Good morning

Under COVID-19 News I start with a report of a new coronavirus descendant related to Delta, called AY.4.2. Next a report from Pfizer on VE for children ages 5-11. Next a CDC update on the pandemic.

Under Journal Review, CDC reports on severity from January through August, comparing outcomes between the pre-delta period (January to June) to when the strain became predominant in the country (July to August). The next is an article comparing dexamethasone doses of 6 mg versus 12 mg. The last article is a retrospective, comparative effectiveness cohort study on RDV. Since this article comes up with different results than earlier RCTs I spent more time comparing prior studies and guidelines. I would be interested in your opinion.

Ed

COVID-19 News

CDC Confirms New Delta Subtype 'AY.4.2' Has Been Identified in the US
A new coronavirus descendant related to Delta, called AY.4.2, is being closely monitored by scientists in the US, UK, and Israel. AY.4.2 is still "very rare" in the US, according to the CDC. Meanwhile, AY.4, the parent lineage of the new variant, represents around 11% of the Delta viruses in the US.

AY.4.2 has caught attention around the world recently because it has two changes located on the viral spike protein, which could perhaps give it some advantages. However, currently there is no evidence that the sub lineage AY.4.2 impacts the effectiveness of our current vaccines or therapeutics per the CDC. The UK Health Security Agency, meanwhile, said on Friday that AY.4.2 is currently expanding in the UK while Israeli health officials reported their first case of it on Tuesday.

Comment: From available data this minor change does not appear to be a threat to the current situation.

Pfizer Data on VE in Children Ages 5-11
Pfizer says its vaccine for children is 90% effective at preventing COVID-19 infections. The Pfizer vaccine for kids ages 5 to 11 is 10 micrograms, roughly one-third of the dose given to adolescents and adults. The VE data comes from a study of more than 2,000 children ages 5 to 11. Two-thirds of the children were randomly assigned to receive a child-sized dose of the Pfizer vaccine, while the other third was sorted into the placebo group. The study got underway as the Delta variant became dominant around the world.

The most common side effect reported was pain at the site of the shot. Kids in the group that received the vaccine also had fatigue, headaches, fever, and chills at higher rates than were seen in the placebo group. These were most common after the second dose. Some skin reactions were seen in the study, like itching and rashes, but these were mostly mild and went away within a few days. No cases of myocarditis were found in the study.

Comment: This is good news. Given size of study, a definitive statement around myocarditis or other rare side effects remains to be answered, however, we know the incidence of side effects like

myocarditis are higher with natural disease. Moderna just announced some preliminary data. Hope to review in the next addition

CDC Updates October 22, 2021

1. The nation's current seven-day case average is 73,079, a 15.1 percent decrease from the previous week's average.
2. The current seven-day hospitalization average for Oct. 13-19 is 6,004, a 10.3 percent drop from the previous week's average.
3. About 219.6 million people — 66.2 percent of the total U.S. population — have received at least one dose of the COVID-19 vaccine, and more than 189.9 million people, or 57.2 percent of the population, have received both doses.
4. About 11.6 million booster doses in fully vaccinated people have been reported.
5. The seven-day average number of vaccines administered daily was 795,156 as of Oct. 21, a 5.5 percent decrease from the previous week.
6. Based on projections for the week ending Oct. 16, the CDC estimates the delta variant accounts for more than 99 percent of all U.S. COVID-19 cases.
7. The current seven-day death average is 1,253, down 4.3 percent from the previous week's average. Some historical deaths have been excluded from these counts, the CDC said.
8. The seven-day average for percent positivity from tests is 5.2 percent, down 6.6 percent from the previous week.
9. The nation's seven-day average test volume for the week of Oct. 8-14 was about 1.42 million, down 7.4 percent from the prior week's average.

Comment: Overall very good news. Vaccination, however, has fallen. A reminder treatment like MCA and molnupiravir are a backup not a substitution for vaccination.

