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Metformin on the Presence of COVID-19 Symptoms 6 Months After Infection: The ACTIV-6 Randomized Clinical Trial

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Background. We conducted a quadruple-blinded, randomized, placebo-controlled trial of metformin for treating acute SARS-CoV-2 infection to prevent long COVID symptoms in low-risk adults.

Methods. The ACTIV-6 platform evaluated repurposed medications for mild to moderate COVID-19. Between 19 September 2023 and 1 May 2024, 2983 outpatient adults ≥30 years with confirmed SARS-CoV-2 infection and ≥2 COVID-19 symptoms were included within 7 days of symptom onset from 90 sites. Participants were randomized to metformin or placebo for 14 days. Postacute sequelae of SARS-CoV-2 or death (PASCD) was ascertained by asking whether participants had symptoms they attributed to COVID-19 on day 180. Secondary outcomes included clinician-diagnosed long COVID.

Results. The median age was 47 years (interquartile range 38–57); 63% were female; 47% were Hispanic/Latino; 83% reported ≥1 prior COVID-19 infections or ≥2 SARS-CoV-2 vaccines. There were no deaths. Overall, 96 (3.2%) reported COVID-19 symptoms on day 90, 101 (3.4%) on day 120, and 79 (2.6%) on day 180. The adjusted risk of symptoms on day 180 was 0.8 percentage points lower with metformin (95% credible interval [CrI] −2.2 to 0.6) with a posterior probability of efficacy (PPE) for preventing symptoms of 0.83, risk ratio 0.79 (95% CrI 0.474 to 1.230). Compared with placebo, the risk of clinician-diagnosed long COVID was 0.7 percentage points lower with metformin (95% CrI −1.5 to 0.1); PPE 0.96; risk ratio 0.495 (95% CrI 0.155–0.995).

Conclusions. In low-risk adults, most with prior immunity, metformin did not exceed the efficacy threshold of 0.975 for PASC. Metformin reduced the risk of clinician-diagnosed long COVID.

Clinical Trail Registration. ClinicalTrials.gov (NCT04885530).

Keywords. SARS-CoV-2; long COVID-19; metformin; outpatient; platform trial.

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Estimates suggest that 7% of adults in the United States have had postacute sequelae of COVID (PASC), often referred to as long COVID [1–3]. Waning immunity, changing vaccination rates, and the potential risk of more severe variants highlight the need for therapies to prevent long COVID.

Interventions to prevent long COVID in low-risk individuals with prior immunity are urgently needed [4, 5]. The definition of long COVID has evolved to include symptom-based and condition-based criteria with clinician judgment, and it is imperative to understand whether treating acute infection can prevent long COVID [6, 7]. Metformin has host-directed anti-inflammatory actions and reduces SARS-CoV-2 viral load [8–10]. One previous randomized trial testing metformin as

outpatient treatment of mild-moderate COVID-19 in normal-risk and high-risk adults found that participants randomized to metformin were less likely to be diagnosed with long COVID [11]. Thus, it was important to replicate this finding in a broader population, including low-risk adults and in the current state of the pandemic.

The Accelerating Coronavirus Disease 2019 Therapeutic Interventions and Vaccines (ACTIV-6) platform randomized clinical trial evaluated repurposed medications for treating acute COVID-19 including in low-risk adults [12]. For this study, the ACTIV-6 platform sought to evaluate the effect of 14 days of immediate-release metformin at the time of acute infection for preventing long-term sequelae.

METHODS

Trial Design and Oversight

ACTIV-6 was a quadruple-blinded, randomized, placebo-controlled, decentralized platform trial of repurposed medications in outpatient adults with mild to moderate COVID-19 [12]. The patients, investigators, outcome assessors, and diagnosing clinicians were blinded to treatment allocation. The protocol and statistical analysis plan are provided with this manuscript [13]. The protocol was approved by a central institutional review board [12]. Each participant provided informed consent. An independent data and safety monitoring committee oversaw the trial.

Participants

The ACTIV-6 platform enrolled participants for randomization to metformin or placebo from 90 US sites between 19 September 2023 and 1 May 2024.

