Outpatient treatment of Covid-19 with metformin, ivermectin, or fluvoxamine: 10-month follow-up and effects on developing Long Covid

NIH Pragmatic Trials Collaboratory

January 6, 2023

Carolyn Bramante, MD, MPH
Assistant Professor, General Internal Medicine
Principal Investigator, COVID-OUT

Thomas Murray, PhD
Assistant Professor, Biostatistics

Disclosures

- Donations:
  - Apotex donated fluvoxamine placebo
  - Edenbridge donated ivermectin and ivermectin placebo

- Funding:
  - The trial was funded by the Parsemus Foundation, Rainwater Charitable Foundation, Fast Grants, and the UnitedHealth Group Foundation.
  - Dr. Bramante funded by National Institutes of Health's National Center for Advancing Translational Sciences, grants KL2TR002492 and UL1TR002494; and the National Institute of Digestive, Diabetes, and Kidney diseases K23 DK124654.
  - Dr. Murray was a Medtronic faculty fellow.

- No financial disclosures

- Will be discussing off-label use of metformin, ivermectin, and fluvoxamine

Overview

- Overview of COVID-OUT Trial
  - Scientific rationale for these agents
  - Design, Study population
  - Results of acute Covid outcomes
- Overview of Long Covid Outcome
- Statistical Considerations
- Results
  - How these results Compare to other trials
  - New pre-clinical Data
  - New observational data
  - Viral load
- Review of metformin's safety
- Next Steps

COVID-OUT Trial: Early outpatient treatment to prevent severe COVID-19

Remotely delivered, de-centralized trial at 6 institutions

- Ivermectin* 390 - 470mcg/kg/day x 3 days, n=187
- Fluvoxamine 50mg BID, n=187
- Metformin titration to 1,500mg/day, n=187
- Metformin / Fluvoxamine, n=188
- Metformin / Ivermectin, n=188
- Placebo, n=187

Primary End Point was a binary 4-part composite endpoint:

1. Hypoxemia
2. ED visit
3. Hospitalization
4. Death

due to Covid-19 by Day 14

Secondary Endpoints:

Acute Covid (Days 1-28)
Primary by Day 28
Symptom severity

Long Covid
9-month follow-up after acute period

14 days of treatment (3 of ivermectin)
Daily symptom log, adherence log, and SpO2 log

Optional viral load and stool samples on Days 1, 5, 10

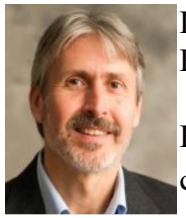
Optional baseline & follow-up blood samples via mobile phlebotomy

*6 weight categories.

Overview

- Overview of COVID-OUT Trial
  - Scientific rationale for these agents
  - Design, Study population
  - Results of acute Covid outcomes
- Overview of Long Covid Outcome
- Statistical Considerations
- Results
  - How these results Compare to other trials
  - New pre-clinical Data
  - New observational data
  - Viral load
- Review of metformin's safety
- Next Steps

Why Metformin? started with in silico modeling



David Odde, PhD
Professor of Biomedical Engineering

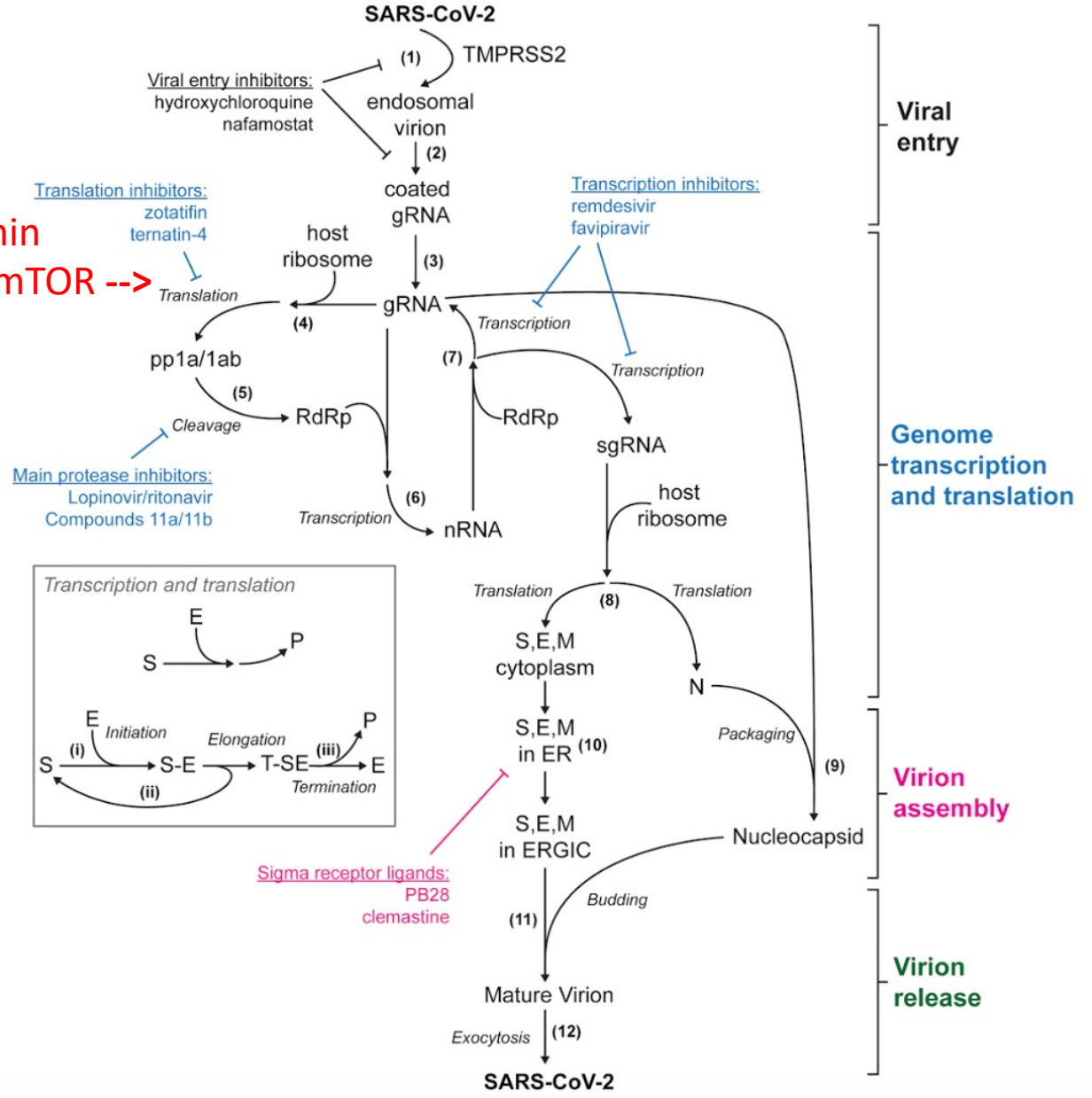
Early 2020 developed simulator on SARS-CoV-2 life cycle