Journal Review

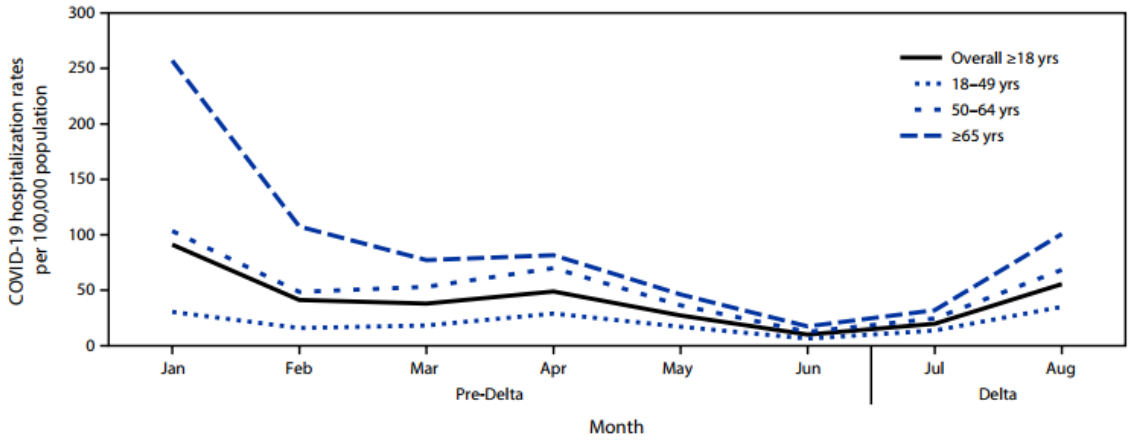
Severity of Disease Among Adults Hospitalized with Laboratory-Confirmed COVID-19 Before and During the Period of SARS-CoV-2 B.1.617.2 (Delta) Predominance — COVID-NET, 14 States, January–August 2021

MMWR October 22, 2021

Researchers looked at 7,615 COVID-19 hospitalizations in the U.S. from January through August, comparing outcomes between the pre-delta period (January to June) to when the strain became predominant in the country (July to August). Hospitalizations included in the analysis were among nonpregnant adults.

Compared to the pre-delta period, researchers did not observe significant differences in the proportion of hospitalized COVID-19 patients who were admitted to an intensive care unit, received invasive mechanical ventilation, or died while hospitalized during the delta period. The report did find the proportion of hospitalized COVID-19 patients aged 18-49 rose from 24.7 percent of all hospitalizations pre-delta to nearly 36 percent when the strain became dominant. No significant differences in severity were observed between the pre-Delta and Delta periods among fully vaccinated or unvaccinated hospitalized patients, overall or when stratified by age and vaccination status. However, during the Delta period, adults aged 18-49 years accounted for a larger proportion of hospitalized patients compared with the pre-Delta period. Among unvaccinated hospitalized patients, the proportion of adults aged 18-49 years increased during the Delta period while the proportion aged ≥65 years decreased, whereas the

age distribution among fully vaccinated hospitalized patients remained stable throughout the study period.