Eligibility criteria included age ≥30 years, confirmed SARS-CoV-2 infection (positive polymerase chain reaction or home-based antigen test) within 10 days, and actively experiencing ≥2 COVID-19 symptoms for ≤7 days at the time of consent. Exclusion criteria included current hospitalization for COVID-19; current or recent use (within 14 days) of metformin, insulin, or sulfonylureas; and known allergy or contraindications to metformin (full criteria in Supplementary Appendix). The modified intention to treat (mITT) sample in this decentralized trial comprised participants who remained after excluding those who did not receive delivery of the study drug or were administratively withdrawn (Figure 1).

Randomization

Enrollment for metformin did not overlap with other agents on the platform. A random number generator completed simple 1:1 randomization to metformin or placebo.

Interventions

Participants received metformin, immediate-release, 500 mg tablets (Aurobindo Pharma USA, Durham, NC) or exact-matching placebo. Before the exact-matching placebo was available on 9 November 2023, 134 participants in the placebo group were enrolled using generic placebo. The 14-day dosing regimen was 500 mg once daily for 1 day; 500 mg twice daily for 4 days; then 500 mg in the morning; and 1000 mg in the evening for 9 days (36 tablets total).

Outcome Measures

The primary outcome was postacute sequelae of SARS-CoV-2 or death (PASCD), a composite outcome of mortality or having symptoms on day 180, assess by this question: "Please choose the response that best describes the severity of your COVID-19 symptoms today," with options for no symptoms, mild, moderate, and severe. Except for participants who reported a new COVID-19 infection within 28 days, participants who reported any COVID-19 symptoms experienced the endpoint. Because no deaths were observed, we shortened the abbreviation to PASC. The primary measure of treatment effect was summarized on the absolute scale, the difference in PASC on day 180 between the metformin group and the placebo group, with a difference less than zero indicating lower risk with metformin.

Secondary Outcome Measures

The presence of PASC on days 90 and 120 were secondary outcomes. A participant might meet the criteria for PASC on follow-up day 90 but not on day 120 or day 180 if they no longer reported symptoms. The treatment effect for PASC was also summarized on the relative scale as a risk ratio.

Two other outcomes were obtained: symptom burden (none, mild, moderate, severe, deceased) on days 90, 120, or 180, and clinician diagnosis of long COVID. Clinician diagnosis was ascertained with the question: "Have you been told by a medical provider that you have long COVID since your last survey?" on days 120 and 180.

Trial Procedures

Current infection was confirmed by sites. The centralized investigational pharmacy packaged and shipped active or placebo study products to participants. Day 1 was the day of delivery, as tracked by the courier. Symptom assessments were sent to participants via the online REDCap electronic data portal on days 90, 120, 150, and 180. Additional study details are in the Supplementary Appendix.

Two safety events of interest were added for the metformin protocol: lactic acidosis or hypoglycemia measured in a medical encounter. Participants were not instructed to monitor blood sugar, and the study did not send glucometers.

Statistical Analysis Plan

The treatment effect for the primary outcome, the PASC risk difference on day 180 in the full mITT sample, was estimated

Figure 1. CONSORT Diagram - Participant study flow.

from a Bayesian multivariate model of PASC based on survey outcomes collected on days 90, 120, and 180.

The multivariate model leveraged all available data, incorporating (a) outcome information from every participant who contributed at least 1 long-term follow-up survey and (b) baseline covariate information from all participants. The multivariate model was constructed as a first-order Markov model, comprising 3 covariate-adjusted regression submodels: (a) day 90 outcomes; (b) day 120 outcomes adjusting for day 90; and (c) day 180 adjusting for day 120. Missing outcome data was accommodated with the observed data likelihood.