Chris Tignanelli, MD MS
Department of Surgery, UMN

Natural language processing, Covid clinical trials
Learning Health System Scholar

Metformin inhibits mTOR -->

SARS-CoV-2 Antiviral Therapies	Model Prediction	NIH Panel Recommendations	Model Accuracy
Remdesivir	Effective	Recommended	Correct
Paxlovid	Effective	Recommended	Correct
Molnupiravir	Effective	Recommended	Correct
Hydroxychloroquine	Not Effective	Not Recommended	Correct
Chloroquine	Not Effective	Not Recommended	Correct
Lopinavir/Ritonavir	Not Effective	Not Recommended	Correct
Darunavir/Cobicistat	Not Effective	Not Recommended	Correct
Not addressed by our model: Interferons, Ivermectin, and Azithromycin			
Excluded due to unclear mechanism of action: Nitazoxanide			

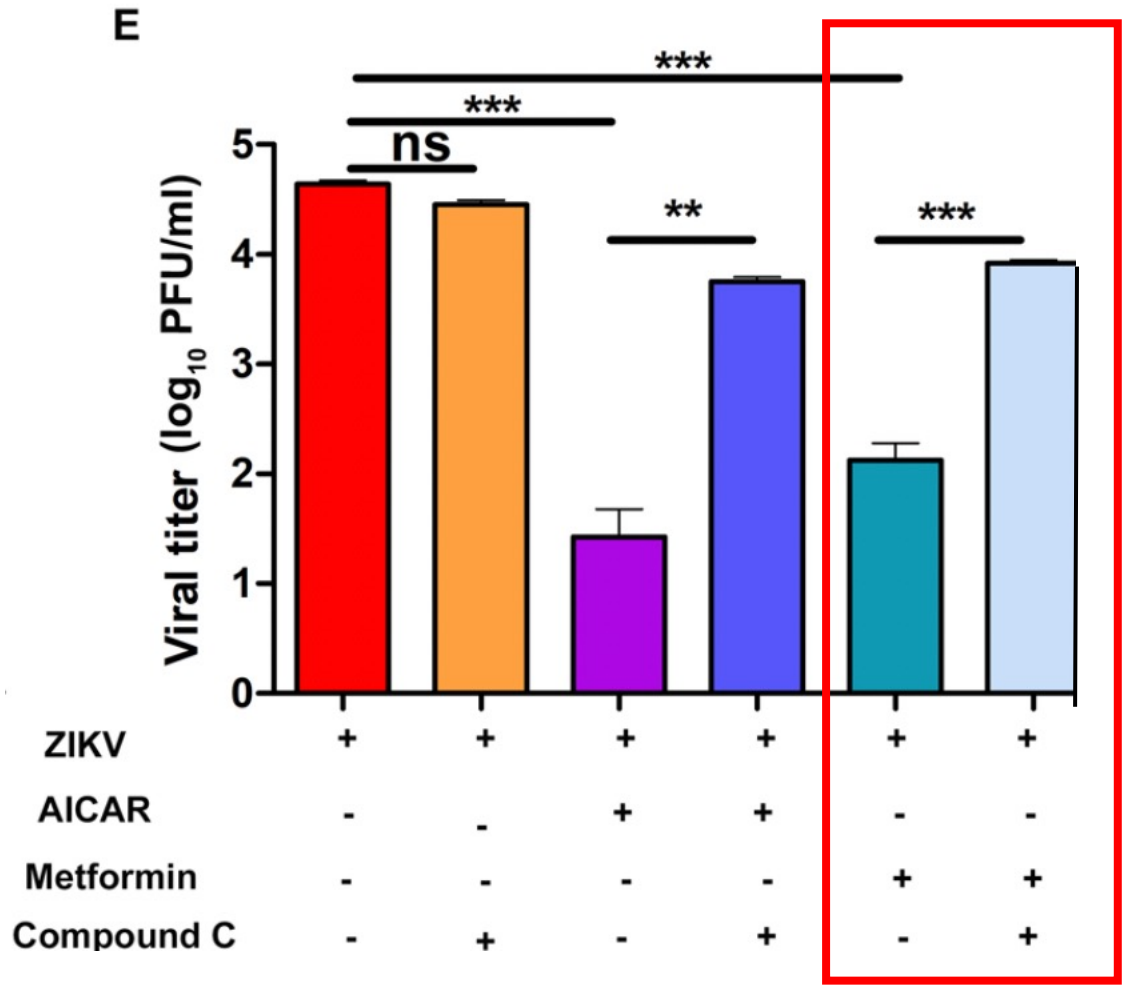


Metformin: initially an antiviral agent

- Discovered in 1922

- 1950s, studied in influenza
  - incidence of H3N2 influenza (5.4 vs 24%, p<0.001)
  - Other biguanides had safety issues
- 1990s FDA approved for diabetes
- 2000s anti-cancer interest
- 2010 anti-viral interest
- Infectious RCT's include: TB, dengue
  - Recent cohorts with improved influenza outcomes

In vitro activity against Zika (RNA virus)