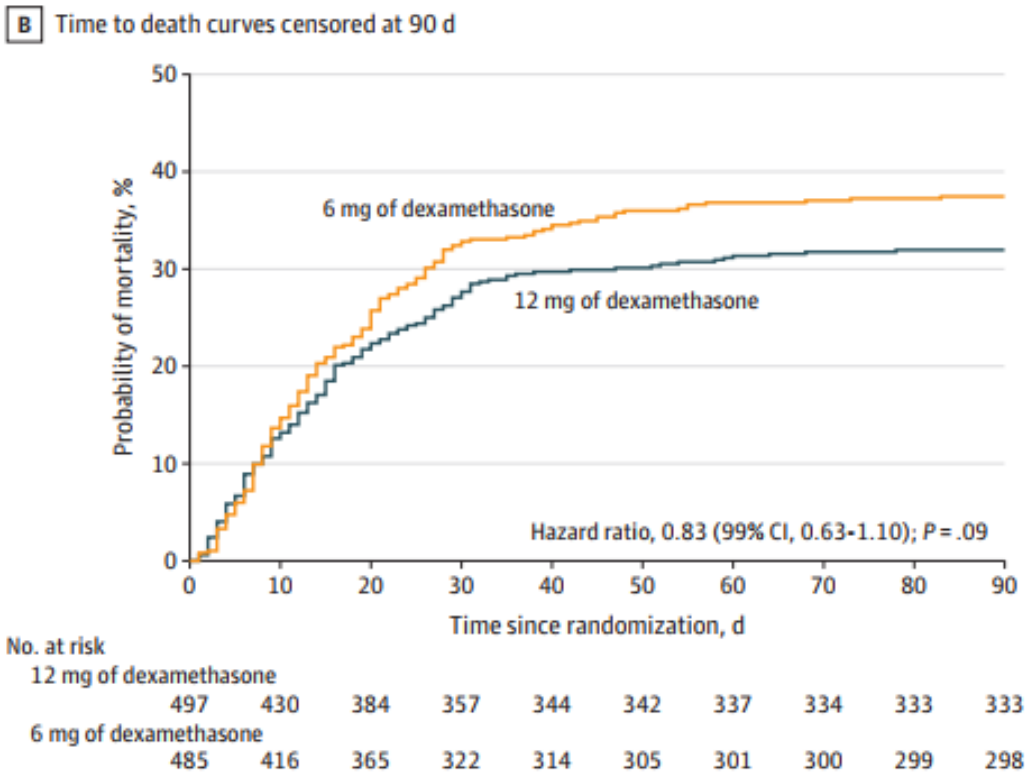


Comment: Lower vaccination coverage in this age group likely contributed to the increase in hospitalized patients during the delta period, but overall, about 72 percent of all COVID-19 related hospitalizations during the delta period were among unvaccinated adults. [this is much lower than others have reported – most have found >90% of persons hospitalized are unvaccinated] A large Canadian study found an increased risk for ICU admission and death among a cohort of persons infected with the Delta variant. [CMAJ 2021;cmaj.211248 – reported in the Briefing several weeks ago] COVID-NET surveillance catchment area represents about 10% of the U.S. population; thus, these findings should not be generalized nationally. The analysis did not account for the propensity of persons to be vaccinated, and therefore could not determine the effectiveness of vaccination in reducing severe outcomes.

Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults with COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial
JAMA published online October 23, 2021
doi:10.1001/jama.2021.18295
The paper reports on the results of an international, multicenter randomized clinical trial that compared 2 alternative doses of glucocorticoids in critically ill patients with COVID-19. The investigators randomly assigned 1000 patients with confirmed SARS-CoV-2 infection who were receiving supplemental oxygen at a flow rate of at least 10 L/min or mechanical ventilation to receive, as blinded study medication, either 12 mg/d of dexamethasone or 6 mg/d of dexamethasone. The primary outcome was the number of days alive without life support (invasive mechanical ventilation, circulatory support, or kidney replacement therapy) at 28 days and was adjusted for stratification variables.

The median number of days alive without life support was 22.0 days (IQR,6-28days) in the 12mg of dexamethasone group and 20.5 days (IQR, 4-28 days) in the 6 mg of dexamethasone group (adjusted mean difference, 1.3 days [95% CI, 0-2.6 days]; *P* = .07). Mortality at 28 days after randomization was 27.1% for patients in the 12-mg/d group and 32.3% for patients in the 6-mg/d group. This mortality difference, if real, would be significant, but there is a possibility that the difference may have arisen due to chance (adjusted relative risk, 0.86 [99% CI, 0.68-1.08]). There was no difference in side effects. Serious adverse reactions, including septic shock and invasive fungal infections, occurred in 11.3% in the

12 mg of dexamethasone group vs 13.4% in the 6 mg of dexamethasone group (adjusted relative risk, 0.83 [99% CI, 0.54-1.29]).



Comment: The results are supportive of improved outcomes with 12 mg/d of dexamethasone, but not definitive since the trial may have been underpowered to identify a significant difference. Some baseline variables such as ethnicity were not collected, and some characteristics such as prevalence of diabetes differed between the groups. The intervention period was only 6 days in some patients per protocol because the trial design allowed up to 4 days of dexamethasone use before enrollment, which may have reduced any effect of the intervention. Lastly, changes in the treatment of COVID-19 during the trial (such as increased use of IL-6 receptor antagonists) may have influenced the results. Nonetheless, the results raise the strong possibility that treatment outcomes for COVID-19 may be improved further using higher doses of glucocorticoids; however, additional trials are needed to confirm this and determine what dose is optimal.

Remdesivir Treatment in Hospitalized Patients with COVID-19: A Comparative Analysis of in Hospital All-Cause Mortality in a Large Multi-Center Observational Cohort

Clin Infect Dis published online October 15, 2021
doi/10.1093/cid/ciab875/6378778

This was a retrospective, comparative effectiveness cohort study using data from the Premier Healthcare Database, that captures diagnosis and procedure codes, medications, and costs per day relative to admission for approximately 20% of all hospitalizations occurring across 45 states and DC. However, actual dates and time stamps are not provided to ensure patient privacy. Hence, all baseline variables are examined within first two days of hospitalization.