Covariate adjustment in each submodel planned terms for randomization assignment, age as restricted cubic splines, body mass index (BMI) as restricted cubic splines with possible shift at the obesity threshold of 30 kg/m^2, sex, duration of symptoms before day 1, prior infection, vaccination status, geographic region, calendar date, call center, and baseline symptom score (the symptom score on the day of drug delivery or the day before delivery if the participant received the medication and took it prior to reporting symptoms). In addition to the planned list of covariates, the plan was updated after the day 28 analysis to include a contingency if fewer than expected

outcomes were observed, specifically increasing the degree of regularization via baseline covariate prior distributions, using weakly informative rather than noninformative prior distributions for the baseline covariates, and performing a sensitivity analysis using a reduced number of covariates: obesity, prior COVID-19 infection, and vaccination status (Supplementary Table 1).

The prior distribution for each model parameter was specified individually. The priors for regression intercept parameters were flat, meaning incidence estimates were unconstrained and estimated from the observed data. All other regression parameters were centered at zero and weakly informative. Computer simulations performed during the planning phase indicated an additional prior on the treatment effect was not needed to achieve type I error control. The posterior distribution was calculated using Markov chain Monte Carlo sampling methods and approximated with a multivariate normal distribution for visualizations.

The marginal risk of PASC on day 180 was derived from the multivariate model for both groups, marginalizing the difference over the observed covariate distribution. The portion of the posterior distribution of the treatment effect less than zero was the posterior probability of efficacy (PPE). The median and highest-density interval of the posterior were the point and interval estimates of the treatment effect, respectively. The risk ratio was calculated from the same model. Symptom burden was calculated using a common odds ratio.

Participant-reported clinician diagnosis of long COVID was modeled with the first-order Markov model among participants responding to the day 120 or day 180 surveys, using the same methods for missing outcomes, priors, and calculation of treatment effect estimates on the absolute and relative risk scales. Unadjusted counts, proportions, and ratios of PASC and clinician diagnosis of long COVID were tabulated for each follow-up survey. A predefined assessment of treatment effect heterogeneity (HTE) encompassed age, symptom duration, BMI, symptom severity on day 1, calendar time, sex, and vaccination status.

Because PPE is inherently a 1-sided measure, the threshold for declaring efficacy was updated after the day 28 analysis to require a PPE of 0.975 for the risk difference of PASC on day 180. Efficacy was defined using the primary outcome and credible intervals for secondary outcomes were not adjusted for multiplicity. Analyses were performed with R^{10} version 4.5 with the following primary packages: rstan and rstanarm [14].

RESULTS

Study Population

Of the 3214 participants randomized, 231 (7.2%) were administratively withdrawn or excluded because study drug was not delivered within 7 days. Thus, the mITT analysis included 2983 participants, of whom 1439 (48.2%) received metformin and 1544 (51.8%) received placebo (Figure 1).

The median age of the mITT population was 47 years (interquartile range, 38–57); 63.4% were female, 80.1% were White, 11.7% were Black, 0.8% were American Indian or Alaska Native, and 46.5% identified as Hispanic/Latino. Overall, 2% had diabetes, 2% had high blood pressure, and 38.2% had obesity, 40.0% in the metformin group and 36.5% in the placebo group. At baseline, 68.3% reported having had at least 2 doses of a SARS-CoV-2 vaccine, and 48.4% (70.7% of those who had been vaccinated) had been vaccinated >6 months prior to baseline. Overall, 53.5% reported having had at least 1 prior COVID-19 infection, with 83% reporting either prior vaccination or infection (Table 1).

The proportion of the mITT population who completed the day 90, 120, and 180 surveys ranged from 79% to 81% (Table 2 and Supplementary Tables 2–4).

Primary Outcome

Overall, 79 (2.6%) participants reported having symptoms that they attributed to COVID-19 on day 180, and there were no observed deaths in the trial. Among participants randomized to metformin, 33 (2.3%) reported symptoms on day 180; among participants randomized to placebo, 46 (3.0%) reported symptoms on day 180. The covariate-adjusted risk of PASC was 0.8 percentage points lower with metformin (95% CrI −2.2 to 0.6), PPE for preventing PASC was 0.83 (Table 3, Figure 2 and Supplementary Figure 1).

Secondary Outcomes

Overall, 96 (3.2%) participants reported COVID-19 symptoms on day 90, with 44 (3.1%) participants in the metformin group and 51 (3.4%) in the placebo group. On day 120, 101 (3.4%) reported COVID-19 symptoms, with 40 (2.8%) in the metformin group and 61 (4.0%) in the placebo group (Tables 2 and 3).