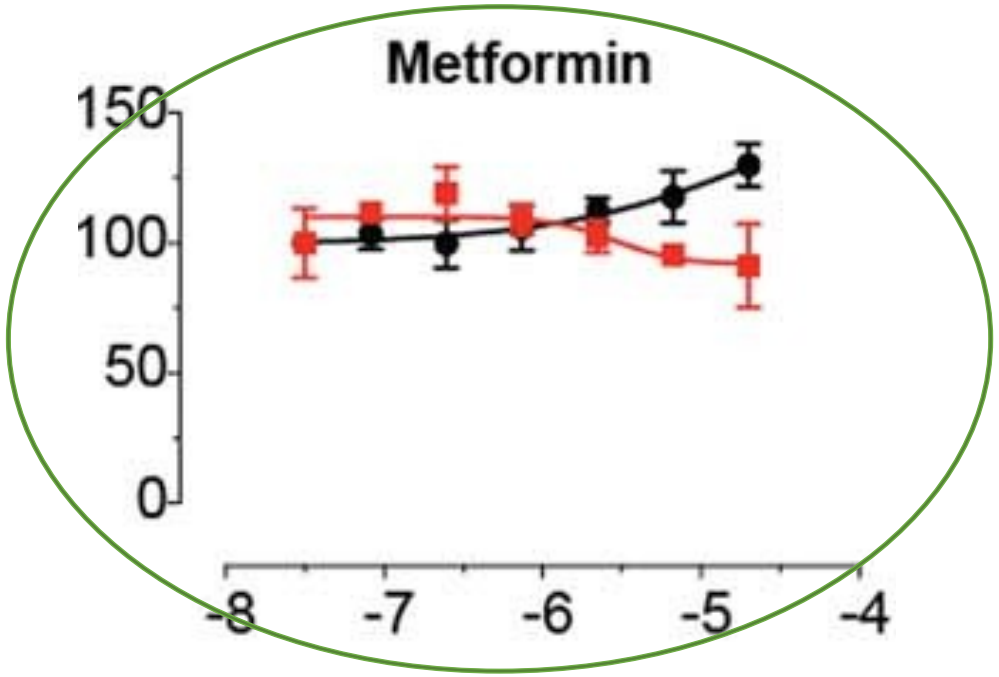


1. Garcia EY (1950) Flumamine, J Philippine Med Assoc 26:287–293
2. Bailey C. Metformin: historical overview. Diabetologia (2017)
3. Boominathan L, Combinatorial Antiviral Therapy (CAT): Metformin, the widely used drug in the treatment of TIIDM, inhibits Hepatitis-B/C, Dengue, Zika, Ebola, HIV-1, 2017
4. Fan Cheng, et ai. *Journal of Virology* Jan 2018,
5. Yu J-W, Sun L-J, Zhao Y-H, Kang P, Yan B-Z. The effect of metformin on the efficacy of antiviral therapy in patients with genotype 1 chronic hepatitis C and insulin resistance. *Int J of Infec Dis.* 2012;16(6):e436-e441.
7. Singh S, et al. AMP-Activated Protein Kinase Restricts Zika Virus Replication in *The Journal of Immunology.* 2020
8. Babinski, 1971

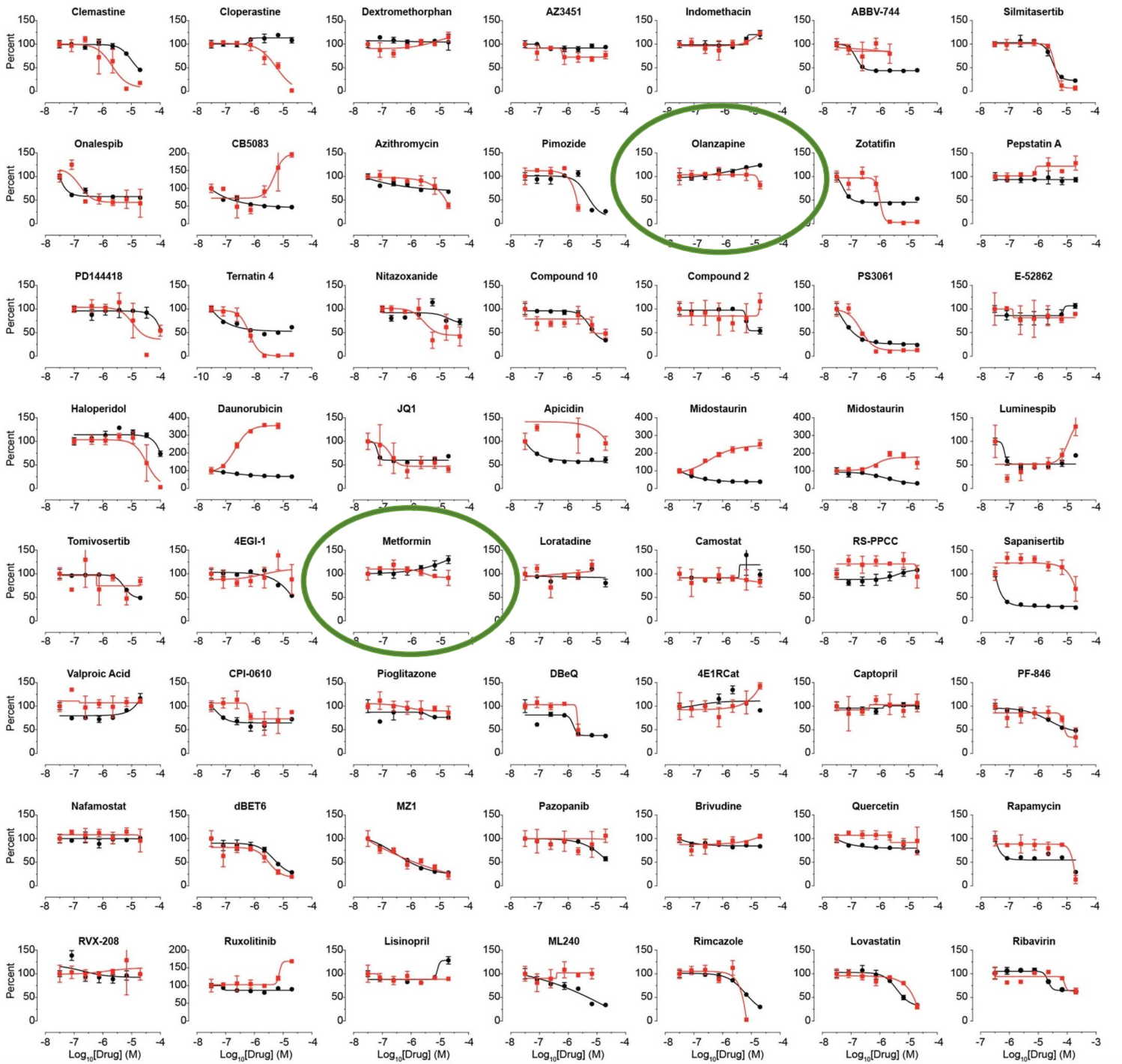
Metformin has in-vitro activity against SARS-CoV-2

Extended Data Fig. 8: Viral growth and cytotoxicity for compounds tested in New York

Viral growth (percentage infection; red) and cytotoxicity (black) results for compounds tested at Mount Sinai in New York. $TCID_{50}$ assay results (green) for zotatifin, hydroxychloroquine and PB28 are also shown. Zotafitin and midostaurin were tested in two independent experiments and data are shown in two individual panels. Data are mean ± s.d.; *n* = 3 biologically independent samples.



