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Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19

Carolyn T. Bramante, M.D., M.P.H.,
Jared D. Huling, Ph.D.,
Christopher J. Tignanelli, M.D.,
John B. Buse, M.D., Ph.D.,
David M. Liebovitz, M.D.,
Jacinda M. Nicklas, M.D., M.P.H.,
Kenneth Cohen, M.D.,
Michael A. Puskarich, M.D.,
Hrishikesh K. Belani, M.D., M.P.H.,
Jennifer L. Proper, B.S.,
Lianne K. Siegel, Ph.D.,
Nichole R. Klatt, Ph.D.,
David J. Odde, Ph.D.,
Darlette G. Luke, Pharm.D.,
Blake Anderson, M.D.,
Amy B. Karger, M.D., Ph.D.,
Nicholas E. Ingraham, M.D.,
Katrina M. Hartman, B.A.,
Via Rao, M.S.,
Aubrey A. Hagen, B.A.,
Barkha Patel, M.S.,
Sarah L. Fenno, M.P.H.,
Nandini Avula, B.S.,
Neha V. Reddy, B.S.,
Spencer M. Erickson, B.A.,
Sarah Lindberg, M.P.H.,
Regina Fricton, B.A.,
Samuel Lee, B.S.,
Adnin Zaman, M.D.,
Hanna G. Saveraid,

*The members of the COVID-OUT trial team are listed in the Supplementary Appendix, available at NEJM.org.

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Walker J. Tordsen, B.A.,
Matthew F. Pullen, M.D.,
Michelle Biros, M.D.,
Nancy E. Sherwood, Ph.D.,
Jennifer L. Thompson, M.D.,
David R. Boulware, M.D., M.P.H.[#],
Thomas A. Murray, Ph.D.[#],
COVID-OUT Trial Team[*]

Departments of Medicine (C.T.B., N.E.I., K.M.H., A.A.H., B.P., S.L.F., N.A., N.V.R., S.M.E., H.G.S., M.F.P., D.R.B.) and Surgery (C.J.T., N.R.K.), Emergency Medicine (M.A.P., M.B.), and Laboratory Medicine and Pathology (A.B.K.), Medical School, the Divisions of Biostatistics (J.D.H., J.L.P., L.K.S., V.R., S. Lindberg, T.A.M.) and Epidemiology and Community Health (N.E.S.), School of Public Health, and the Department of Biomedical Engineering (D.J.O.), University of Minnesota, the Department of Emergency Medicine, Hennepin County Medical Center (M.A.P., W.J.T., M.B.), and the Investigational Drug Service Pharmacy, University of Minnesota–Fairview (D.G.L.), Minneapolis, and UnitedHealth Group, Optum Labs, Minnetonka (K.C.) — all in Minnesota; the Department of Medicine, School of Medicine, University of North Carolina, Chapel Hill (J.B.B.); the Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago (D.M.L., R.F., S. Lee); the Department of Medicine, School of Medicine, University of Colorado–Anschutz Medical Campus, Aurora (J.M.N., A.Z.); the Department of Medicine, Olive View–University of California, Los Angeles (H.K.B.); Atlanta Veterans Affairs Medical Center and the Department of Medicine, Emory University School of Medicine — both in Atlanta (B.A.); and the Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville (J.L.T.).

[#] These authors contributed equally to this work.

Abstract

BACKGROUND—Early treatment to prevent severe coronavirus disease 2019 (Covid-19) is an important component of the comprehensive response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic.

METHODS—In this phase 3, double-blind, randomized, placebo-controlled trial, we used a 2-by-3 factorial design to test the effectiveness of three repurposed drugs — metformin, ivermectin, and fluvoxamine — in preventing serious SARS-CoV-2 infection in nonhospitalized adults who had been enrolled within 3 days after a confirmed diagnosis of infection and less than 7 days after the onset of symptoms. The patients were between the ages of 30 and 85 years, and all had either overweight or obesity. The primary composite end point was hypoxemia (≤93% oxygen saturation on home oximetry), emergency department visit, hospitalization, or death. All analyses used controls who had undergone concurrent randomization and were adjusted for SARS-CoV-2 vaccination and receipt of other trial medications. CoV-2 vaccination and receipt of other trial medications.

RESULTS—A total of 1431 patients underwent randomization; of these patients, 1323 were included in the primary analysis. The median age of the patients was 46 years; 56% were female

(6% of whom were pregnant), and 52% had been vaccinated. The adjusted odds ratio for a primary event was 0.84 (95% confidence interval [CI], 0.66 to 1.09; P = 0.19) with metformin, 1.05 (95% CI, 0.76 to 1.45; P = 0.78) with ivermectin, and 0.94 (95% CI, 0.66 to 1.36; P = 0.75) with fluvoxamine. In prespecified secondary analyses, the adjusted odds ratio for emergency department visit, hospitalization, or death was 0.58 (95% CI, 0.35 to 0.94) with metformin, 1.39 (95% CI, 0.72 to 2.69) with ivermectin, and 1.17 (95% CI, 0.57 to 2.40) with fluvoxamine. The adjusted odds ratio for hospitalization or death was 0.47 (95% CI, 0.20 to 1.11) with metformin, 0.73 (95% CI, 0.19 to 2.77) with ivermectin, and 1.11 (95% CI, 0.33 to 3.76) with fluvoxamine.