The covariate-adjusted risk of PASC was 0.3 percentage points lower (95% CrI −1.9 to 1.2), PPE 0.66 on day 90, and 1.1 percentage points lower (95% CrI −2.7 to 0.4), PPE 0.93 on day 120 (Table 3).

On day 120, 29 (0.97%) participants reported having received a clinician diagnosis of long COVID, with 13 (0.90%) in the metformin group and 16 (1.04%) in the placebo group, 0.1 percentage points lower with metformin (−1.0 to 0.7), PPE 0.63, and risk ratio 0.879 (95% CrI 0.349–1.632). On day 180, 26 (0.87%) participants had a clinician diagnosis of long COVID, 8 (0.56%) in the metformin group and 18 (1.17%) in the placebo group, 0.7 percentage points lower with metformin (95% CrI −1.5 to 0.1; PPE 0.96), risk ratio 0.50 (95% CrI 0.16–0.99) (Table 3 and Figure 2).

Exploratory heterogeneity of treatment effect analyses suggest that participants reporting no known prior infection may be more likely to benefit from the intervention (Supplementary Figure 2). In those with any prior immunity (from infection or vaccination), 0.7% of the metformin group and 1.6% of the

Table 1. Baseline Characteristics of Participants With Acute SARS-COV-2 Infection by Randomized Arm

	Metformin (n = 1439)	Placebo (n = 1544)	Overall (n = 2983)
Age, median (IQR), y	47 (38–57)	48.0 (37–58)	47 (38–58)
Age <50 y, No. (%)	796 (55.3)	843 (54.6)	1639 (54.9)
Sex, No. (%)			
Female	917 (63.7)	973 (63.02)	1890 (63.4)
Male	519 (36.1)	566 (36.66)	1085 (36.4)
Undifferentiated, unknown, prefer not to answer	3 (0.2)	5 (0.32)	8 (0.3)
Race,[a] No. (%)			
American Indian or Alaska Native	18 (1.3)	7 (0.45)	25 (0.8)
Asian	37 (2.6)	40 (2.59)	77 (2.6)
Black or African American	164 (11.4)	184 (11.92)	348 (11.7)
Middle Eastern or North African	35 (2.4)	23 (1.49)	58 (1.9)
Native Hawaiian or Other Pacific Islander	4 (0.3)	4 (0.26)	8 (0.3)
White	1158 (80.5)	1232 (79.79)	2390 (80.1)
None of the above	31 (2.2)	37 (2.40)	68 (2.3)
Prefer not to answer	25 (1.7)	28 (1.81)	53 (1.8)
Hispanic/Latino, No. (%)	679 (47.2)	712 (46.1)	1391 (46.6)
Region,[b] No. (%)			
Midwest	295 (20.5)	308 (20.0)	603 (20.2)
Northeast	117 (8.1)	133 (8.6)	250 (8.4)
South	888 (61.7)	942 (61.0)	1830 (61.3)
West	139 (9.7)	161 (10.43)	300 (10.1)
Recruited via call center,[c] No. (%)	41 (2.8)	42 (2.72)	83 (2.8)
Medical history[d]			
BMI, median (IQR), kg/m^2	28.6 (25.4–32.6)	28.3 (25.1–31.9)	28.4 (25.2–32.2)
BMI >30 kg/m^2, No. (%)	576 (40.0)	563 (36.5)	1139 (38.2)
Heart disease, No./total (%)	41/1382 (3.0)	48/1479 (3.2)	89/2861 (3.1)
Diabetes, No./total (%)	30/1382 (2.2)	27/1479 (1.8)	57/2861 (2.0)
High blood pressure, No./total (%)	281/1382 (20.3)	316/1479 (21.37)	597/2861 (20.9)
COPD, No./total (%)	30/1382 (2.2)	28/1479 (1.9)	58/2861 (2.0)
Asthma, No./total (%)	141/1382 (10.2)	135/1479 (9.13)	276/2861 (9.6)
Chronic kidney disease, No./total (%)	1/1382 (0.1)	6/1479 (0.4)	7/2861 (0.2)
Smoker, past year, No./total (%)	196/1382 (14.2)	229/1479 (15.5)	425/2861 (14.9)
Malignant cancer, No./total (%)	29/1380 (2.10)	31/1474 (2.10)	60/2854 (2.10)
Prior infection, No./total (%)	739/1350 (54.74)	764/1459 (52.36)	1503/2809 (53.51)
SARS-CoV-2 vaccine doses, No. (%)			
None	462 (32.1)	479 (31.0)	941 (31.5)
1	2 (0.14)	2 (0.13)	4 (0.13)
2+	975 (67.8)	1063 (68.9)	2038 (68.3)
Any immunity (prior infection or any vaccine), No./total (%)	1170/1401 (83.5)	1252/1505 (83.2)	2422/2906 (83.3)
Days between symptom onset and receipt of drug, median (IQR)	5 (4–7)	5 (4–7)	5 (4–7)
Days between symptom onset and enrollment, median (IQR)	3 (2–5) [n = 1407]	3 (2–5) [n = 1509]	3 (2–5) [n = 2916]
Symptom burden on/before day of drug receipt,[e] No./total (%)			
None	67/1405 (4.8)	71/1508 (4.7)	138/2913 (4.7)
Mild	624/1405 (44.4)	675/1508 (44.8)	1299/2913 (44.6)
Moderate	668/1405 (47.5)	711/1508 (47.1)	1379/2913 (47.3)
Severe	46/1405 (3.3)	51/1508 (3.4)	97/2913 (3.3)
Use of remdesivir, No. (%)	1 (0.07)	0 (0.00)	1 (0.03)
Use of nirmatrelvir/ritonavir, No. (%)	204 (14.2)	229 (14.8)	433 (14.5)