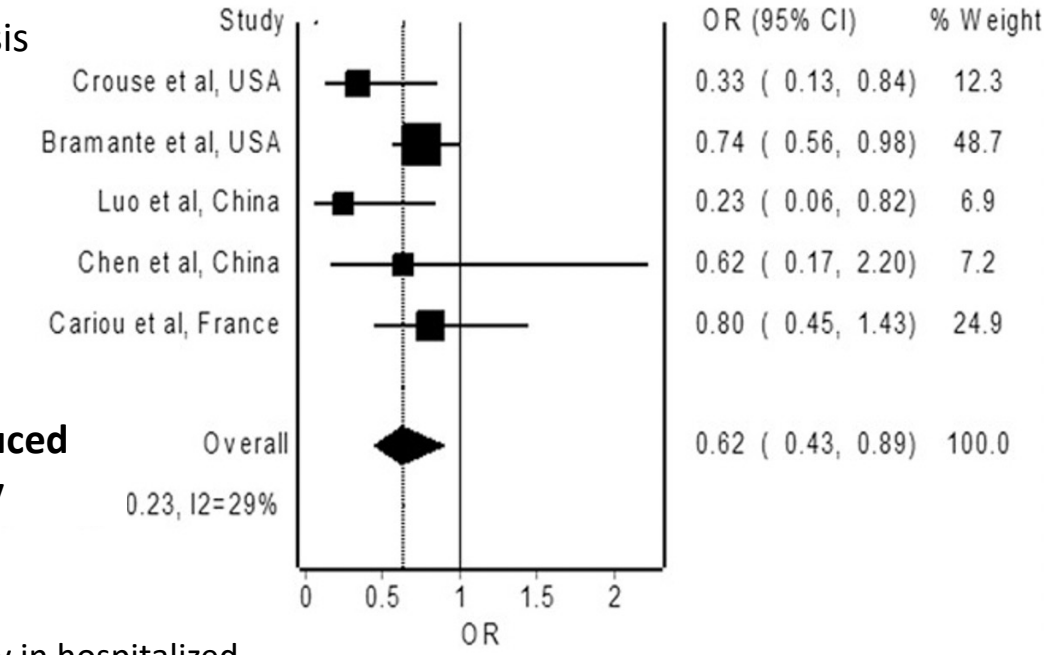
From Gordon et al, **A SARS-CoV-2 protein interaction map reveals targets for drug repurposing.** *Nature* 2020.



Observational analyses; potentially lower inflammation in Covid-19

Meta-analysis

Kow et al,
J Med Virol, 2021



38% reduced mortality

Forest Plot: Pooled risk of mortality in hospitalized COVID-19 patients with diabetes with or without preadmission metformin. (heterogeneity: I^2 = 29%; p = .23).
COVID-19, coronavirus disease 2019

Data in patients with Covid-19 showing favorable lab results	
Chen et al. *Diabetes Care,* 2020 Retrospective cohort adults with Type 2 DM	Metformin users had lower IL-6: 4.07 vs 11.1, p=0.02

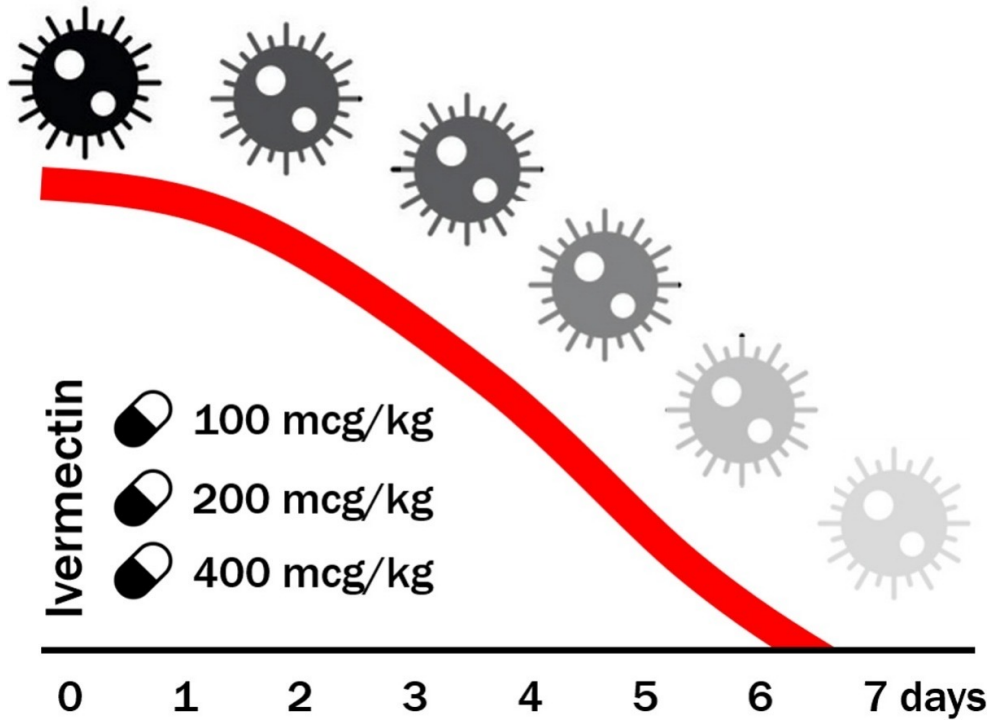
Initial Ivermectin data

Initial data suggested anti-viral activity of ivermectin, at high doses.

Combination treatment that included ivermectin suggested prevention of hospitalization.

A small double-blinded RCT suggested significant increased chance of viral clearance after a 5-day course of ivermectin.

Safe, orally administered, few contraindications, widely available.



-Portmann-Baracco A, Bryce-Alberti M, Accinelli RA. Antiviral and Anti-Inflammatory Properties of Ivermectin and Its Potential Use in COVID-19. *Arch Bronconeumol.* 2020;56(12):831.
-Lima-Morales R, Méndez-Hernández P, Flores YN, et al. Effectiveness of a multidrug therapy consisting of ivermectin, azithromycin, montelukast and acetylsalicylic acid to prevent hospitalization and death among ambulatory COVID-19 cases in Tlaxcala, Mexico. *International Journal of Infectious Diseases.* 2021.
-Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *International Journal of Infectious Diseases.* 2021;103:214-216.