CONCLUSIONS—None of the three medications that were evaluated prevented the occurrence of hypoxemia, an emergency department visit, hospitalization, or death associated with Covid-19. (Funded by the Parsemus Foundation and others; COVID-OUT ClinicalTrials.gov number, NCT04510194.)

Widely available early outpatient treatments for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are still needed to prevent severe coronavirus disease 2019 (Covid-19) owing to waning vaccine efficacy and the emergence of new variants.[1–3] Access to current outpatient therapeutics remains limited, serious drug–drug interactions may prevent use, and the effectiveness of monoclonal antibodies is challenged by viral evolution.[4–7]

Medications filling this need may include metformin, ivermectin, and fluvoxamine on the basis of biophysical modeling, which predicted that protein translation may be an antiviral therapy target. Previous studies have shown that metformin has actions against proteins involved in translation.[8,9] In addition, metformin is under investigation as an antiviral agent[10,11] and has shown in vitro activity against SARS-CoV-2 and other RNA viruses.[12–15] Metformin has also shown antiinflammatory actions, including reducing levels of interleukin-1β and interleukin-6 and decreasing the risk of thrombosis and inflammasome activation;[16,17] the drug has also shown protection against lipopolysaccharide-induced lung injury in mice inoculated with SARS-CoV-2.[18] Observational studies have shown associations between the use of metformin and less severe Covid-19 in patients who were already receiving metformin.[19–24]

Ivermectin has shown in vitro activity against SARS-CoV-2 but at levels that were 50 to 100 times as high as those that are achievable in humans.[25,26] In a small, randomized trial involving 398 volunteers, investigators assessed the use of ivermectin at a dose of 300 μg per kilogram of body weight per day for 5 days and found no effect on symptom resolution, although the study population was young and had few coexisting illnesses.[27] The ongoing use of ivermectin, possibly because of concern that the evaluated dose was too low, has suggested the need for more data.

Fluvoxamine has antiinflammatory actions that are mediated by the sigma-1 receptor,[28] and the same biophysical model predicted that fluvoxamine would perturb sigma-1 receptor–mediated virion assembly as viral proteins transfer from the cytoplasm to the endoplasmic reticulum.[8] Two randomized trials of fluvoxamine at a dose of 100 mg two or three times per day showed a reduction of approximately 25% in hospitalizations or prolonged acute care visits[29–31]; however, starting fluvoxamine at 100 mg can cause side effects. In a

nonrandomized prospective cohort study, investigators found that fluvoxamine at a dose of 50 mg twice daily may be effective and had a better side-effect profile than the 100-mg dose, which suggested a need to study the lower dose.[32]

We conducted COVID-OUT, a phase 3, randomized, double-blind, placebo-controlled trial, using a 2-by-3 factorial design to test these three oral, generic medications for early outpatient treatment of SARS-CoV-2 infection. We hypothesized that each medication would prevent progression to severe Covid-19.

METHODS

TRIAL DESIGN AND PATIENTS

This was an investigator-initiated clinical trial conducted at six institutions in the United States. On December 30, 2020, we began the enrollment of patients to evaluate metformin as compared with placebo. In the portion of the trial involving the 2-by-3 factorial design, enrollment began on May 21, 2021. The original randomization of patients to receive either metformin or placebo continued for all pregnant women. All the trial patients were recruited remotely, and trial drugs were delivered to the patients at home. Enrollment ended on January 28, 2022.

Follow-up for the primary end point in the last patients who were enrolled ended on February 14, 2022, during which time all the investigators except the statistician remained unaware of group-level results. The investigators continue to remain unaware of individual-level treatment assignments because follow-up assessments of long Covid-19 are ongoing. Details regarding the trial design are provided in the protocol, available with the full text of this article at NEJM.org.

Eligibility criteria included an age of 30 to 85 years; a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) associated with overweight or obesity; proof of SARS-CoV-2 infection within the past 3 days; and an onset of symptoms within 7 days before randomization. Details regarding the inclusion and exclusion criteria and BMI values are provided in the Supplementary Appendix, available at NEJM.org. All the patients provided written informed consent.

RANDOMIZATION

The patients underwent randomization with equal probability of assignment to each trial group that was recruiting at the time of enrollment. The six trial groups were assigned to receive the following drugs or combinations of drugs: group 1, metformin plus fluvoxamine; group 2, metformin plus ivermectin; group 3, metformin plus placebo; group 4, placebo plus fluvoxamine; group 5, placebo plus ivermectin; and group 6, placebo plus placebo. The main effect of each medication in the trial was assessed while controlling for the effects of other medications in the trial. Randomization was stratified according to trial site, and schedules were pregenerated by means of a mass-weighted urn design that limits deviations from the targeted equal allocation similar to permuted blocks. Details regarding the randomization procedures are provided in the Supplementary Appendix.