The study included adult (≥18 years) patients hospitalized 8/1/2020–11/31/2020 with a primary or secondary discharge diagnosis of COVID-19. Laboratory confirmation of COVID-19 was not feasible in the database. However, the accuracy of ICD-10-CM code U07.1 has been previously validated in the Premier Healthcare Database as a specificity of 99.04% and sensitivity of 98.01%. Because not all hospitals consistently bill for oxygen supply or devices, particularly LFO (low flow), it is possible that the group with no supplementary oxygen (NSO) could include patients who received some level of oxygen that was not billed but instead subsumed in the room charge. To minimize this limitation and permit a clear classification of the NSO group, only those patients from hospitals that reported charges for supplemental oxygen such as LFO for at least one patient were included in the NSO group (defined as no supplemental oxygen charge in hospitals that demonstrably charge for supplemental oxygen). Patients receiving RDV were matched to non-RDV patients with same baseline severity in two-month blocks of admission (August-September, October-November) in the same hospital. Unmatched patients in the RDV group were matched to non-RDV patients with same baseline severity in two-month blocks of admission (August-September, October-November) in another RDV-using hospital of same bed-size category. Mortality at 14- and 28-days was assessed using Kaplan-Meier curves and compared using log-rank tests. Cox proportional hazards models were used to derive hazard ratios (HR) and 95% CI. Models were adjusted for hospital-level cluster effects and following covariates: age at admission, admission month, treatment at baseline (anticoagulants, convalescent plasma, corticosteroids, tocilizumab), hospital ward upon admission as well as any baseline covariate with an absolute standardized difference of >0.15 in subgroups of patients receiving NSO, LFO, HFO/NIV and IMV/ECMO. RDV patients were those administered with at least one dose of RDV in the first two days of hospitalization.

Following matching, 28,855 patients receiving RDV were matched to 16,687 unique patients not receiving RDV (28,855 weighted due to matching with replacement with up to 1:10 variable ratio matching). Most covariates had a standardized difference absolute value of <0.10 after matching, except primary payor (0.11), cardiovascular disease (0.11), renal disease (0.16), and age group (0.17).

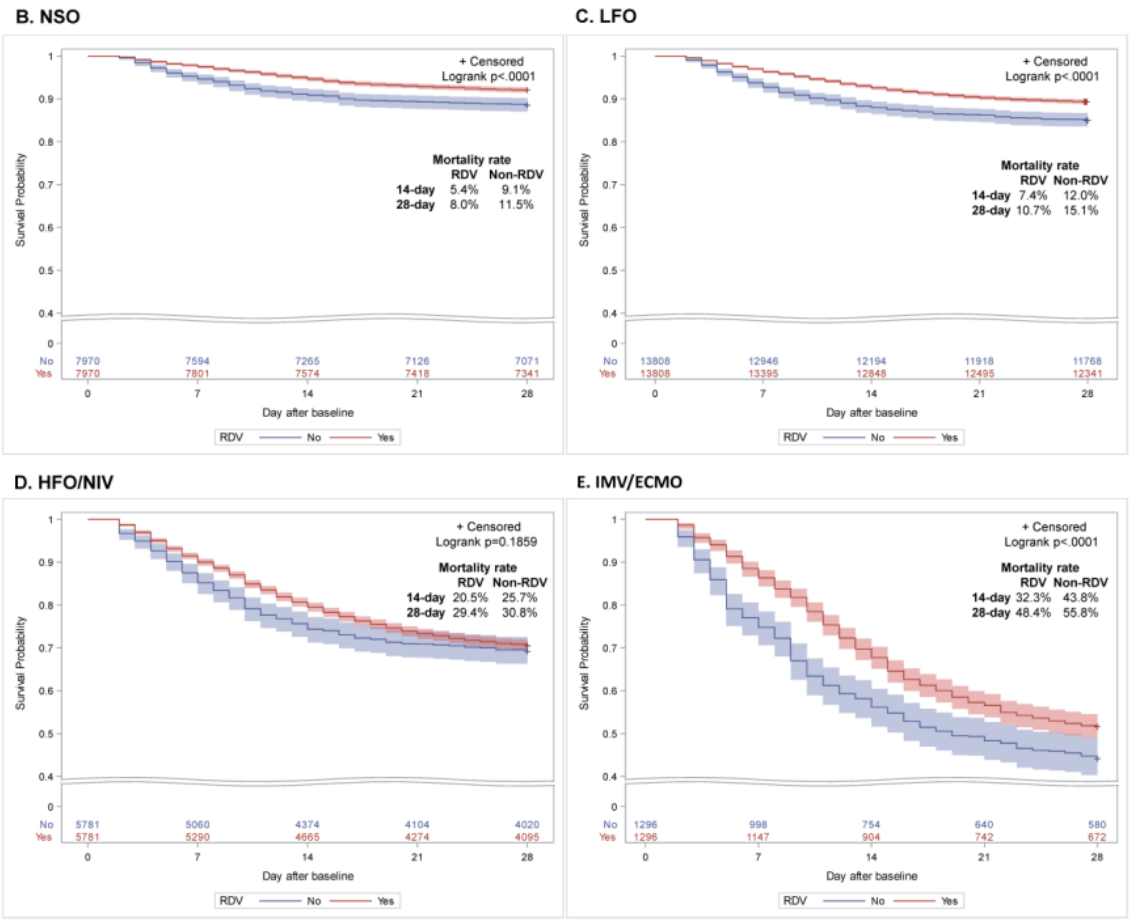
Overall, 3,057 (10.6%) and 4,441 (15.4%) patients who received RDV died within 14- and 28-days, respectively, whereas 4,437 (15.4%) and 5,499 (19.1%) patients who did not receive RDV died within 14- and 28-days, respectively. After adjusting for baseline and clinical covariates, there was a significant reduction in mortality among RDV treated patients compared to non-RDV group (14-day adjusted HR (aHR): 0.76, 95% CI:0.69-0.83; 28-day aHR:0.88, 95% CI:0.81-0.96).