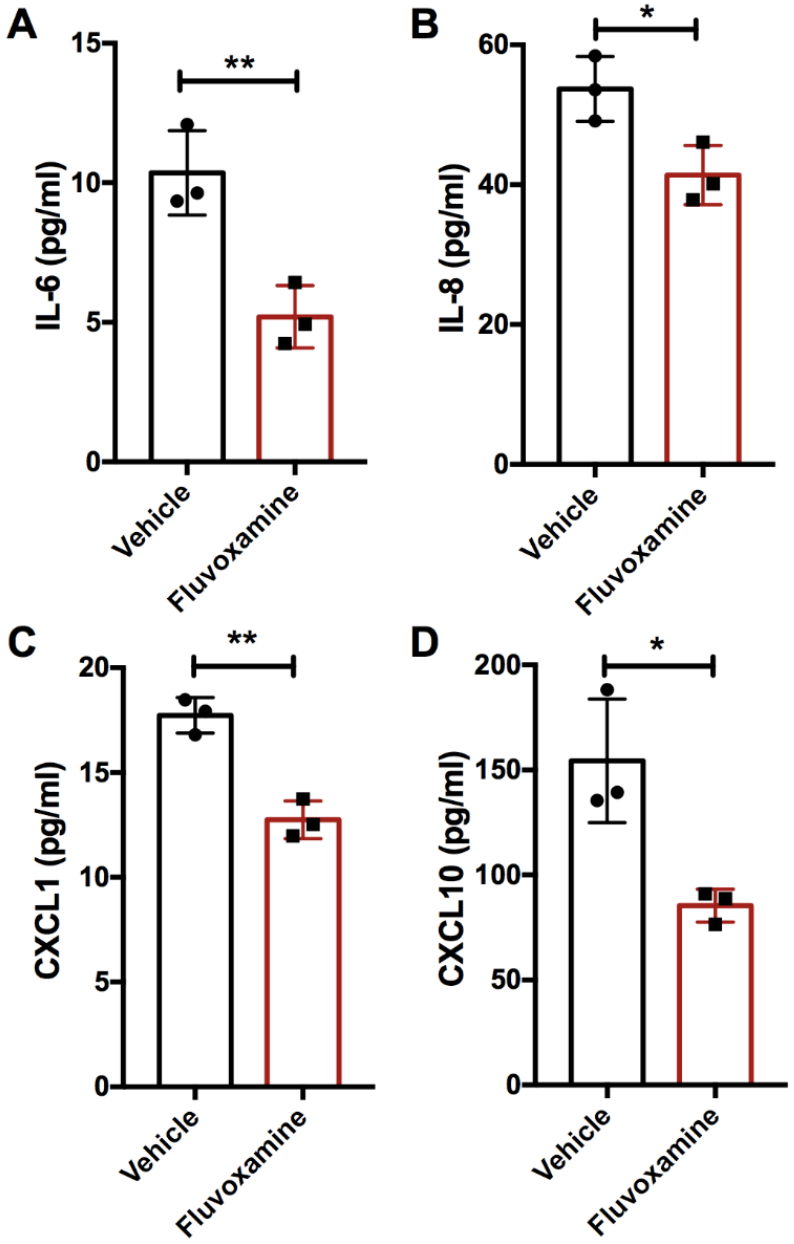
Fluvoxamine: In Vitro Anti-Inflammatory Action

CACO2 cells were infected with SARS-CoV-2 at **MOI of 0.01** in the **presence or absence of fluvoxamine.**

Fluvoxamine was able to block the production of a subset of cytokines/chemokines, including:

IL-6 IL-8 CXCL1 CXCL10

Possible Mechanism:
Activation of S1R with fluvoxamine may overcome Nsp6 inhibition of S1R to allow autophagy to clear SARS-CoV-2.



(Alban Gaultier, et al.)
Courtesy of Angela Reiersen, MD

Multi-arm trials of distinct treatments: no adjustment

- Do not adjust for multiplicity
- Factorial trials often publish each treatment separately
- Allows for presentation of the depth of results expected from phase 3 trials

Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial

*Janusz A Z Jankowski, John de Caestecker, Sharon B Love, Gavin Reilly, Peter Watson, Scott Sanders, Yeng Ang, Danielle Morris, Pradeep Bhandari, Claire Brooks, Stephen Attwood, Rebecca Harrison, Hugh Barr, Paul Moayyedi, the AspECT Trial Team**

Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial

Jozefien Declercq, Karel F A Van Damme*, Elisabeth De Leeuw*, Bastiaan Maes*, Cedric Bosteels*, Simon J Tavernier, Stefanie De Buyser, Roos Colman, Maya Hites, Gil Verschelden, Tom Fivez, Filip Moerman, Ingel K Demedts, Nicolas Dauby, Nicolas De Schryver, Elke Govaerts, Stefaan J Vandecasteele, Johan Van Laethem, Sebastien Anguille, Jeroen van der Hilst, Benoit Misset, Hans Slabbynck, Xavier Wittebole, Fabienne Liénart, Catherine Legrand, Marc Buyse, Dieter Stevens, Fre Bauters, Leen J M Seys, Helena Aegerter, Ursula Smole, Victor Bosteels, Levi Hoste, Leslie Naesens, Filomeen Haerynck, Linos Vandekerckhove, Pieter Depuydt, Eva van Braeckel, Sylvie Rottey, Isabelle Peene, Catherine Van Der Straeten, Frank Hulstaert, Bart N Lambrecht*

Parker RA, Weir CJ. Non-adjustment for multiple testing in multi-arm trials of distinct treatments: Rationale and justification. *Clinical Trials*. 2020;17(5):562-566. doi:10.1177/1740774520941419

Marine n−3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

JoAnn E. Manson, M.D., Dr.P.H., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., Sc.D., William Christen, Sc.D., Shari S. Bassuk, Sc.D., Samia Mora, M.D., M.H.S., Heike Gibson, Ph.D., Christine M. Albert, M.D., M.P.H., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedenberg, M.P.H., et al., for the VITAL Research Group*

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

JoAnn E. Manson, M.D., Dr.P.H., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., Sc.D., William Christen, Sc.D., Shari S. Bassuk, Sc.D., Samia Mora, M.D., M.H.S., Heike Gibson, Ph.D., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedenberg, M.P.H., Claire Ridge, M.P.H., et al., for the VITAL Research Group*

Polypill with or without Aspirin in Persons without Cardiovascular Disease

Salim Yusuf, D.Phil., Philip Joseph, M.D., Antonio Dans, M.D., Peggy Gao, M.Sc., Koon Teo, Ph.D., Denis Xavier, M.D., Patricio López-Jaramillo, Ph.D., Khalid Yusoff, M.B., B.S., Anwar Santoso, Ph.D., Habib Gamra, M.D., Shamim Talukder, M.B., B.S., Courtney Christou, B.Sc., et al., for the International Polycap Study 3 Investigators*

Factorial trial of distinct treatments

	Metformin	Placebo
Fluvoxamine	1: Met + Fluvoxamine	4: Placebo + Fluvoxamine
Ivermectin	2: Met + Ivermectin	5: Placebo + Ivermectin
Placebo	3: Met + Placebo	6: Placebo + Placebo

All participants received a metformin-appearing pill: either active or exact-matching placebo
All participants received 2 types of pills to maintain the blind.
Each medication had exact-matching placebo