TREATMENT

The groups received the trial drugs according to the following doses: immediate-release metformin administered with an increase in dose over 6 days to 1500 mg per day for 14 days, ivermectin at a dose of 390 to 470 μg per kilogram per day for 3 days, and fluvoxamine at a dose of 50 mg twice daily for 14 days. For the analysis, the metformin group included the patients who had received metformin alone or metformin in combination with either fluvoxamine or ivermectin. The metformin control group included the patients who had received placebo, fluvoxamine alone, or ivermectin alone. The ivermectin group included the patients who had received ivermectin alone or ivermectin in combination with metformin. Patients in the ivermectin control group were randomly assigned to receive either placebo or metformin alone. The fluvoxamine and fluvoxamine control groups were constructed similarly. The control groups that were used in the comparisons with the active-drug groups included only concurrently randomly assigned patients.

All the patients who were not pregnant and who had been enrolled after the trial had been expanded to include ivermectin and fluvoxamine received two blinded trial drugs that were prepacked into a pillbox. Although groups 1 and 2 (metformin in combination with either fluvoxamine or ivermectin) were the only groups with two active medications, all the patients received two types of pills to maintain the blinding and have a similar pill burden in each group.

End Points

The primary end point was severe Covid-19 through 14 days, defined as a composite of hypoxemia (≤93% oxygen saturation on home oximetry), emergency department visit, hospitalization, or death. At the time that the investigational new drug application was obtained for all the trial drugs, primary end points were typically assessed at 14 days in Covid-19 treatment trials.[31,33] Hypoxemia was defined as a home oximeter reading of 93% or less or the need for supplemental oxygen to maintain an oxygen saturation of at least 94%. As so defined, hypoxemia was used as a marker of severe Covid-19, as previously defined by the Food and Drug Administration (FDA) and used in other Covid-19 trials.[34] The FDA later issued a safety communication on the accuracy of pulse oximeters after the trial began.[34] In addition, numerous patients recorded apparently spurious readings. (Details regarding sources of bias in the ascertainment of hypoxemia are provided in the Supplementary Appendix.) The statistical analysis plan prespecified the performance of secondary analyses, including an analysis that was limited to only the health care components of the primary end point. (FDA guidance recommends analyzing the components of a composite primary end point that are less common but indicate severe disease [in this case, emergency department visit, hospitalization, or death],[35] a method that has been commonly used in Covid-19 trials.)

Key secondary end points were daily symptom severity,[36] a modified total symptom score based on current standards for Covid-specific symptoms,[37] and drug discontinuations. The confidence intervals for secondary analyses were not adjusted for multiplicity, and each medication had its own hypothesized mechanism of action. Participants could opt into three optional substudies of biospecimens that were obtained on days 1, 5, and 10.[38]

OVERSIGHT

The trial was approved by the central institutional review board of consultant Advarra and was conducted in compliance with the provisions of the Declaration of Helsinki, Good Clinical Practice Guidelines, and local regulatory requirements.[39] The trial was funded by the Parsemus Foundation, Rainwater Charitable Foundation, Fast Grants, and UnitedHealth Group Foundation. The funders had no role in the design or conduct of the trial and were not involved in the collection or analysis of the data, in the writing of the manuscript, or in making the decision to submit the manuscript for publication. The authors assume responsibility for the fidelity of the trial to the protocol and for the accuracy and completeness of the data and analyses.

STATISTICAL ANALYSIS

We selected an enrollment target of 1350 patients to ensure the participation of 728 patients in the analysis cohorts for fluvoxamine and ivermectin, assuming a frequency of withdrawal of 10%. We determined that this sample size would provide 80% power to detect a 35% relative risk reduction in the active-drug group, assuming a 28% event rate in the control group and additive effects of each trial drug on the log-odds scale. We also determined that this enrollment target would provide at least 90% power to detect a 35% relative risk reduction with metformin under the same assumptions. The statistical power would be higher if the other trial drugs were not efficacious. A prespecified recalculation of the final overall enrollment target was conducted by the statistician in an unblinded manner on November 23, 2021, after a prespecified blinded review of interim event rates in the placebo group, according to baseline vaccination status and a lower-than-anticipated frequency of withdrawal.

Safety, efficacy, and futility were monitored by the members of an independent data and safety monitoring board who reviewed three full interim reports. Efficacy monitoring boundaries for each trial drug were calculated with the use of a Kim–DeMets alpha-spending function after control of the overall one-sided type I error rate at 0.025; futility monitoring guidelines were based on conditional power under the hypothesized effect. At the third interim review, after enrollment of approximately 1100 patients, the data and safety monitoring board recommended stopping fluvoxamine because of futility, with a conditional power of less than 3%.

