Metformin on Time to Sustained Symptom Recovery: ACTIV-6 Randomized Clinical Trial

Poster#00719
03/12/2025
CROI 2025
Session: G-05

Carolyn T. Bramante, MD, MPH,[1] Thomas G. Stewart, PhD,[2] David R. Boulware, MD, MPH,[1] Matthew W. McCarthy, MD,[3] Russell L. Rothman, MD, MPP,[4] Ahmad Mourad, MD,[5,6] Florence Thicklin,[7] Yue Gao, MS[4], G. Michael Felker, MD,[5,6] Sean Collins, MD, MSci,[4,23] Sarah E. Dunsmore, PhD,[24] Stacey J. Adam, PhD,[25] Christopher J. Lindsell, PhD,[6] Adrian F. Hernandez, MD, MHS,[6] Susanna Naggie, MD, MHS[6] for the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group and Investigators

[1]University of Minnesota Medical School, Minneapolis, MN; [2]School of Data Science, University of Virginia, Charlottesville, VA; [3]Weill Cornell Medicine, New York, NY; [4]Vanderbilt University Medical Center, Nashville, TN; [5]Dept of Medicine, Duke University School of Medicine, Durham, NC; [6]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC; [7]Stakeholder Advisory Committee, Pittsburgh, PA; [8]Veterans Affairs Tennessee Valley Healthcare System, Geriatric Research, Education and Clinical Center (GRECC), Nashville, TN; [9]National Center for Advancing Translational Sciences, Bethesda, MD; [10]Foundation for the National Institutes of Health, Bethesda, MD.

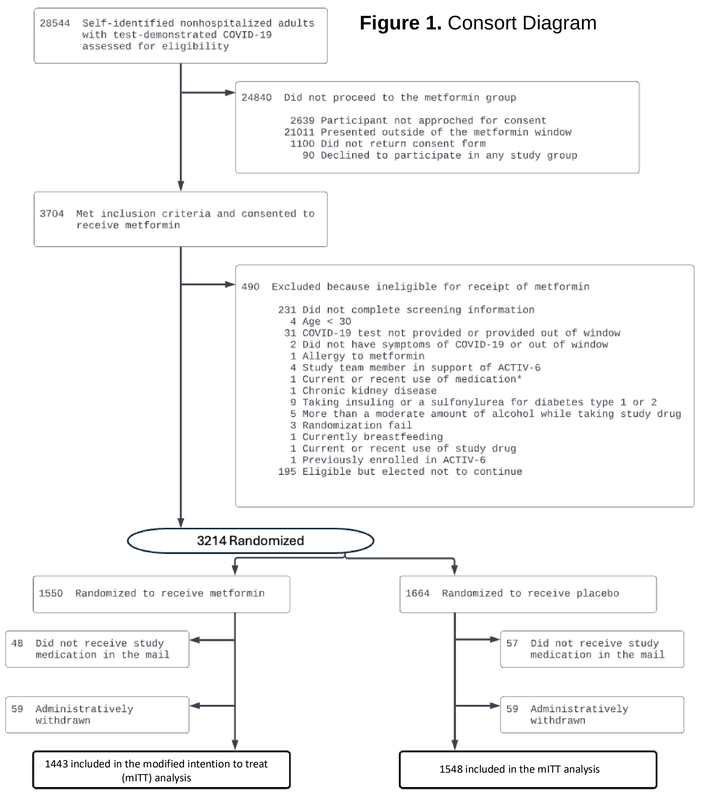
Background

- The effect of metformin on speeding the time to outpatient symptom resolution from infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has not been studied. Our objective was to test metformin compared to placebo for time to symptom resolution among adults with mild-moderate COVID-19.
- Metformin has not been studied in low-risk adults with a normal body mass index (BMI) for COVID-19
- Several studies have published *in vitro* and *in vivo* antiviral actions of metformin against SARS-CoV-2
- This was the last medication studied on the Accelerating COVID-19 Therapeutic Interventions and Vaccines 6 (ACTIV-6) decentralized, double-blind, randomized controlled platform trial (NCT04885530) at 90 sites.

Methods

- Non-hospitalized adults age >30 with confirmed positive SARS-CoV-2 test within 10 days were eligible if they reported having at least 2 symptoms attributed to COVID-19 and consented in ≤ 7 days of symptom onset
- Recruitment and consent were completed remotely
- There was no minimum BMI requirement for eligibility
- A simple randomization assigned participants 1:1 to immediate release metformin or placebo, no other medications were open on the platform
- Study drug was then sent via courier from a single central pharmacy
- Participants were not given glucometers or told to track their blood glucose
- Participants were asked to complete daily symptom reporting for at least 14 days or until symptom resolution via a participant portal link that was sent via text or email
- Reminders were sent if participants did not complete the daily symptom survey
- The primary outcome for this arm was time to sustained symptom recovery
- Time to sustained recovery was defined as the third day of three consecutive days without symptoms that the participant attributed to COVID-19