Metformin trial: 1 + 2 + 3 versus 4 + 5 + 6

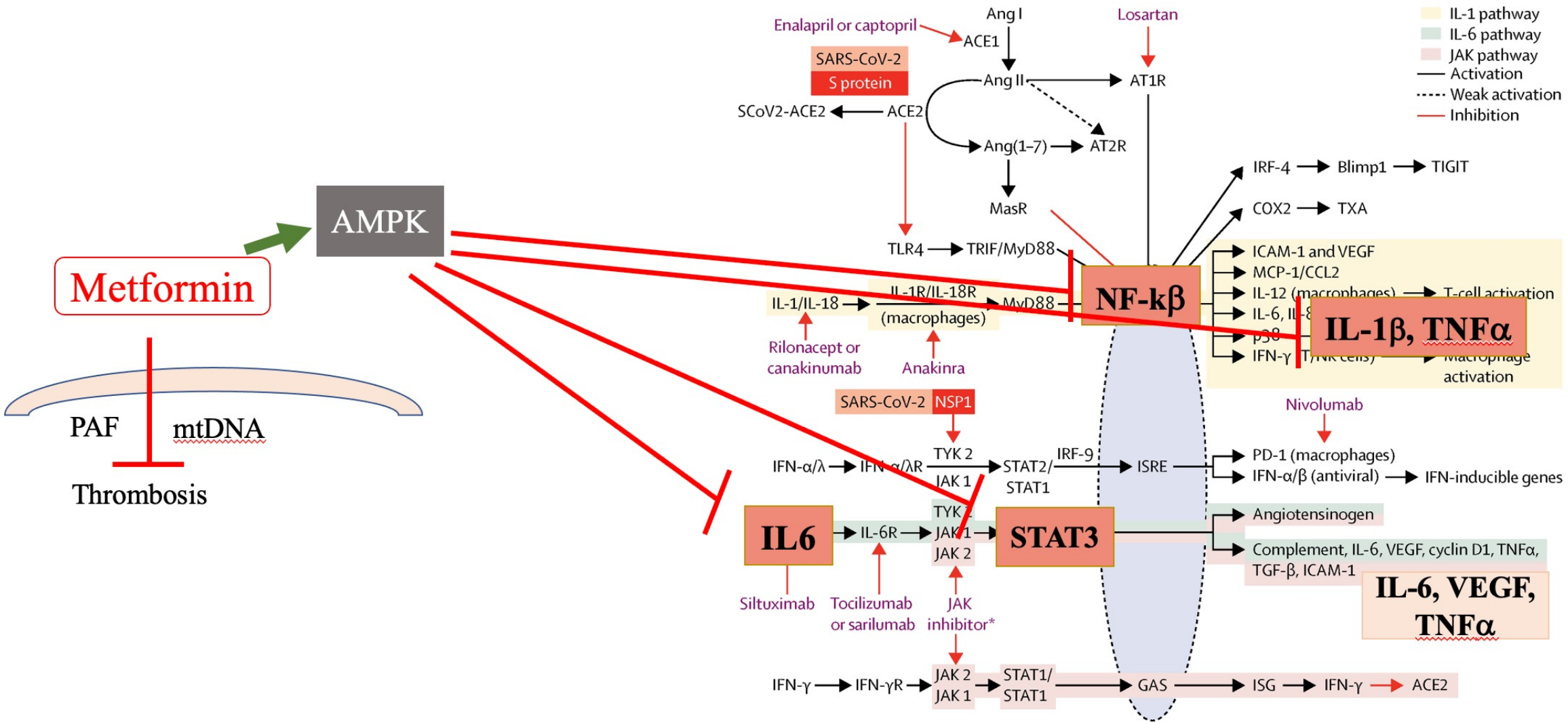
Ivermectin trial: 2 + 5 versus 3 + 6

Fluvoxamine trial: 1 + 4 versus 3 + 6

COVID-OUT: Study Population

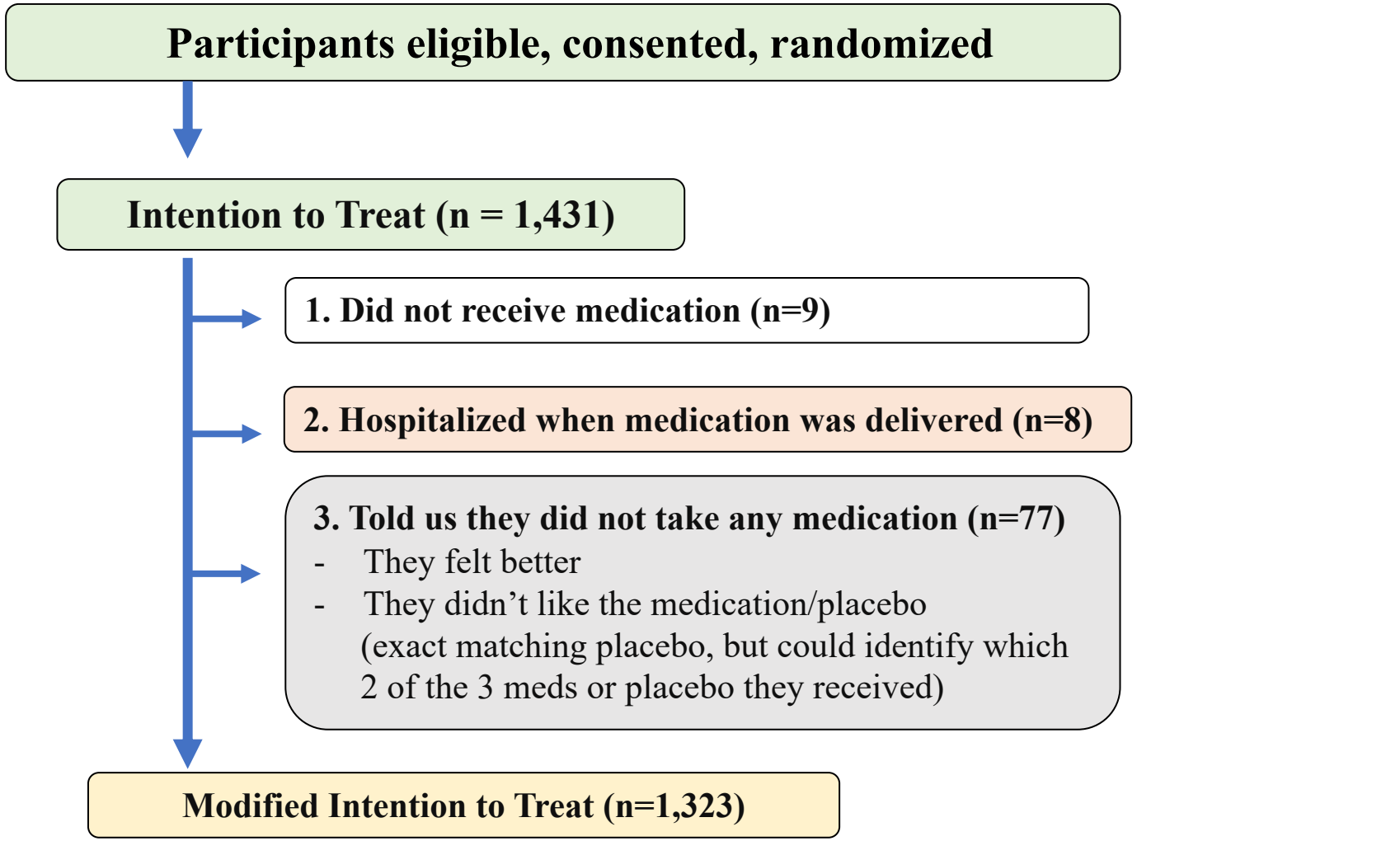
- Adults age 30 - 85
- +SARS-CoV-2 within 3 days
- < 7 days of symptoms
- No known prior infection with SARS-CoV-2
- No severe kidney, liver, or heart failure
  - Tested GFR on persons > 75 or persons with a history of heart, liver, or kidney disease
- Not excluding or restricting to patients with diabetes or prediabetes
  - Excluding those on insulin or sulfonylurea
- Pregnancy not excluded
- With overweight or obesity