The prespecified analysis in the modified intention-to-treat population excluded patients who had confirmed that they had not received any trial drug. This approach was informed by prior remote trials showing that 5 to 10% of participants who had provided consent had withdrawn before receiving trial materials.[33,40,41] The results in the intention-to-treat population are provided in Tables S6 to S8 in the Supplementary Appendix. The main effect of each trial drug on the primary end point was estimated with the use of logistic regression after adjustment for other trial-drug assignments and SARS-CoV-2 vaccination status. All analyses were performed with the use of concurrently randomized controls only.

The control group for each drug consisted of patients who had been enrolled when the trial drug had been available. Missing data for primary end points and vaccination status were

multiply imputed with the use of chained equations and predictive mean matching. Testing for statistical significance was based on a likelihood-ratio test; a two-sided P value of less than 0.05 was considered to indicate statistical significance.[42] There was no prespecified plan to adjust for multiple testing, so the results of secondary analyses are reported with point estimates and 95% confidence intervals without P values. The widths of the confidence intervals have not been adjusted for multiple testing and should not be used to infer definitive treatment effects.

We assessed symptom severity using generalized estimating equations after adjustment for baseline symptom severity, receipt of other trial medications, and SARS-CoV-2 vaccination status. Missingness of data in daily symptom logs was approximately 25% across symptoms and was not imputed. All analyses were performed with the use of R software, version 4.1.

RESULTS

PATIENTS

A total of 1431 patients were enrolled in the trial from December 30, 2020, through January 28, 2022. Of these patients, 108 (7.5%) were excluded from the modified intention-to-treat population, which left 1323 patients for inclusion in the primary analysis (Fig. 1). The median age of the patients was 46 years (interquartile range [IQR], 37 to 55); 741 (56.0%) were female, of whom 45 (6.1%) were pregnant. The median BMI was 30 (IQR, 27 to 34). The mean (±SD) number of days from symptom onset to the initiation of a trial drug was 4.8±1.9 days. Overall, 690 of the patients (52.2%) had received Covid-19 vaccination (Table 1).

END POINTS

A primary event (hypoxemia, emergency department visit, hospitalization, or death) occurred in 333 of 1305 patients with complete data (25.5%); of these patients, 134 of 686 (19.5%) were vaccinated, as compared with 199 of 615 (32.4%) who were were unvaccinated. The adjusted odds ratio for a primary event was 0.84 (95% confidence interval [CI], 0.66 to 1.09; P = 0.19) with metformin, 1.05 (95% CI, 0.76 to 1.45; P = 0.78) with ivermectin, and 0.94 (95% CI, 0.66 to 1.36; P = 0.75) with fluvoxamine.

The results of a prespecified secondary analysis that included the components of the primary end point are detailed in Table 2. The adjusted odds ratio for emergency department visit, hospitalization, or death was 0.58 (95% CI, 0.35 to 0.94) with metformin, 1.39 (95% CI, 0.72 to 2.69) with ivermectin, and 1.17 (95% CI, 0.57 to 2.40) with fluvoxamine. For hospitalization or death, the adjusted odds ratio was 0.47 (95% CI, 0.20 to 1.11) with metformin, 0.73 (95% CI, 0.19 to 2.77) with ivermectin, and 1.11 (95% CI, 0.33 to 3.76) with fluvoxamine.

We assessed the effect of the three drugs by a priori subgroups for the overall and more severe components of the primary composite end point (Figs. S1 and S2). Effects were consistent across subgroups, including according to vaccination history, variant period, and the presence or absence of pregnancy. Because hospitalization and death were rare, subgroups were not assessed again after sequential removal of the variable for the

emergency department visit. Through day 28, hospitalization or death occurred in 8 of 596 patients (1.3%) receiving metformin and in 19 of 601 controls (3.2%) (Figs. S7 and S8).

SYMPTOMS AND ADVERSE EVENTS

Patients were asked to circle the severity of daily symptoms in paper diaries during a period of 14 days. Neither overall symptoms nor Covid-19–specific symptoms were reduced faster with placebo than with any of the trial drugs (Fig. 2). Individual symptoms are provided in Figure S5. No medication-related serious adverse events occurred.

DISCUSSION

In this placebo-controlled clinical trial of metformin, ivermectin, and fluvoxamine for early outpatient treatment of SARS-CoV-2 infection, none of the three drugs had a significant effect on the composite primary end point of hypoxemia, emergency department visit, hospitalization, or death. A possible benefit for the prevention of the more severe components of the primary end point (emergency department visit, hospitalization, or death) was shown for metformin. However, this finding was a prespecified secondary end point and thus cannot be considered to be definitive pending the results of other trials.

