Table 7c. Metformin: Selected Clinical Trial Data

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The Panel's recommendations for metformin are based on data from the clinical trials described in this table.

Methods	Results	Limitations and Interpretation
TOGETHER: RCT of Metformin in Nonhospitalized Patients With COVID-19 in Brazil[1]		

Key Inclusion Criteria
• Aged ≥50 years or aged ≥18 years with ≥1 comorbidities
• Positive rapid antigen test result for SARS-CoV-2 infection
• ≤7 days of COVID-19 symptoms
Key Exclusion Criteria
• Acute respiratory symptoms that required hospitalization
• Receipt of a COVID-19 vaccine
Interventions
• Extended-release metformin 750 mg PO twice daily for 10 days (n = 215)
• Placebo PO twice daily for 10 days (n = 203)
Primary Endpoint
• Composite of ED observation >6 hours or hospitalization for COVID-19 by Day 28
Key Secondary Endpoints
• Clinical improvement by Day 28
• Viral clearance by Day 7
• Time to hospitalization or death
• Occurrence of AEs
• Study adherence
	Participant Characteristics
	• Median age 52 years; 57% women; 91% self-identified as mixed race
	• 45% with BMI ≥30; 40% with HTN; 15% with DM
	• 44% had COVID-19 symptoms for 0–3 days at enrollment
	Primary Outcome
	• Study was stopped early by DSMB for futility. At the time the study was stopped, primary endpoint had occurred in 16% in metformin arm vs. 14% in placebo arm (relative risk 1.14; 95% CI, 0.73–1.81; probability of superiority 28%).
	Secondary Outcomes
	• No difference between arms in:
	  • Clinical improvement by Day 28 (OR 1.05; 95% CI, 0.71–1.56)
	  • Viral clearance by Day 7 (OR 0.99; 95% CI, 0.88–1.11)
	  • Time to hospitalization or death ($P = 0.53$)
	  • Occurrence of treatment-emergent, grade 3 AEs: 9.8% in metformin arm vs. 4.4% in placebo arm (relative risk 2.11; 95% CI, 1.05–4.61)
	• Did not complete all phases of the study: 22% in metformin arm vs. 12% in placebo arm
		Key Limitations
		• The >6-hour ED observation endpoint has not been used in other studies of interventions for nonhospitalized patients who are at high risk of hospitalization and death.
		• Study was stopped early for futility.
		• Vaccinated individuals were excluded from trial.
		Interpretation
		• This trial demonstrated no clinical benefit of metformin in nonhospitalized patients with COVID-19.
		• The use of metformin was associated with more grade 3 AEs than placebo.

Methods	Results	Limitations and Interpretation
COVID-OUT: RCT of Metformin, Ivermectin, and Fluvoxamine in Nonhospitalized Adults With COVID-19 in the United States[2]		

Key Inclusion Criteria
• Aged 30–85 years
• BMI ≥25 or ≥23 if Asian or Latinx
• Laboratory-confirmed SARS-CoV-2 infection within 3 days of randomization
• ≤7 days of COVID-19 symptoms
Key Exclusion Criteria
• Immunocompromised
• Hepatic impairment
• Stage 4–5 chronic kidney disease or eGFR of <45 mL/min/1.73m^2
Interventions
• Immediate-release metformin 500 mg PO on Day 1, 500 mg twice daily on Days 2–5, and 500 mg in morning and 1,000 mg in evening on Days 6–14 (n = 663) in the following arms:
  • Metformin alone (n = 284)
  • Metformin plus IVM 390–470 µg/kg PO once daily for 3 days (n = 204)
  • Metformin plus fluvoxamine 50 mg PO twice daily for 14 days (n = 175)
• Control (n = 655), which included the following arms:
  • Placebo alone (n = 293)
  • IVM or fluvoxamine alone (n = 362)
Primary Endpoints
• Composite of hypoxemia (SpO_2 ≤93%, as measured by a home pulse oximeter), ED visit, hospitalization, or death by Day 14
• A prespecified secondary analysis evaluated the occurrence of ED visits, hospitalization, or death by Day 14.
	Participant Characteristics
	• Median age 46 years; 56% women; 82% White
	• Median BMI 30
	• 27% with CVD
	• 52% received primary COVID-19 vaccination series
	• Mean duration of symptoms was 4.8 days
	• Approximately 66% enrolled while Delta was the dominant variant; approximately 22% enrolled while Omicron was dominant
	Primary Outcomes
	• Composite of hypoxemia, ED visit, hospitalization, or death by Day 14: 154 (24%) in metformin arm vs. 179 (27%) in control arm (aOR 0.84; 95% CI, 0.66–1.09; *P* = 0.19)
	• No difference between metformin alone arm and placebo alone arm in occurrence of primary endpoint (aOR 0.91; 95% CI, 0.62–1.33)
	• ED visit, hospitalization, or death by Day 14 in a prespecified secondary analysis: 27 (4.1%) in metformin arm vs. 48 (7.3%) in control arm (aOR 0.58; 95% CI, 0.35–0.94)
	• Hospitalization or death by Day 14 in a prespecified secondary analysis: 8 (1.2%) in metformin arm vs. 18 (2.7%) in control arm (aOR 0.47; 95% CI, 0.20–1.11)
	Secondary Outcomes
	• No difference between arms in total symptom severity score by Day 14
	• Drug discontinuation or interruption: 29% in metformin arm vs. 25% in control arm
	• Hospitalization or death by Day 28: 8 of 596 (1.3%) in metformin arm vs. 19 of 601 (3.2%) in control arm
		Key Limitations
		• Analyses of secondary endpoints were not adjusted for multiple comparisons.
		• Study included SpO_2 measurements using home pulse oximeters as 1 of the composite measures of the primary endpoint. However, the FDA has issued a statement concerning the accuracy of these home pulse oximeters, making this study endpoint less reliable.
		Interpretation
		• The use of metformin did not prevent the occurrence of the primary composite endpoint of hypoxemia, ED visit, hospitalization, or death by Day 14.
		• Although the results of the prespecified secondary analyses of ED visits, hospitalization, or death by Day 14 and the secondary endpoint of hospitalization or death by Day 28 suggest a potential benefit of metformin, these results are not considered definitive.

Methods	Results	Limitations and Interpretation
COVID-OUT: RCT of Metformin, Ivermectin, and Fluvoxamine in Nonhospitalized Adults With COVID-19 in the United States[2], continued		
Key Secondary Endpoints • Total symptom severity score by Day 14, as measured by a symptom severity scale • Drug discontinuation or interruption • Hospitalization or death by Day 28		

Key: AE = adverse event; BMI = body mass index; CVD = cardiovascular disease; DM = diabetes mellitus; DSMB = data and safety monitoring board; ED = emergency department; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; HTN = hypertension; IVM = ivermectin; the Panel = the COVID-19 Treatment Guidelines Panel; PO = oral; RCT = randomized controlled trial; SpO_2 = oxygen saturation

References

1. Reis G, Dos Santos Moreira Silva EA, Medeiros Silva DC, et al. Effect of early treatment with metformin on risk of emergency care and hospitalization among patients with COVID-19: the TOGETHER randomized platform clinical trial. *Lancet Reg Health Am*. 2022;6:100142. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34927127.
2. Bramante CT, Huling JD, Tignanelli CJ, et al. Randomized trial of metformin, ivermectin, and fluvoxamine for COVID-19. *N Engl J Med*. 2022;387(7):599-610. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36070710.