Metformin may inhibit SARS-CoV2 induced adipokine cascade



Ingraham N, …, Tignanelli CJ, Immunomodulation in COVID-19, Lancet Respiratory Medicine, 2020
Xin et al. 2016.

Modified Intention to Treat Sample was the a priori primary sample

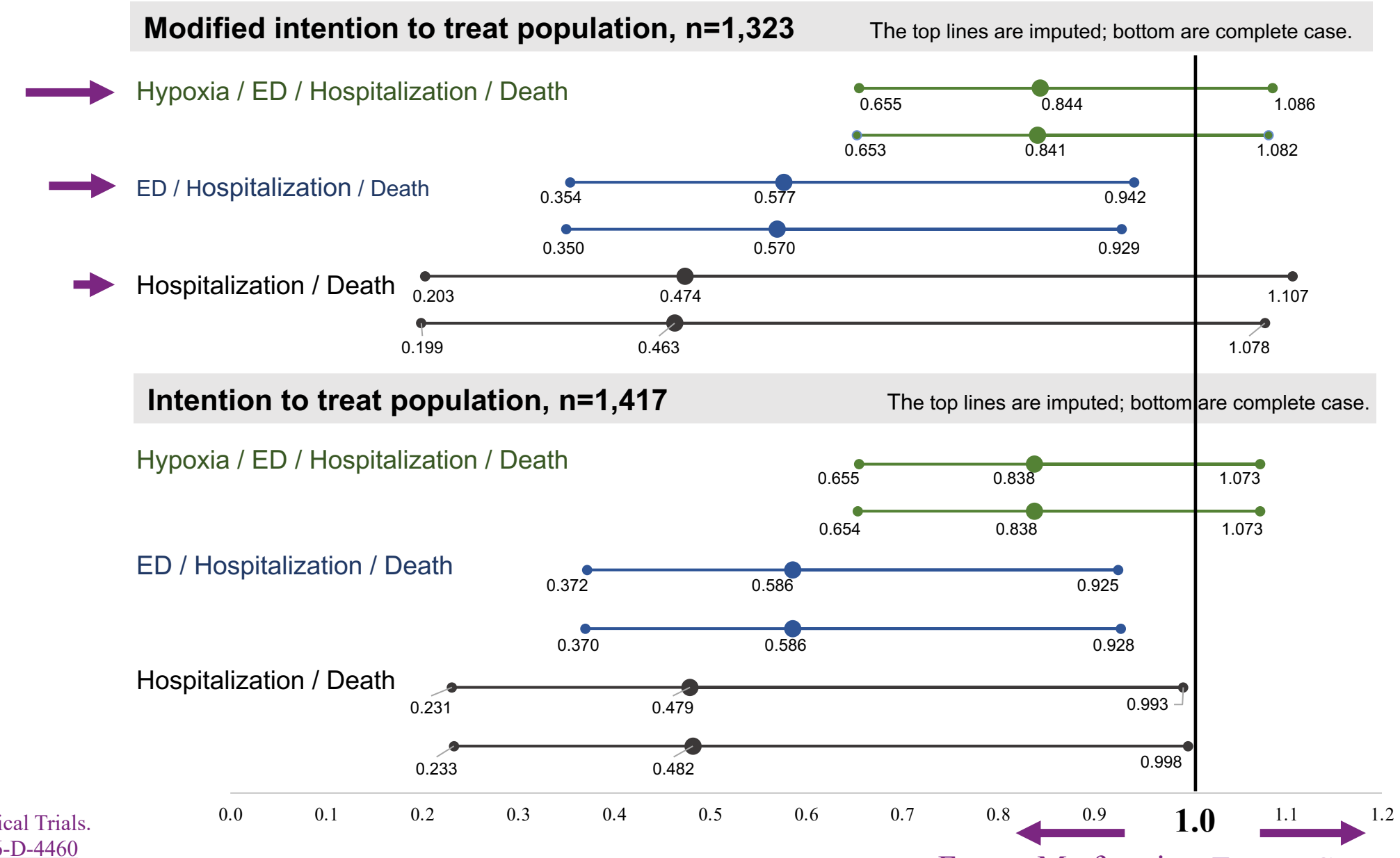


Includes those for whom we don't know whether or not they took study drug

Primary Outcome – data published this summer

Binary, 4-part composite outcome

Sequentially remove components less associated with severe disease.[1]



1. FDA. Multiple Endpoints in Clinical Trials. 2017; January. Docket FDA-2016-D-4460
2. Bramante et al, *NEJM* Aug 18, 2022

Objective of today is to present Long Covid data

- Ivermectin* 390 - 470mcg/kg/day x 3 days, n=187
- Metformin titration to 1,500mg/day, n=187
- Fluvoxamine 50mg BID, n=187
- Metformin / Fluvoxamine, n=188
- Metformin / Ivermectin, n=188
- Placebo, n=187

Primary End Point was a 4-part composite endpoint:

1. Hypoxemia
2. ED visit
3. Hospitalization
4. Death

due to Covid-19 by Day 14

Secondary Endpoints:

Acute Covid (Days 1-28)
Primary by Day 28
Symptom severity

Long Covid
9-month follow-up after acute period

14 days of treatment (3 of ivermectin)
Daily symptom log, adherence log, and SpO2 log

Optional viral load and stool samples on Days 1, 5, 10

Optional baseline & follow-up blood samples via mobile phlebotomy

Overview

- Overview of COVID-OUT Trial
  - Scientific rationale for these agents
  - Design, Study population
  - Results of acute Covid outcomes
- **Overview of Long Covid Outcome**
- Statistical Considerations
- Results
  - How these results Compare to other trials
  - New pre-clinical Data
  - New observational data
  - Viral load
- Review of metformin's safety
- Next Steps

Long Covid Outcome

- Submitted the PIND in Aug 2020
  - No follow-up beyond 60 days
- Added Long Covid follow-up in spring 2021
  - Before first DSMB meeting
  - Wanted more than 6 months
  - Budget

Long Covid Outcome Ascertainment

- Surveys sent every 30 days after acute Covid period (Day 1 – 28)
  - Days 60, 90…Day 300
  - Sent via participant's preferred mode (text or email)

Has a medical provider told you that you have Long Covid?