In patients requiring NSO (i.e., without charges for supplemental oxygen) at baseline 427 (5.4%) and 635 (8.0%) patients who received RDV died within 14- and 28-days respectively, whereas 726 (9.1%) and 916 (11.5%) patients who did not receive RDV died within 14- and 28-days respectively. After adjusting for baseline and clinical covariates, there was a significant reduction in mortality among RDV treated patients compared to non-RDV group (14-day aHR:0.69, 95% CI:0.57-0.83; 28-day aHR:0.80, 95% CI:0.68-0.94).

Patients requiring LFO at baseline among patients requiring LFO, 1,028 (7.4%) and 1,478 (10.7%) patients who received RDV died within 14- and 28-days respectively, whereas 1,661 (12.0%) and 2,078 (15.1%) patients who did not receive RDV died within 14- and 28-days respectively. Kaplan-Meier curves revealed a significantly lower risk of mortality in RDV vs. non-RDV group (p<0.0001). After adjusting for baseline and clinical covariates, there was a significant reduction in mortality among RDV treated patients compared to non-RDV group (14-day aHR:0.67, 95% CI:0.59-0.77; 28-day aHR:0.76, 95% CI:0.68-0.86).

Patients requiring HFO/NIV at baseline among patients requiring HFO/NIV, 1,184 (20.5%) and 1,701 (29.4%) patients who received RDV died within 14- and 28-days respectively, whereas 1,483 (25.7%) and 1,782 (30.8%) patients who did not receive RDV died within 14- and 28-days respectively. According to the log-rank test, there was no significant difference in risk of mortality between RDV and non-RDV groups at 28-days (p=0.1859). After adjusting for baseline and clinical covariates, patients receiving RDV had a significantly lower risk of mortality at day 14 (aHR:0.81, 95% CI:0.70-0.93) compared to non-RDV group, but there was no significant difference between the two groups at 28 days (aHR:0.97, 95% CI:0.84-1.11).