In a previous clinical trial of metformin, investigators enrolled 421 adults during different waves of SARS-CoV-2 variants to evaluate whether extended-release metformin at a dose of 750 twice daily would convey benefit over placebo, including in patients who were already taking up to 1000 mg of immediate-release metformin for such conditions as diabetes, prediabetes, weight loss, polycystic ovarian syndrome, or nonalcoholic fatty liver disease.[43] The relative risk of hospitalization or a prolonged emergency department visit with metformin was 1.03 (95% Bayesian credible interval, 0.64 to 1.66). In this trial, patients started metformin at a dose of 1500 mg per day without dose adjustment, which may have caused side effects and discontinuations; in the per-protocol analysis, hospitalization occurred in 8 of 168 patients (4.8%) in the metformin group and in 14 of 179 patients (7.8%) in the control group.[43] A higher dose of metformin may not improve antiinflammatory actions, as suggested in a recent study of macular degeneration.[44] Also, immediaterelease metformin may have higher peak systemic exposure than the extended-release formulation, which may be relevant in SARS-CoV-2 infection.[45]

We did not find evidence that fluvoxamine at a low dose of 50 mg twice daily prevented a primary event in this population. In two randomized, double-blind, placebo-controlled trials, investigators found that higher-dose fluvoxamine (100 mg two to three times daily) resulted in a 25 to 30% reduction in hospitalization or a prolonged emergency department stay.[29] Because agonism of the sigma-1 receptor may be an important mechanism of fluvoxamine against Covid-19, the dose may need to be higher to produce an effect, especially in patients who have overweight or obesity.[46,47]

Likewise, we did not find evidence that ivermectin prevented a primary event in this population of U.S. adults who were 30 years of age or older and who had overweight or obesity. Because a previous randomized trial of ivermectin at a dose of 300 μg per kilogram per day did not show any significant effect, we chose a higher dose, a median of

430 μg per kilogram (range, 390 to 470 μg per kilogram) per day.[27] Ivermectin has been studied around the world, and the effect of ivermectin would be expected to be greater in patients with chronic *Strongyloides stercoralis* parasitic infection who had Covid-19 progression and received dexamethasone, thereby preventing life-threatening hyperinfection with strongyloides species. However, strongyloidiasis is rare in the United States outside of Appalachia.[48,49]

As in other fields of medicine, it appears that there may be a role for both repurposed generic medications as well as newly developed, targeted therapies. For example, in the field of obesity medicine, new agents (e.g., semaglutide) are used alongside repurposed generic medications, such as topiramate and bupropion, and even concurrently in the same patients. Previous studies have suggested that metformin improved the sustained virologic response of antiviral drugs against hepatitis C.[50] The proposed mechanisms of action against Covid-19 for metformin include antiinflammatory and antiviral activity and the prevention of hyperglycemia during acute illness. Further investigation is needed to determine whether any of these proposed mechanisms has any clinically meaningful activity in the treatment of Covid-19.

Our trial has several limitations. Since enrollment was limited to patients who were between 30 and 85 years of age and who had overweight or obesity in the United States (where the prevalence of overweight or obesity was >72% in 2018), the findings may not be generalizable beyond this population.[51] The percentage of patients who identified as Black or Latinx was smaller than that in the U.S. population, a discrepancy that is exacerbated among patients with Covid-19. The composite end point that included hypoxemia was defined before statements from the FDA pointed to accuracy problems with home oxygen monitors, especially nonprescription brands.[34] The hypoxemia component of the primary end point is the most susceptible to bias owing to inherent limits of oximetry to accurately detect and report oxygen saturation,[34] measurement error caused by cold hands or improper fit, misclassification caused by transient atelectasis-induced hypoxemia, and recall bias for hypoxemia reported by the patients (19%) without written documentation. A visit to an emergency department or hospitalization is more memorable and less susceptible to recall bias than a reduced oxygen level. Although we could objectively verify emergency department visits by medical record review, emergency department visits are influenced by the patient's willingness and ability to seek health care. Thus, hospitalization is perhaps the most accurate and well-documented end point, because objective criteria are necessary for admission.

Our loss to follow-up for the primary analysis was 1.4%, and the frequency of missing data regarding daily symptoms (21 to 24%) was similar to that in other remotely managed trials of Covid-19 treatments.[52] Due to the rarity of the hospitalization (2.0% overall) or mortality (0.2%), small numbers of missing unknown events could have affected the precision of estimates. Given the number of comparisons that were made by assessing a secondary outcome within subgroups, any suggestion of metformin activity in a subgroup should be interpreted with caution because there was no control for multiplicity. Finally, the factorial design that included trial drug groups that were open to enrollment during different waves of viral variants does not permit comparisons of marginal event rates between drugs, because

such rates may be confounded by temporal trends. Thus, all comparisons were performed against concurrent randomized controls.