Table 1. Continued

	Metformin (n = 1439)	Placebo (n = 1544)	Overall (n = 2983)
Use of monoclonal antibodies, No. (%)	31 (2.2)	43 (2.8)	74 (2.5)
Use of molnupiravir, No. (%)	10 (0.7)	13 (0.8)	23 (0.8)

Abbreviations: BMI, body mass index (kg/m^2); COPD, chronic obstructive pulmonary disease.

[a]Participants were presented with each of these options and may have selected any combination of the race descriptors, including "none of the above" and "prefer not to answer." Consequently, the sums of counts over all categories do not match the column totals.

[b]The following state groups define each region. Northeast includes Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, and Pennsylvania; Midwest includes Indiana, Illinois, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota; South includes Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, and Texas; West includes Arizona, Colorado, Idaho, New Mexico, Montana, Utah, Nevada, Wyoming, Alaska, California, Hawaii, Oregon, and Washington.

[c]Patients may have alternatively been recruited at local clinical sites.

[d]Medical history was provided by participants responding to the following prompts: "Has a doctor told you that you have any of the following?" "Have you ever experienced any of the following? (select all that apply)," and "Have you ever smoked tobacco products?".

[e]Each day, participants were asked, "Please choose the response that best describes the severity of your COVID-19 symptoms today.".

Table 2. Observed Counts and Percentage Points for PASC and Clinician Diagnosis of Long COVID

	Overall (n = 2983)	Metformin (n = 1439)	Placebo (n = 1544)
PASC, n (%)			
Day 90			
Yes	96 (3.2)	44 (3.1)	52 (3.4)
No	2335 (78.3)	1119 (77.8)	1216 (78.8)
Missing	552 (18.5)	276 (19.2)	276 (17.9)
Day 120			
Yes	101 (3.4)	40 (2.8)	61 (4.0)
No	2316 (77.7)	1119 (77.8)	1197 (77.5)
Missing	566 (19.0)	280 (19.5)	286 (18.5)
Day 180			
Yes	79 (2.7)	33 (2.3)	46 (3.0)
No	2311 (77.5)	1106 (76.9)	1205 (78.0)
Missing	593 (19.9)	300 (20.9)	293 (19.0)
Clinician diagnosis of long COVID, n (%)			
Day 120			
Yes	29 (0.97)	13 (0.90)	16 (1.04)
No	2387 (80.0)	1146 (79.6)	1241 (80.4)
Missing	567 (19.0)	280 (19.5)	287 (18.6)
Day 180			
Yes	26 (0.87)	8 (0.56)	18 (1.17)
No	2362 (79.2)	1130 (78.5)	1233 (79.9)
Missing	594 (19.9)	301 (20.9)	293 (19.0)