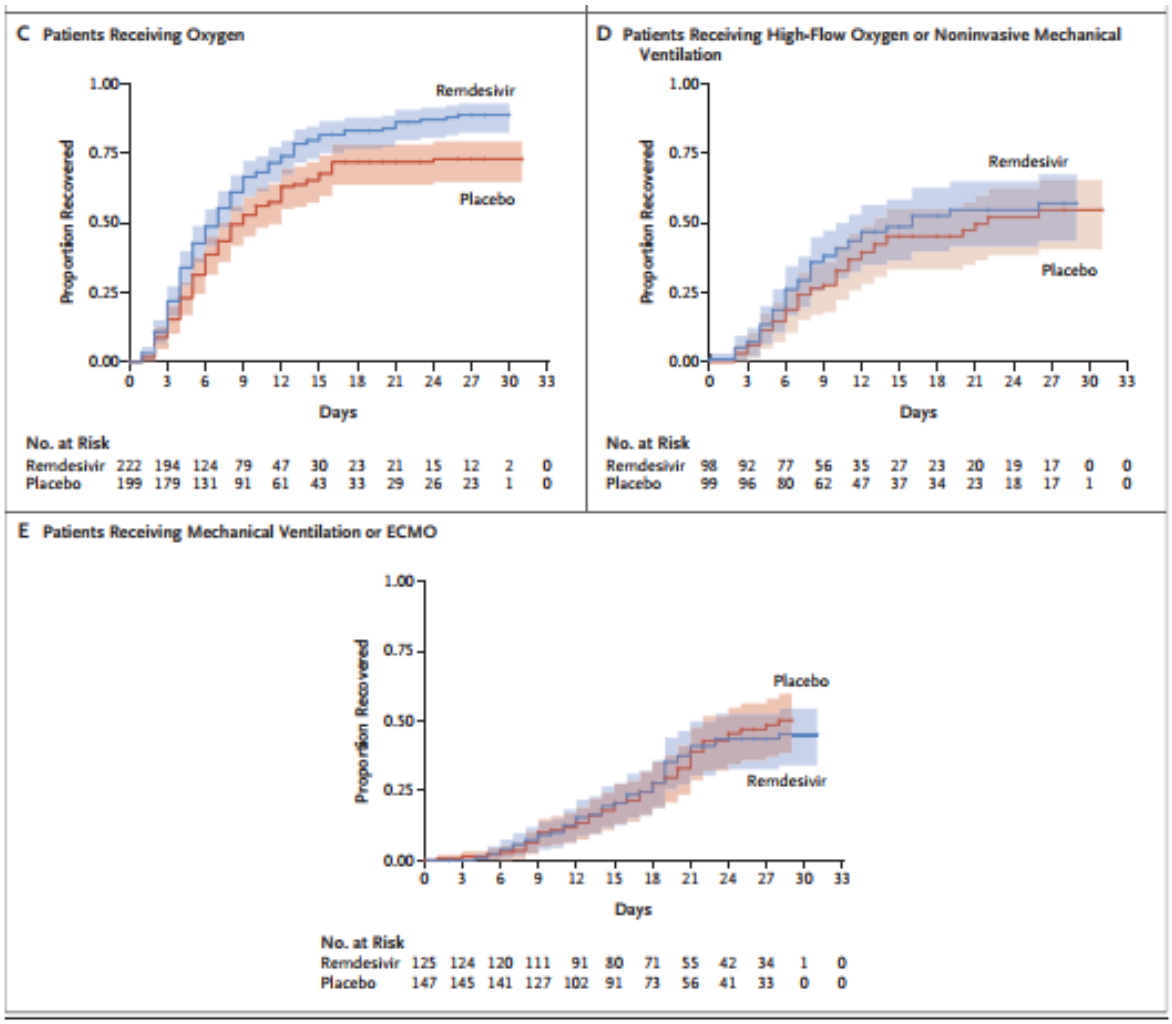
Patients requiring IMV/ECMO at baseline Among patients requiring IMV/ECMO, 418 (32.3%) and 627 (48.4%) patients who received RDV died within 14- and 28-days respectively, whereas 568 (43.8%) and 724 (55.8%) patients who did not receive RDV died within 14- and 28-days respectively. Kaplan-Meier curves revealed a significantly lower risk of mortality in RDV vs. non-RDV group (p<0.0001). After adjusting for baseline and clinical covariates, there was a significant reduction in mortality among RDV treated patients compared to non-RDV group (14-day aHR:0.70, 95% CI:0.58-0.84; 28-day aHR:0.81, 95% CI:0.69-0.94).