In this randomized trial involving adults with overweight and obesity, none of the three trial drugs prevented a primary event of hypoxemia, emergency department visit, hospitalization, or death. The analysis of a prespecified secondary outcome suggested a possible reduction in a composite end point of emergency department visit, hospitalization, or death with metformin. None of the trial drugs resulted in a lower severity of symptoms than identically matched placebo.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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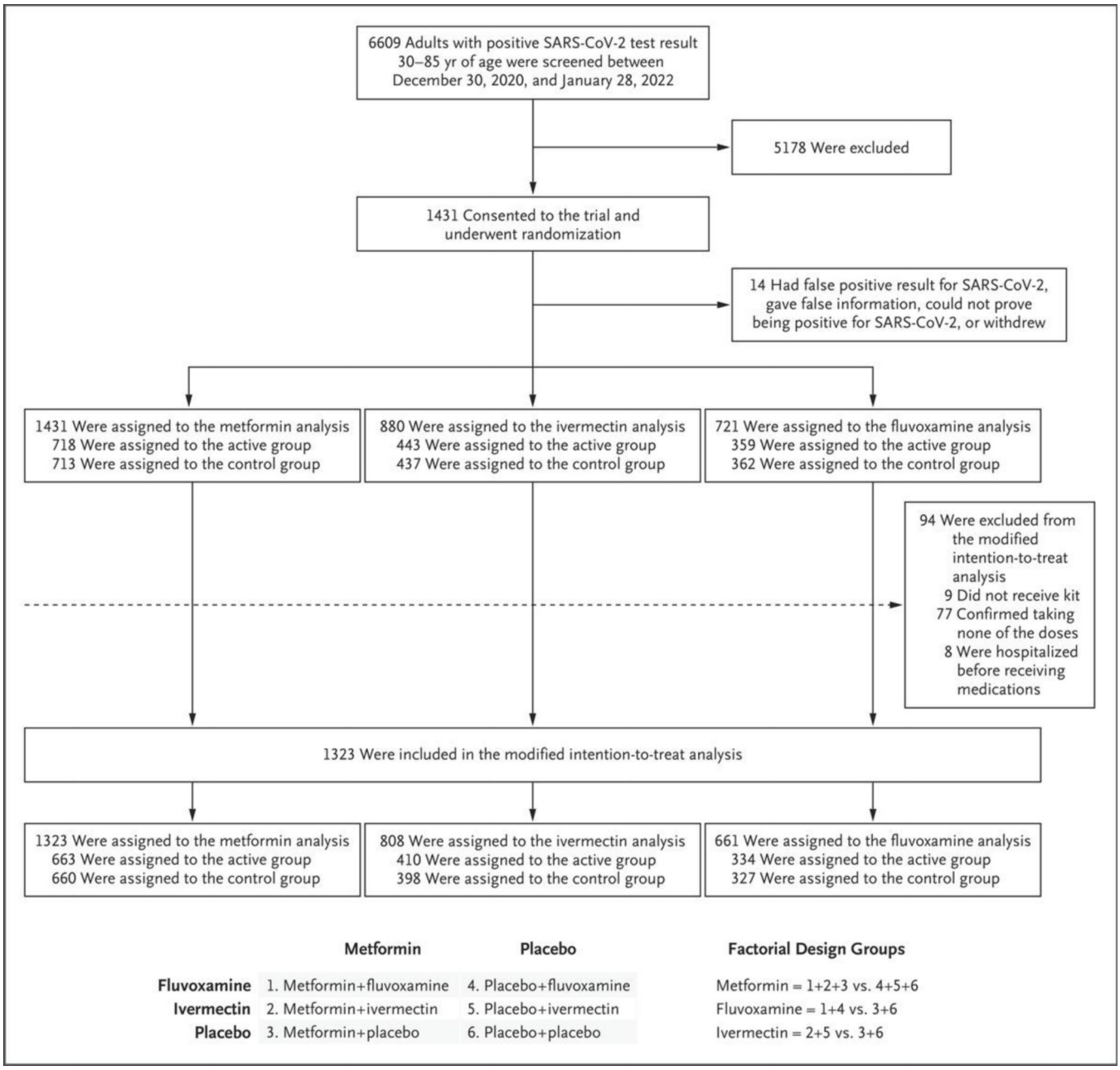

Figure 1. Enrollment and Factorial Design.

Shown is the 2-by-3 factorial design that was developed to test the effectiveness of three repurposed drugs — metformin, ivermectin, and fluvoxamine — in preventing serious coronavirus disease 2019 (Covid-19) in nonhospitalized adults. Although groups 1 and 2 were the only groups with two active drugs, all the patients received two types of pills to maintain the blind and have a similar pill burden in each group. The primary analysis was performed in the modified intention-to-treat population, which excluded patients who had confirmed that they had not received any trial drug. Details regarding the number of patients who were excluded from the trial are provided in the Supplementary Appendix.