Figure 1. Consort Diagram



Results

Table 1	Metformin (n=1443)	Placebo (n=1548)
Age, median (IQR), yrs	47.0 (38.0-57.5)	48.0 (37.0-58.0)
Age < 50 yrs, no. (%)	798 (55.3)	846 (54.7)
Female, no. (%)	918 (63.62)	977 (63.11)
Race, not mutually exclusive, no. (%)		
American Indian or Alaska Native	18 (1.25)	7 (0.45)
Asian	37 (2.56)	40 (2.58)
Black, African American, or African	164 (11.37)	186 (12.02)
Middle Eastern or North African	35 (2.43)	24 (1.55)
Native Hawaiian, Other Pacific Islander	4 (0.28)	4 (0.26)
White	1162 (80.53)	1233 (79.65)
None of the above	31 (2.15)	37 (2.39)
Ethnicity, no (%): Hispanic or Latino	680 (47.12)	712 (45.99)
Not Hispanic or Latino	763 (52.88)	836 (54.01)
Region, no. (%)		
Midwest	295 (20.44)	308 (19.90)
Northeast	119 (8.25)	135 (8.72)
South	890 (61.68)	942 (60.85)
West	139 (9.63)	163 (10.53)
Medical history, no./total (%)		
BMI >30 kg/m², no./total (%)	579/1443 (40.1)	566/1547 (36.6)
High blood pressure	282/1386 (20.35)	316/1481 (21.34)
Diabetes	31/1386 (2.24)	27/1481 (1.82)
Smoker, past year	197/1386 (14.21)	229/1481 (15.46)
Asthma	142/1386 (10.25)	135/1481 (9.12)
Heart disease	41/1386 (2.96)	48/1481 (3.24)
Malignant cancer	29/1384 (2.10)	31/1476 (2.10)
COPD	30/1386 (2.16)	28/1481 (1.89)
Not vaccinated	463 (32.09)	480 (31.01)
Vaccinated, 1 dose	2 (0.14)	2 (0.13)
Vaccinated, 2+ doses	978 (67.78)	1066 (68.86)
Days between symptom onset & delivery	5 (4-7)	5 (4-7)
COVID-19 medications, no. (%), for this infection or for a prior infection		
Remdesivir	1 (0.07)	0 (0.00)
Nirmatrelvir + ritonavir	204 (14.14)	229 (14.79)
Monoclonal antibodies	31 (2.15)	43 (2.78)
Molnupiravir	10 (0.69)	13 (0.84)

Figure 2. Bar chart of days (left) and percentages (right).