PASC was the primary endpoint: symptoms attributed to COVID-19 on day 180 or mortality. Of note, there were no deaths.

placebo group had been diagnosed with long COVID by day 180 (Supplementary Table 5), and 3.2% of the metformin group and 4.1% of the placebo group had PASC on day 180 (Supplementary Table 6). Posterior distributions are presented in Supplementary Figures 3–8. For the safety events of interest for metformin, there were no episodes of lactic acidosis. Six episodes of participant-reported hypoglycemia were reported, 2 in the metformin group and 4 in the placebo group.

DISCUSSION

This ACTIV-6 COVID-19 trial included low-risk, standard-risk, and high-risk adults, most of whom had prior vaccination and/or prior infection. Among this relevant sample of outpatient adults, the posterior probability that treatment with immediate-release metformin effectively prevents symptoms at 6 months was 0.83. This did not meet the 0.975 threshold for declaring efficacy in reducing PASC. Some secondary outcomes did have high posterior probabilities of efficacy, including 0.98 for symptom burden on day 120 and 0.96 for clinician diagnosis of long COVID on day 180.

In the context of other literature, the direction of these results is consistent with existing data on the use of metformin at the time of acute infection and subsequent development of PASC. For the death component of PASC, meta-analyses in adults with type 2 diabetes reported that prevalent metformin use

Table 3. Model-Based Estimate of the Treatment Effect on the Risk Difference Scale (Credible Interval) for the Primary and Secondary Outcomes

Outcome	Metformin (n = 1439)	Placebo (n = 1544)	Risk Difference, Percentage Points,[a] (95% CrI)[b]	Posterior P (efficacy)
Primary endpoint: PASC[c,d]				
Day 180	2.9% (2.0, 3.9)	3.6% (2.7, 4.7)	−0.8 (−2.2, 0.6)	0.83
Secondary time points				
Day 90	3.9% (2.9, 5.0)	4.3% (3.3, 5.5)	−0.3 (−1.9, 1.2)	0.66
Day 120	3.6% (2.5, 4.6)	4.7% (3.7, 5.9)	−1.1 (−2.7, 0.4)	0.93
PASC[d,e]				
Day 90	3.9% (2.8, 5.0)	4.1% (3.1, 5.3)	−0.3 (−1.9, 1.3)	0.63
Day 120	3.5% (2.5, 4.6)	4.8% (3.7, 6.0)	−1.2 (−2.8, 0.4)	0.94
Day 180	2.9% (2.0, 3.9)	3.6% (2.6, 4.6)	−0.7 (−2.1, 0.6)	0.85
Secondary endpoints:				
Clinician diagnosis of long COVID[d,e]				
Day 120	1.1% (0.6, 1.7)	1.2% (0.7, 1.9)	−0.1 (−1.0, 0.7)	0.63
Day 180	0.7% (0.3, 1.2)	1.4% (0.8, 2.1)	−0.7 (−1.5, 0.1)	0.96
Symptom burden, relative risk scale[e]	…	…	**Odds Ratio (95% CrI)[f]**	…
Day 90 (n = 2431)	…	…	0.90 (0.57, 1.34)	0.69
Day 120 (n = 2417)	…	…	0.65 (0.43, 0.95)	0.98
Day 180 (n = 2390)	…	…	0.86 (0.51, 1.32)	0.74

Abbreviations: Δ, risk difference; CrI, credible interval; *P*, probability; PASC, the primary endpoint was symptoms attributed to COVID-19 on day 180 or mortality. Of note, no deaths occurred.