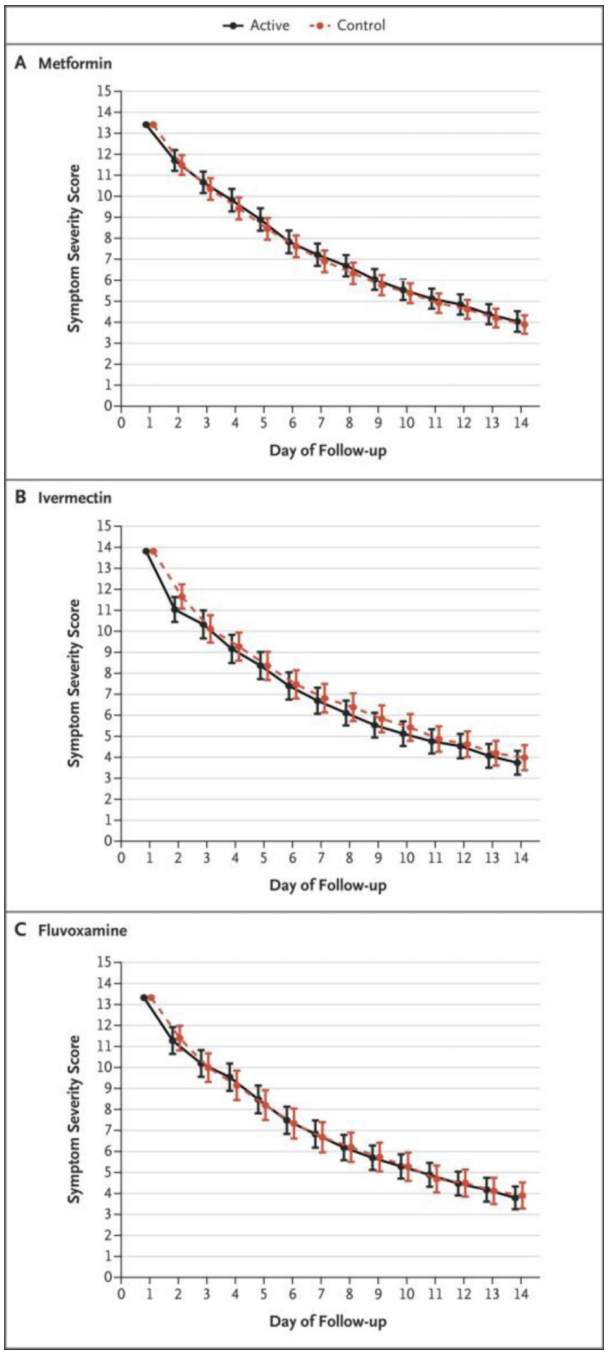

Figure 2. Total Scores on a Symptom Severity Scale during a 14-Day Period.

The three panels present the composite symptom scores in the active treatment groups and the control groups among the patients who received metformin, ivermectin, or fluvoxamine. Scores were calculated with the use of a generalized estimating equation after adjustment for the baseline score, vaccination status, and receipt of other medications during the trial. Shown on the y axis is the composite score of 14 symptoms, which were graded as none (0), mild (1), moderate (2), or severe (3). Overall, 80% of the patients contributed data on the symptom logs; the frequency of missing data was approximately 25% on each of the 14

days. Additional details regarding specific symptoms are provided in Figures S4 and S5 in the Supplementary Appendix.

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Table 1.

Characteristics of the Patients at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Metformin		Ivermectin		Fluvoxamine†	
	Active (N = 663)	Control (N = 660)	Active (N = 410)	Control (N = 398)	Active (N = 334)	Control (N = 327)
Demographic						
Median age (IQR) —yr	46 (38–55)	45 (37–55)	46 (39–55)	45 (37–56)	46 (38–53)	43 (37–53)
Female sex — no. (%)‡	359 (54.1)	382 (57.9)	216 (52.7)	226 (56.8)	170 (50.9)	188 (57.5)
Race or ethnic group§						
Native American	10 (1.5)	17(2.6)	7 (1.7)	9 (2.3)	8 (2.4)	9 (2.8)
Asian	25 (3.8)	26 (3.9)	19 (4.6)	18 (4.5)	9 (2.7)	12 (3.7)
Hawaiian or Pacific Islander	5 (0.8)	4 (0.6)	2 (0.5)	3 (0.8)	2 (0.6)	3 (0.9)
Black	55 (8.3)	45 (6.8)	30 (7.3)	29 (7.3)	28 (8.4)	23 (7.0)
White	545 (82.2)	546 (82.7)	340 (82.9)	322 (80.9)	272 (81.4)	267 (81.7)
Other	43 (6.5)	37 (5.6)	24 (5.9)	29 (7.3)	21 (6.3)	23 (7.0)
Latinx	76 (11.5)	84 (12.7)	41 (10.0)	57(14.3)	42 (12.6)	46 (14.1)
Medical history						
Body-mass index						
Median (IQR)	30 (27–34)	30 (27–34)	30 (27–34)	30 (27–34)	29 (27–34)	30 (27–34)
≥30 — no. (%)	316 (47.7)	330 (50.0)	194 (47.3)	189 (47.5)	155 (46.4)	157 (48.0)
Cardiovascular disease¶	178 (26.8)	175 (26.5)	94 (22.9)	90 (22.6)	104 (31.1)	74 (22.6)
Diabetes	10(1.5)	16 (2.4)	8 (2.0)	5 (1.3)	4 (1.2)	3 (0.9)
Primary series of vaccines	359 (54.1)	331 (50.2)	222 (54.1)	227 (57.0)	186 (55.7)	187 (57.2)
Symptom duration						
No. of days	4.8±1.9	4.8±1.9	4.6±l.9	4.8±1.8	5.0±2.2	4.7±1.8
≤4 days — no./total no. (%)	298/653 (45.6)	305/642 (47.5)	199/406 (49.0)	174/391 (44.5)	147/330 (44.5)	146/322 (45.3)
Predominant variant — no. (%)						
Alpha before 6/19/21	79 (11.9)	80(12.1)	11 (2.7)	11 (2.8)	12 (3.6)	11 (3.4)
Delta from 6/19/21 to 12/12/21	440 (66.4)	431 (65.3)	278 (67.8)	275 (69.1)	278 (83.2)	275 (84.1)
Omicron after 12/12/21	144 (21.7)	149 (22.6)	121 (29.5)	112 (28.1)	46 (14.0) ‖	41 (12.5)‖
Insurance status — no. (%)						
Medicaid	92 (13.9)	108 (16.4)	70 (17.1)	60 (15.1)	43 (12.9)	42 (12.8)

