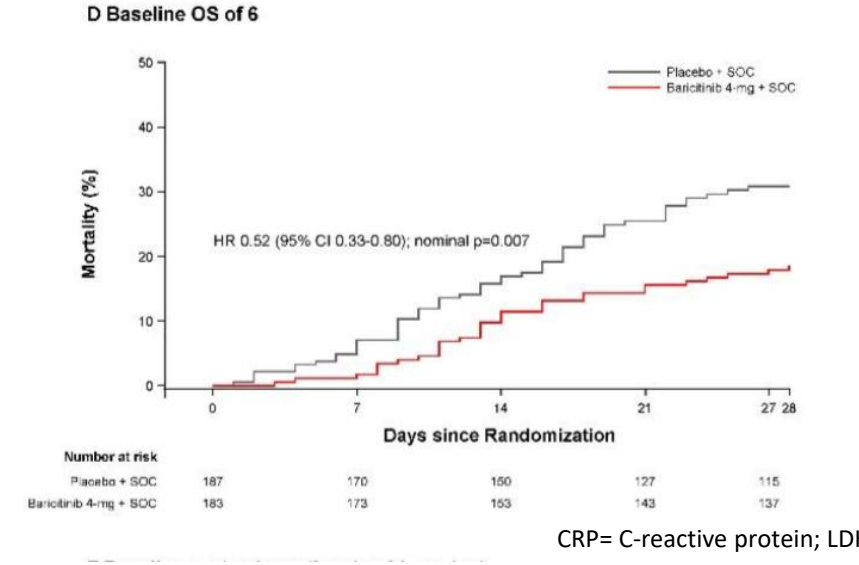
COV-BARRIER

- International, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial

- Hospitalized adults with COVID-19 requiring at least baseline O_2 support & w/ >/= 1 elevated inflammatory marker
  - CRP, D-dimer, LDH, or ferritin
  - Bari + SOC (764) vs. placebo + SOC (761)
  - 79.3% received steroids & 18.9% received remdesivir

- Outcomes
  - No dif. In % who progressed by day 28 (primary)
  - **Significant decrease in 28-day all-cause mortality** (8.1% vs. 13.1%, HR 0.57; 95% CI 0.41-0.78; *P*=0.002)
    - **Those on HF or NIMV had most significant decrease**





CRP= C-reactive protein; LDH= lactate dehydrogenase

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Marconi, V. C., Ramanan, A. V., de Bono, S., Kartman, C. E., Krishnan, V., Liao, R., ... & Zirpe, K. (2021). Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. The Lancet Respiratory Medicine, 9(12), 1407-1418.

COVID-19 Severity	Therapeutics
Severe and on O_2 but not yet HF	• Remdesivir IV 200 mg x1 day 1, then 100 mg IV Q24hr x 4 days (up to 9 days w/ progression) • Dexamethasone 6 mg IV/PO x 10 days or until discharge • **+/- baricitinib 4 mg PO x 14 days or until discharge (if cannot take dexamethasone or if progressively worsening)**
Severe on escalating O_2 (HF, NIMV, etc.)	• Remdesivir IV 200 mg x1 day 1, then 100 mg IV Q24hr x 4 days (up to 9 days w/ progression) • Dexamethasone 6 mg IV/PO x 10 days or until discharge • **baricitinib 4 mg PO x 14 days or until discharge**
Critical requiring MV or ECMO	• Dexamethasone 6 mg IV/PO x 10 days or until discharge

PO= by mouth; Q24hr= every 24 hours

Tocilizumab (Actemra)

- MOA: anti-interleukin 6 (IL-6) receptor monoclonal antibody
  - SARS-CoV-2 associated with production of IL-6 in bronchial epithelial cells → reducing IL-6 effects may reduce disease duration/severity
- EUA for COVID-19
  - FDA-approved for CRS related to CAR T-cell therapy, giant cell arteritis, rheumatoid arthritis, and severe interstitial lung disease
- IV or SQ formulation
- Dose adjustments/suspensions
  - Hold during other concomitant infections or evidence of diverticulitis due to GI perforation risk
  - Assess risk vs. benefit if ANC <1000 cells/mm^3, Plt <50,000 cells/mm^3, or ALT >10x ULN

CRS= cytokine release syndrome; SQ= subcutaneous; Plt= platelet count; GI= gastrointestinal

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Abani, O., Abbas, A., Abbas, F., Abbas, M., Abbasi, S., Abbass, H., ... & Ali, M. (2021). Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet, 397(10285), 1637-1645.
Derde, L. P., & REMAP-CAP Investigators. (2021). Effectiveness of tocilizumab, sarilumab, and anakinra for critically ill patients with COVID-19 the REMAP-CAP COVID-19 immune modulation therapy domain randomized clinical trial. medRxiv.

Tocilizumab (Actemra)

- **RECOVERY** (4/2020 – 1/2021)
  - Hospitalized patients w/ severe COVID-19 & CRP >75 mg/L
  - 2,022 on toci +SOC vs. 2,094 on SOC
  - 8 mg/kg IV x 1 (2nd dose if no improvement)
    - 800 mg max
  - Outcomes
    - **Reduction in 28-day mortality** (31% vs. 35%; RR 0.85; 95% CI, 0.76-0.94; *P*=0.003)
    - **Potential reduction in need for MV**
    - No reduction for patients already on MV

- **REMAP-CAP** (4/2020 – 4/2021)
  - ICU (w/in 24 hours) COVID-19 patients on MV, NIMV, or cardiovascular support
  - Excluded immunocompromised
  - 8 mg/kg toci IV x 1 (2nd dose in 12-24 hours if no improvement)
    - 952 toci + SOC vs. 406 SOC
  - Outcomes
    - **Increase in median number of organ support-free days** (7 vs. 0; OR 1.46; 95% CI, 1.13-1.87)
    - **Increase in in-hospital survival** (66% vs. 63%; aOR 1.51; 95% CI, 1.05-1.93)

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Severe and on O_2 but not yet HF	• Remdesivir IV 200 mg x1 day 1, then 100 mg IV Q24hr x 4 days (up to 9 days w/ progression) • Dexamethasone 6 mg IV/PO x 10 days or until discharge • +/- baricitinib 4 mg PO x 14 days or until discharge (if cannot take dexamethasone or if progressively worsening) • **+/- tocilizumab 8 mg/kg x 1 (if progressively worsening and did not start baricitinib)**
Severe on escalating O_2 (HF, NIMV, etc.)	• Remdesivir IV 200 mg x1 day 1, then 100 mg IV Q24hr x 4 days (up to 9 days w/ progression) • Dexamethasone 6 mg IV/PO x 10 days or until discharge • baricitinib 4 mg PO x 14 days or until discharge **OR tocilizumab 8 mg/kg x 1 IV**
Critical requiring MV or ECMO	• Dexamethasone 6 mg IV/PO x 10 days or until discharge • **Tocilizumab 8 mg/kg x 1 (if w/in 24 hours since ICU admission)**