[a]Treatment effect estimates derived from Bayesians model. Prior distributions for intercept terms were flat and noninformative. Prior distributions for covariate terms were weakly informative when included in the model with some degree of shrinkage. All outcomes are participant-reported.

[b]Unless otherwise noted, a highest-density credible interval is shown. Δ that is <0 is in the direction of benefit for metformin.

[c]Adjusted for covariates: age, body mass index, calendar date, sex, prior infection, duration of symptoms prior to treatment, vaccination status, geographic region (Northeast, Midwest, South, and West), baseline symptom burden, and an indicator for enrollment to a remote site using baseline characteristics for the full modified intention to treat cohort.

[d]Missing responses were handled using an observed data likelihood.

[e]Not covariate adjusted.

[f]Odds ratio <1.0 favors metformin.

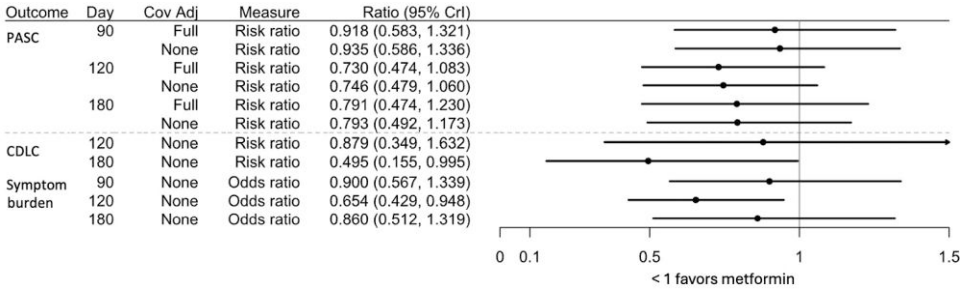

Figure 2. Relative differences in long COVID outcomes among those receiving metformin or placebo during acute COVID illness. The rows for PASC and independent, blinded clinician diagnosis of long COVID display the relative risk calculated from Bayesian models of the respective longitudinal outcomes using all available outcome and covariate data. Missing outcome data was handled with the complete data likelihood. Prior distributions for the intercept were noninformative and were weakly informative for all other parameters. Full covariate adjustment included the following covariates: age, body mass index, calendar date, sex, prior infection, duration of symptoms prior to treatment, vaccination status, geographic region (Northeast, Midwest, South, and West), baseline symptom burden, and an indicator for enrollment to a remote site, from the full modified intention to treat sample. The rows for symptom burden report the odds ratios at each time point, calculated from Bayesian proportional odds ordinal outcome models using the subset of participants who responded to the survey for the day in question. Symptom burden is an ordinal outcome with none, mild, moderate, and severe as possible responses. An odds ratio less than 1.0 indicates a treatment benefit for metformin. All outcomes are participant-reported. Abbreviations: CDLC, clinician-diagnosed long COVID; CrI, credible interval; PASC, the primary endpoint was symptoms attributed to COVID-19 on day 180 or mortality, of note there were no deaths observed.

was associated with an approximately 35% lower risk [15, 16]. Among medications administered to nursing home residents, verified by bar-code, in the Veterans Health Administration, metformin was associated with a hazard ratio of 0.48 (95% confidence interval [CI] 0.28–0.84) [17]. Another Veterans Health Administration analysis reported a relative risk of 0.33 (95% CI 0.25–0.43) for metformin use, similar to a prospective cohort in adults with type 2 diabetes [18, 19]. These studies reflect a time in the pandemic when mortality was higher, before the availability of vaccines, therapeutics, and prior immunity.

For the long COVID component of PASC, observational studies of prevalent metformin use for type 2 diabetes have reported a hazard ratio of 0.72 (95% CI 0.67–0.77) when long COVID was ascertained using natural language processing and a hazard ratio of 0.79 (95% CI 0.71–0.88) when long COVID was ascertained using the electronic health record diagnosis code; and an odds ratio of 0.32 (0.13 to 0.73) when long COVID was prospectively ascertained with participant-reported surveys [20–22].