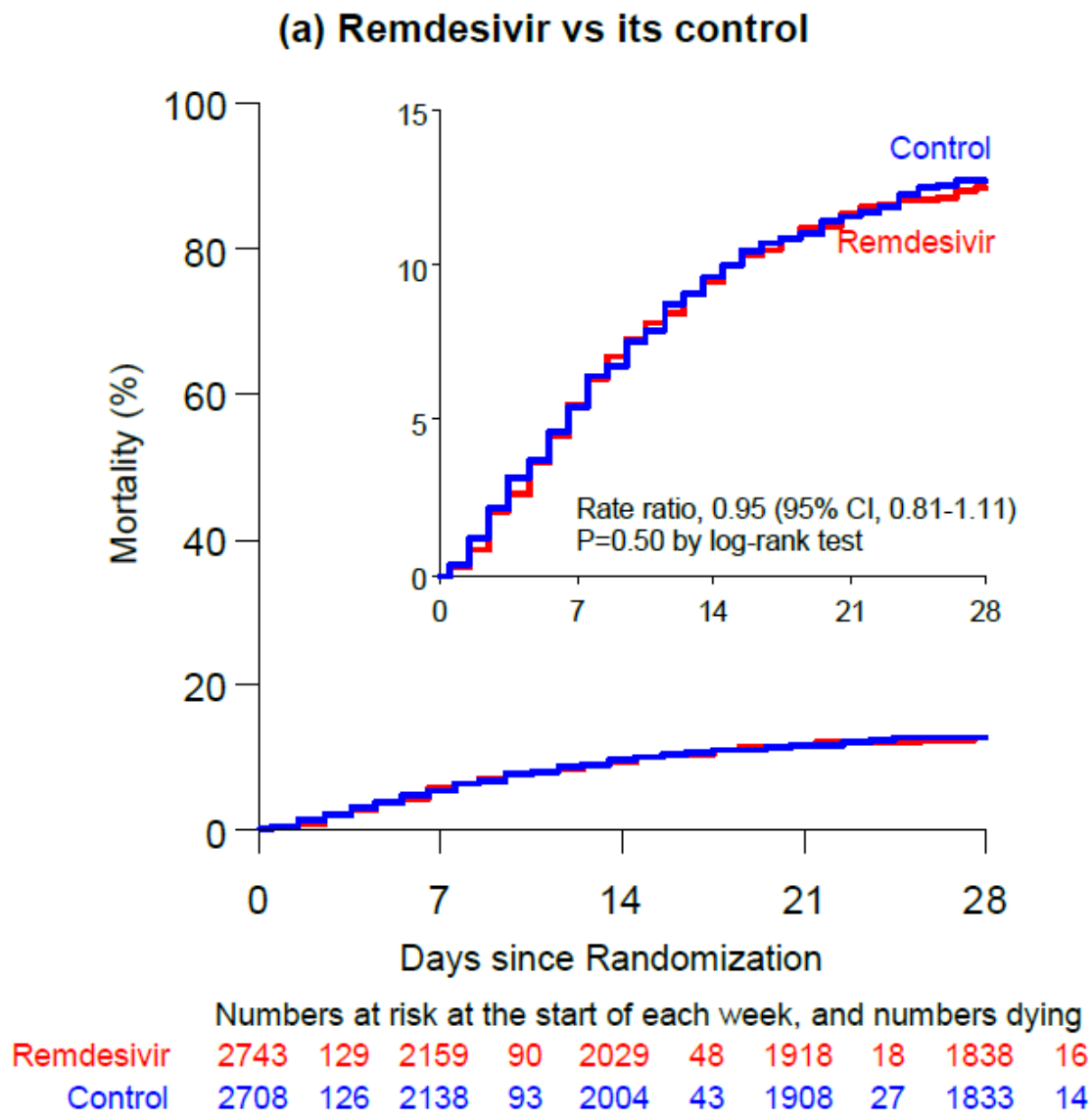


Comment: RDV initiation within the first two days of COVID-19 hospitalization was associated with improved survival as compared with non-RDV group. The beneficial effects of RDV at 14- and 28-day timepoints were most prominent among patients with NSO, LFO, or IMV/ECMO at baseline. A benefit at 14-days among patients requiring HFO was also observed. I have a hard time understanding why there

wasn't a mortality benefit at 28 days seen in the high-flow oxygen/non-invasive ventilation (HFO/NIV), but there was in the invasive mechanical ventilation/ECMO (IMV/ECMO) group. It makes sense that the benefit of RDV given early would only be seen in patients that still have moderate or higher viral loads. I cannot see how RDV would make much difference in a patient who's past the viral phase and now in the inflammatory phase which applies to most patients on IMV, HFO, and ECMO. Unfortunately, this study doesn't include viral loads. There can be many limitations with claims-based observational analyses like this, but I appreciate they tried to balance the groups with propensity matching.

