Table 7c. Metformin: Selected Clinical Trial Data

Last Updated: October 10, 2023

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

Methods	Results	Limitations and Interpretation
COVID-OUT: RCT of Metformin, Ivermectin, and Fluvoxamine in Nonhospitalized Adults With COVID-19 in the United States[1]		

Key Inclusion Criteria
• Aged 30–85 years
• BMI ≥25 (≥23 if Asian or Latinx)
• Laboratory-confirmed SARS-CoV-2 infection
• ≤7 days of COVID-19 symptoms
Key Exclusion Criteria
• Immunocompromised
• Hepatic impairment
• Stage 4–5 chronic kidney disease or eGFR of <45 mL/min/1.73m²
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 = 660), which included the following arms:
  • Placebo alone (n = 293)
  • IVM or fluvoxamine alone (n = 367)
	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 those who received metformin alone vs. placebo alone 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)
		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 COVID-19–related 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[1]		
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 risk of ED visit, hospitalization, or death by Day 14 **Key Secondary Endpoints** • Total symptom score by Day 14, as measured by a symptom severity scale • Drug discontinuation or interruption • Hospitalization or death by Day 28	**Secondary Outcomes** • No difference between arms in total symptom 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	
TOGETHER: RCT of Metformin in Nonhospitalized Patients With COVID-19 in Brazil[2]		

Key Inclusion Criteria
• Aged ≥50 years or aged ≥18 years with at least 1 comorbidity
• 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 retention in ED for >6 hours or hospitalized for progression of COVID-19 by Day 28
	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 symptom onset within 0–3 days
	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)
		Key Limitations
		• The >6-hour ED retention endpoint has not been used in other studies of patients who are at high risk of hospitalization or 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
TOGETHER: RCT of Metformin in Nonhospitalized Patients With COVID-19 in Brazil[2], continued		
Key Secondary Endpoints • Clinical improvement by Day 28 • Viral clearance by Day 7 • Time to hospitalization or death • Occurrence of AEs • Study adherence	• Did not complete all phases of the study: 22% in metformin arm vs. 12% in placebo arm	

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. 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.
2. 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.