In adults without type 2 diabetes, a sequential target trial emulation found a hazard ratio of 0.36 (95% CI 0.32–0.41) for metformin preventing long COVID, ascertained by diagnosis code or symptoms in the electronic health record [23]. A new-user, active-comparator target trial emulation reported a hazard ratio of 0.47 (95% CI 0.25–0.89) for metformin prescribed within a week of infection preventing long COVID, defined using diagnosis code or computable phenotype [24]. In the COVID-OUT randomized trial, the hazard ratio for clinician diagnosis of long COVID in those randomized to metformin was 0.59 (95% CI 0.39–0.89), using the same 14-day dose regimen as the ACTIV-6 trial reported herein [11].

In ACTIV-6, the presence of symptoms and incidence of clinician diagnoses of long COVID on day 180 were lower than these observational and prospective studies, likely indicating a favorable evolution of COVID-19 severity. A lower incidence of long COVID may be due to prior immunity, as ACTIV-6 is unique in that persons with prior infection were eligible. Additionally, most participants were enrolled when the JN-1 variant dominated, which was a variant with higher infectivity but lower morbidity than previous and subsequent variants [25–29]. The symptom burden for JN-1 also appears lower as the median days to sustained recovery was 9 for metformin (95% CI 9–10) and 10 for placebo (95% CI 9–10) but ranged from 10 to 14 in active and placebo groups during previous variants on the ACTIV-6 platform [30–35].

A consistent mechanistic finding is that SARS-CoV-2 activates the mammalian target of rapamycin (mTOR) complex 1, which can decrease the epithelial barrier function in the gut [36–38]. Dysfunctional gut epithelium has been implicated in long COVID via dysregulated signaling to the brain [39]. Decreased epithelial barrier function may explain findings that decreased short-chain fatty acid (SCFA)-producing bacteria strongly correlate with long COVID [40–43]. Decreased epithelial function can mean harmful proteins from the gut cause disease over time [44]. This could explain why some develop long COVID after a symptom-free period and potentially why the total number of participants reporting symptoms was higher at day 120 than day 90 in this trial. Metformin can inhibit mTOR in the gut and increase the relative abundance of SCFA-producing bacteria, actions that might be protective during acute infection to prevent long-term morbidity [45–47]. During acute infection, metformin has been associated with favorable levels of interleukin-6, lymphocytes, and the open reading from 1ab gene cycle threshold [48].

This is the first phase 3 trial to randomize adults without chronic disease or increased BMI to metformin, and there was no concern for hypoglycemia or lactic acidosis.

LIMITATIONS

This study does have limitations. It is possible that the COVID-19 symptoms that participants reported on day 90, 120, or 180 were long COVID symptoms that preceded their enrollment in ACTIV-6. The proportion of missing data for the primary and secondary outcomes was around 20% in this long-term follow-up. Metformin has antiviral actions, and enrollment of participants was later in the course of infection than other outpatient trials [9, 49, 50]. The lower overall incidence of symptoms may also be due to the ACTIV-6 survey only capturing symptoms on the day of the survey because symptoms can be intermittent. Beyond the events of special interest (lactic acidosis and medically diagnosed hypoglycemia), ACTIV-6 did not assess tolerability, although the same dose of metformin was well tolerated in the COVID-OUT trial [51].

CONCLUSIONS

This was a phase 3 trial of outpatient COVID-19 treatment in a relevant population for the current evolution of the pandemic: low-risk adults with a high degree of immunity from vaccination and prior infection. Metformin did not exceed the primary outcome threshold for declaring efficacy for reducing PASC. The posterior PPE for metformin was high for preventing a clinician diagnosis of long COVID and for symptom burden, consistent with prior clinical trial and observational data. No safety concerns occurred in this trial of metformin in low-risk adults. While a low event rate makes it challenging to evaluate therapeutics, it is encouraging that the proportion of participants reporting new clinician diagnosis of long COVID at 6 months was low.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. Drs Naggie, Hernandez, and Lindsell had full access to all the blinded data in the study. Dr Stewart was provided curated study data and takes responsibility for the integrity of the data analysis. All authors contributed to the drafting and review of the manuscript and agreed to submit for publication.

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