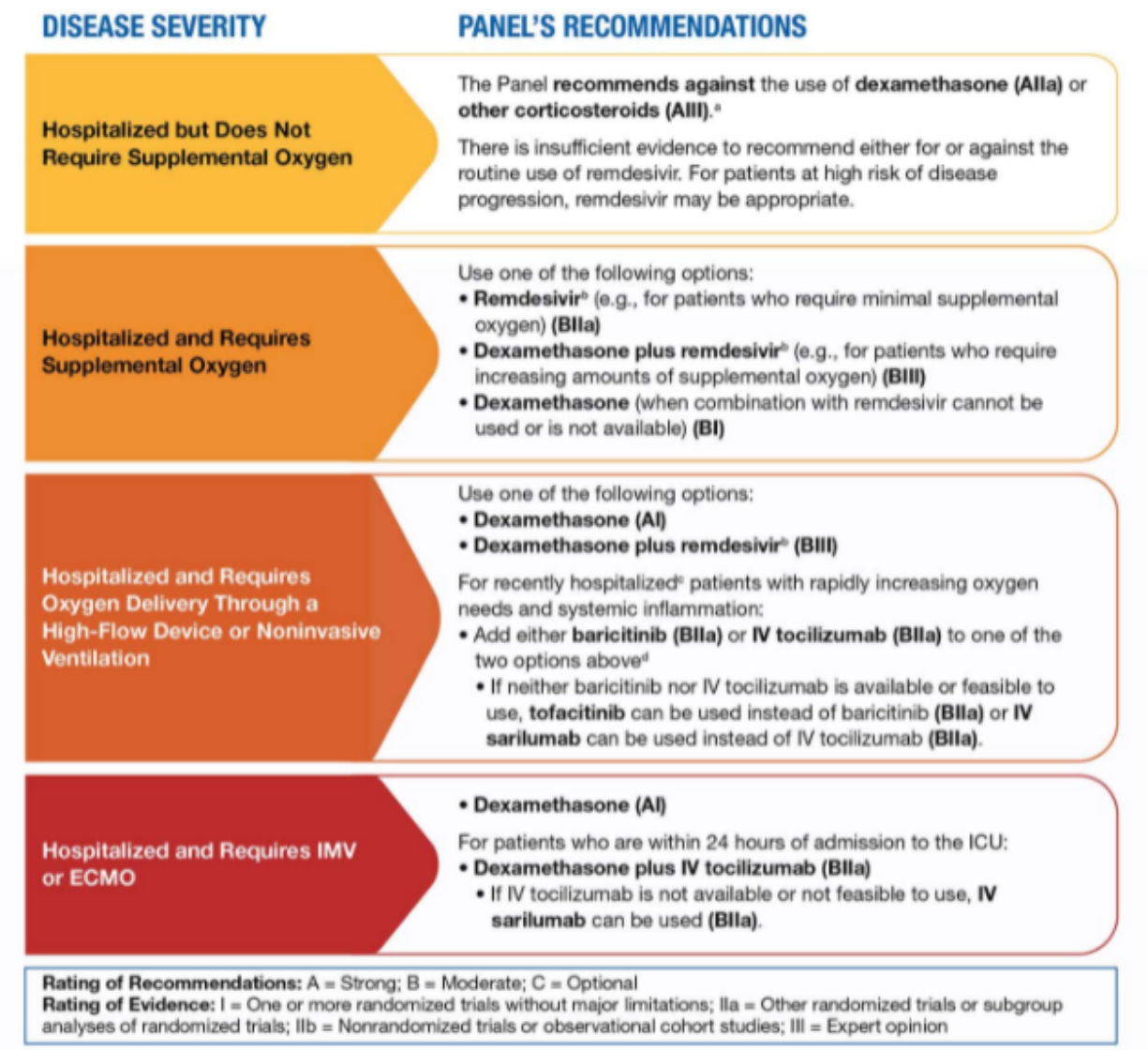
Can we compare high-level claims-based observation studies like this with the findings in well conducted RCTs like ACTT-1 and Solidarity which failed to show a mortality difference? Below are Kaplan Meir curves from ACTT-1 and Solidarity.





The WHO does not recommend RDV at all based on the Solidarity Trial. See below

Before this publication the preponderance of evidence supported using RDV early (probably best in patient with symptoms < 7days) on <15 liters of oxygen**.** IDSA COVID-19 Guideline's state in patients with COVID-19 on invasive ventilation and/or ECMO, the IDSA panel suggests against the routine initiation of remdesivir. The NIH is shown below favoring use of RDV in patients on LFO.



I spent more time on this article due to the differences in outcomes compared to other publications. I welcome to hear from others how they interpret this paper and would it change your current guidelines.