Characteristic	Metformin		Ivermectin		Fluvoxamine†	
	Active (N = 663)	Control (N = 660)	Active (N = 410)	Control (N = 398)	Active (N = 334)	Control (N = 327)
Medicare	52 (7.8)	48 (7.3)	27 (6.6)	31 (7.8)	27 (8.1)	21 (6.4)
Private	410 (61.8)	413 (62.6)	257 (62.7)	230 (57.8)	206 (61.7)	197 (60.2)
None	97 (14.6)	81 (12.3)	52 (12.7)	67 (16.8)	55 (16.5)	58 (17.7)

*Plus-minus values are means ±SD. IQR denotes interquartile range.

†A total of 6% of the women were pregnant during the trial.

‡Race or ethnic group was reported by the patients. The category of “other” included patients for whom data were not provided.

§Cardiovascular disease defined as hypertension, hyperlipidemia, coronary artery disease, past myocardial infarction, heart failure, pacemaker placement, arrhythmias or pulmonary hypertension.

¶Enrollment in the fluvoxamine group was stopped on January 7, 2022, by the data and safety monitoring board for a lack of conditional power.

Table 2.

Primary Composite End Point and Its Components.*

End Point	Metformin			Ivermectin			Fluvoxamine		
	Active (N = 663)	Control (N = 660)	Adjusted Odds Ratio (95% CI)†	Active (N = 410)	Control (N = 398)	Adjusted Odds Ratio (95% CI)†	Active (N = 334)	Control (N = 327)	Adjusted Odds Ratio (95% CI)†
	no./total no. (%)			*no. /total no. (%)*			*no./total no. (%)*		
Primary composite	154/652 (23.6)	179/653 (27.4)	0.84 (0.66–1.09)	105/407 (25.8)	96/391 (24.6)	1.05 (0.76–1.45)	79/329 (24.0)	80/321 (24.9)	0.94 (0.66–1.36)
Hypoxemia only	147/650 (22.6)	158/651 (24.3)	0.94 (0.72–1.22)	96/406 (23.6)	88/390 (22.6)	1.04 (0.75–1.46)	71/328 (21.6)	73/320 (22.8)	0.93 (0.64–1.35)
Emergency department visit, hospitalization, or death	27/652 (4.1)	48/655 (7.3)	0.58 (0.35–0.94)	23/406 (5.7)	16/394 (4.1)	1.39 (0.72–2.69)	18/329 (5.5)	15/324 (4.6)	1.17 (0.57–2.40)
Hospitalization or death	8/652 (1.2)	18/655 (2.7)	0.47 (0.20–1.11)	4/406 (1.0)	5/394 (1.3)	0.73 (0.19–2.77)	6/329 (1.8)	5/324 (1.5)	1.11 (0.33–3.76)
Death	1/657 (0.2)	0/655 (0)	NA	1/408 (0.2)	0/396 (0)	NA	0/330 (0)	0/325 (0)	NA

*The primary end point was a composite of hypoxemia (≤93% on home oximetry), emergency department visit, hospitalization, or death by 14 days. Analyses used concurrently randomized controls and were adjusted for SARS-CoV-2 vaccination and other trial medications. The primary analysis was performed in the modified intention-to-treat cohort. Comparison of absolute event rates across groups is not valid because of differences in timing of enrollment, which resulted in differences in vaccination rates and the prevalence of SARS-CoV-2 variants.

†Adjusted odds ratios and 95% confidence intervals are based on a logistic-regression model that was adjusted for baseline vaccination status and the receipt of other medications during the trial; multiple imputation was used with chained equations and predictive mean matching. The complete case-analysis results without imputation are provided in Table S4; the analysis in the intention-to-treat population is presented in Tables S6 to S8.