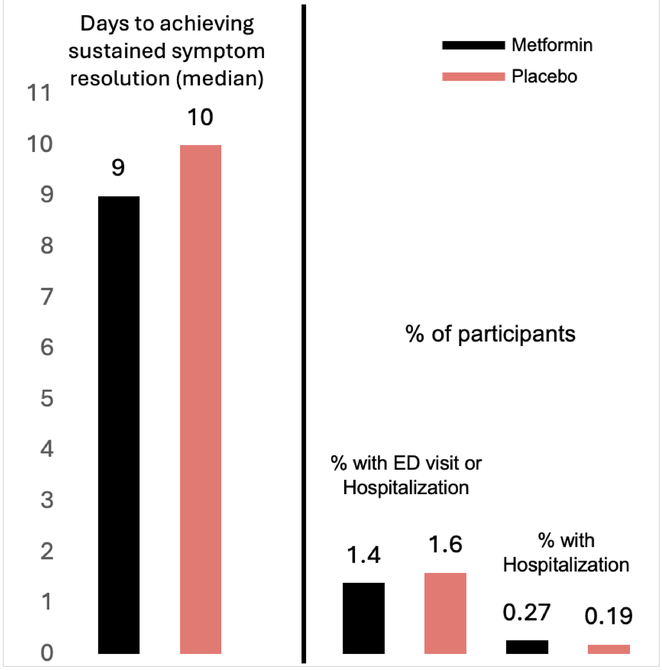
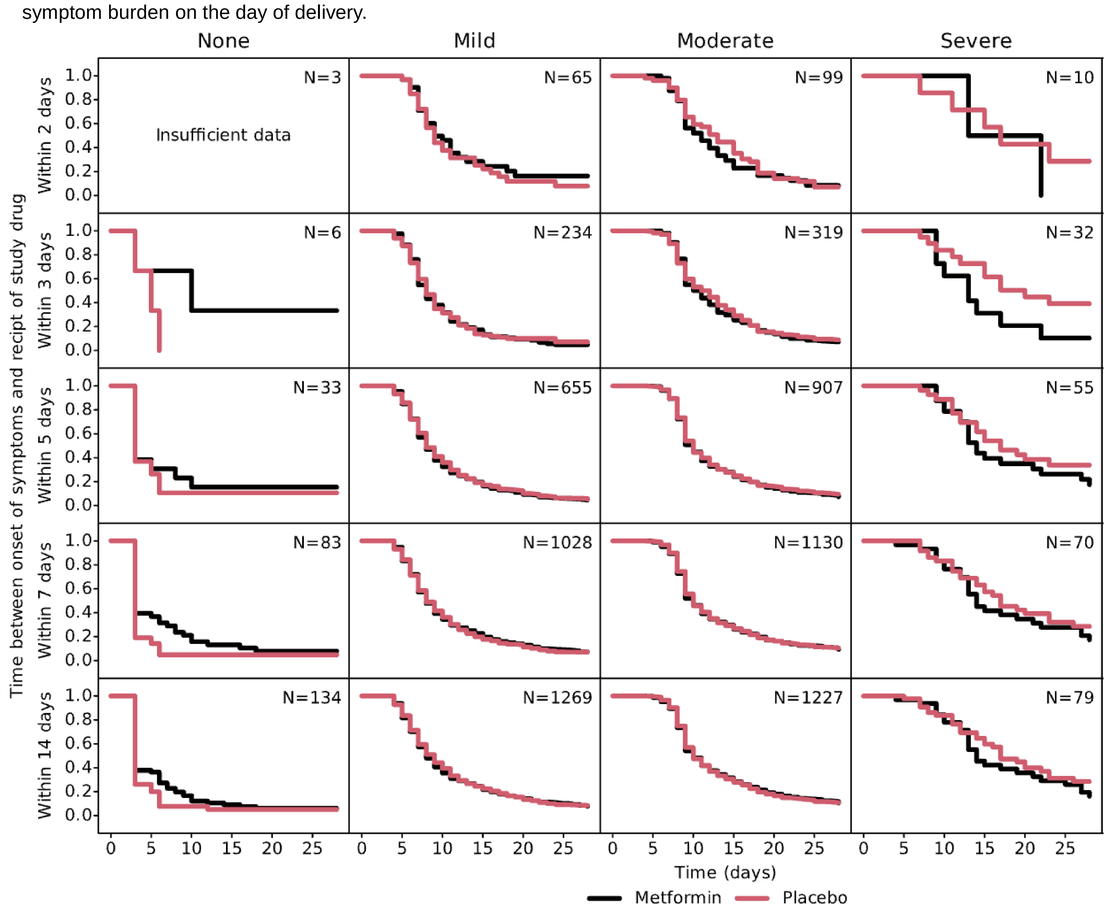


Figure 3. Kaplan-Meier curves of sustained recovery by days between symptom onset and delivery of drug and symptom burden on the day of delivery.



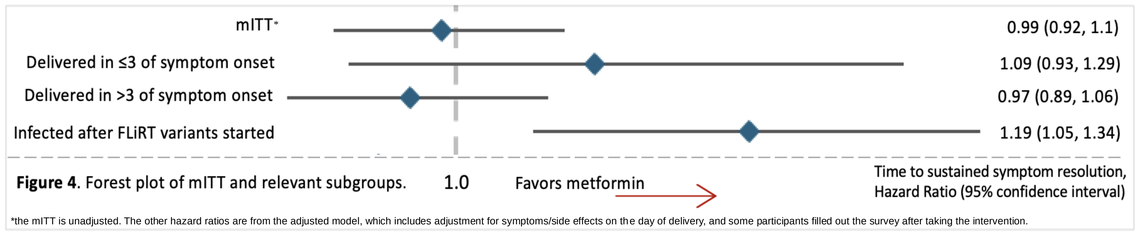


Figure 4. Forest plot of mITT and relevant subgroups.

*the mITT is unadjusted. The other hazard ratios are from the adjusted model, which includes adjustment for symptoms/side effects on the day of delivery, and some participants filled out the survey after taking the intervention.

Limitations and Conclusions

- The placebo group was 7% larger than metformin, post-randomization exclusions were 7% in both, the metformin group had more with obesity
- < 21% of participants received study drug within 3 days of symptom onset and 25% received study drug ≥7 days from symptom onset. Starting treatment within 3 days of symptom onset is the target population for this medication and is also realistic given cost and access.
- Participants with no symptoms on or before the day study drug was delivered were not excluded from the analysis of time to symptom resolution
- Median days to symptom resolution was numerically but not significantly lower for metformin compared to placebo.
- Emergency department visits and hospitalizations were too infrequent to draw conclusions on clinical outcomes.
- This was the first phase 3 trial to randomize adults without chronic disease or disease risk to metformin, and there were no safety concerns. There were no differences in the subgroup with BMI < 25kg/m²

Funding

ACTIV-6 is funded by the National Center for Advancing Translational Sciences (NCATS) (3U24TR001608-06S1). Additional support for this study was provided by the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority (No. 75A50122C00037). The Vanderbilt University Medical Center Clinical and Translational Science Award from NCATS (UL1TR002243) supported the REDCap infrastructure.