- Yes / No
  - *If Yes, further options popped up:*
- When *[with calendar pop-up]*
- Who told you
  - My primary care provider
  - A provider specializing in Long Covid
  - A specialist
  - A chiropractor
  - Other *[with free text]*

Long Covid Outcome Ascertainment

- Patient-report of clinician-diagnosed Long Covid
  - Participants consented to medical record review for confirmation
- Good balance of sensitivity and specificity
- Susceptible to under- or over-ascertainment
  - Distributed by randomization across treatment arms
  - All forms of ascertainment appeared to have issues:
    - Symptoms, patient-report of Long Covid may have low specificity
    - Medical record diagnosis may have low sensitivity, and potentially specificity
- Prospective assessment of Long Covid diagnosis by medical provider in this large sample

Overview

- Overview of COVID-OUT Trial
  - Scientific rationale for these agents
  - Design, Study population
  - Results of acute Covid outcomes
- Overview of Long Covid Outcome
- **Statistical Considerations**
- Results
  - How these results Compare to other trials
  - New pre-clinical Data
  - New observational data
  - Viral load
- Review of metformin's safety
- Next Steps

Factorial Design Analysis

- Efficient design to evaluate three drugs in randomized and blinded fashion
  - Each active group includes persons randomized to the active drug
  - Each blinded control group member randomized to a placebo instead of the drug
  - Blinded controls are concurrently randomized (at risk of randomization to active)
  - Background therapy is varied by randomization (i.e. the second pill)

	Metformin	**Placebo**
Fluvoxamine	1: Met + Fluvoxamine	4: Placebo + Fluvoxamine
Ivermectin	2: Met + Ivermectin	5: Placebo + Ivermectin
Placebo	3: Met + Placebo	6: Placebo + Placebo

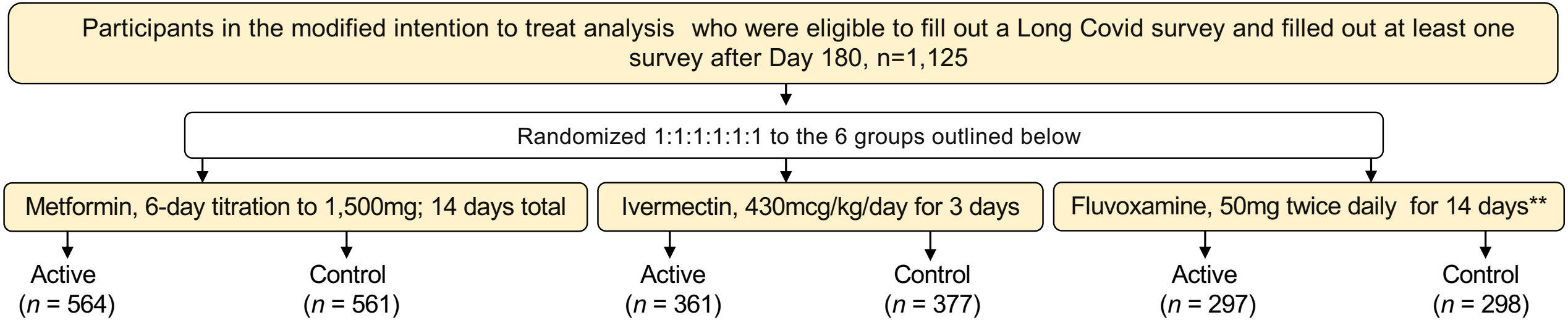
Analysis of Long Covid

- mITT cohort who consented to long covid follow-up and completed 1+ survey with the long covid diagnosis questions
- Long Covid Diagnosis treated as a time to event outcome
  - Time to long covid diagnosis from randomization
  - Time of diagnosis set to 15th day of month participant reported getting the diagnosis
    - Those missing valid timing information set to the day of the earliest survey on which they reported the diagnosis (n=9)
  - Censoring times reflect latest survey that participant completed
- Cumulative incidence (1 minus K-M survival estimate)
  - Log-rank test
  - Cox models for estimating hazard ratio (unadjusted and adjusted for other study drugs and baseline vax status)
- Descriptive statistics about who provided the diagnosis
- A priori subgroup analysis to evaluate treatment effect heterogeneity
  - Unadjusted hazard ratios from Cox models fit to pre-specified subgroups

Overview

- Overview of COVID-OUT Trial
  - Scientific rationale for these agents
  - Design, Study population
  - Results of acute Covid outcomes
- Overview of Long Covid Outcome
- Statistical Considerations
- **Results**
  - How these results Compare to other trials
  - New pre-clinical Data
  - New observational data
  - Viral load
- Review of metformin's safety
- Next Steps

Consort diagram.



† Enrollment in the fluvoxamine arm was stopped on January 7, 2022 by the DSMB, for lack of conditional power.

Table 1. Baseline characteristics of participants

Demographics		Metformin n=564	Blinded Control n=561
Age, median (IQR)		46.0 (37 to 54)	45.0 (37 to 54)
Female, 7% were pregnant		305 (54.1)	326 (58.1)
Race	Native American	9 (1.6)	15 (2.7)
	Asian	21 (3.7)	21 (3.7)
	Black	43 (7.6)	40 (7.1)
	White	469 (83.2)	463 (82.5)
	Other & unknown	40 (7.2)	37 (6.6)
Hispanic or Latino		66 (11.8)	76 (13.7)
Medical history			
BMI, Median (IQR)		29.7 (27 to 34)	30.0 (27 to 34)
BMI >= 30 kg/m^2		266 (47.2)	282 (50.3)
Cardiovascular disease		147 (26.1)	138 (24.6)
Diabetes		6 (1.1)	11 (2.0)
Insurance status	Private	358 (64.4)	345 (62.5)
	Medicare	41 (7.4)	38 (6.9)
	Medicaid	75 (13.5)	97 (17.6)
	No Insurance	82 (14.7)	72 (13.0)
Vaccination			
Primary vaccine		326 (57.8)	292 (52.0)
Vaccine booster		30 (5.3)	27 (4.8)
Symptoms			
Days symptoms drug		5 (4 to 6)	5 (3 to 6)
<=3 Days with Symptoms		254 (45.6)	264 (48.0)
SARS-CoV-2 Variant period	Alpha	34 (6.0)	29 (5.2)
	Delta	399 (70.7)	401 (71.5)
	Omicron	131 (23.2)	131 (23.4)

Overall incidence of Long Covid

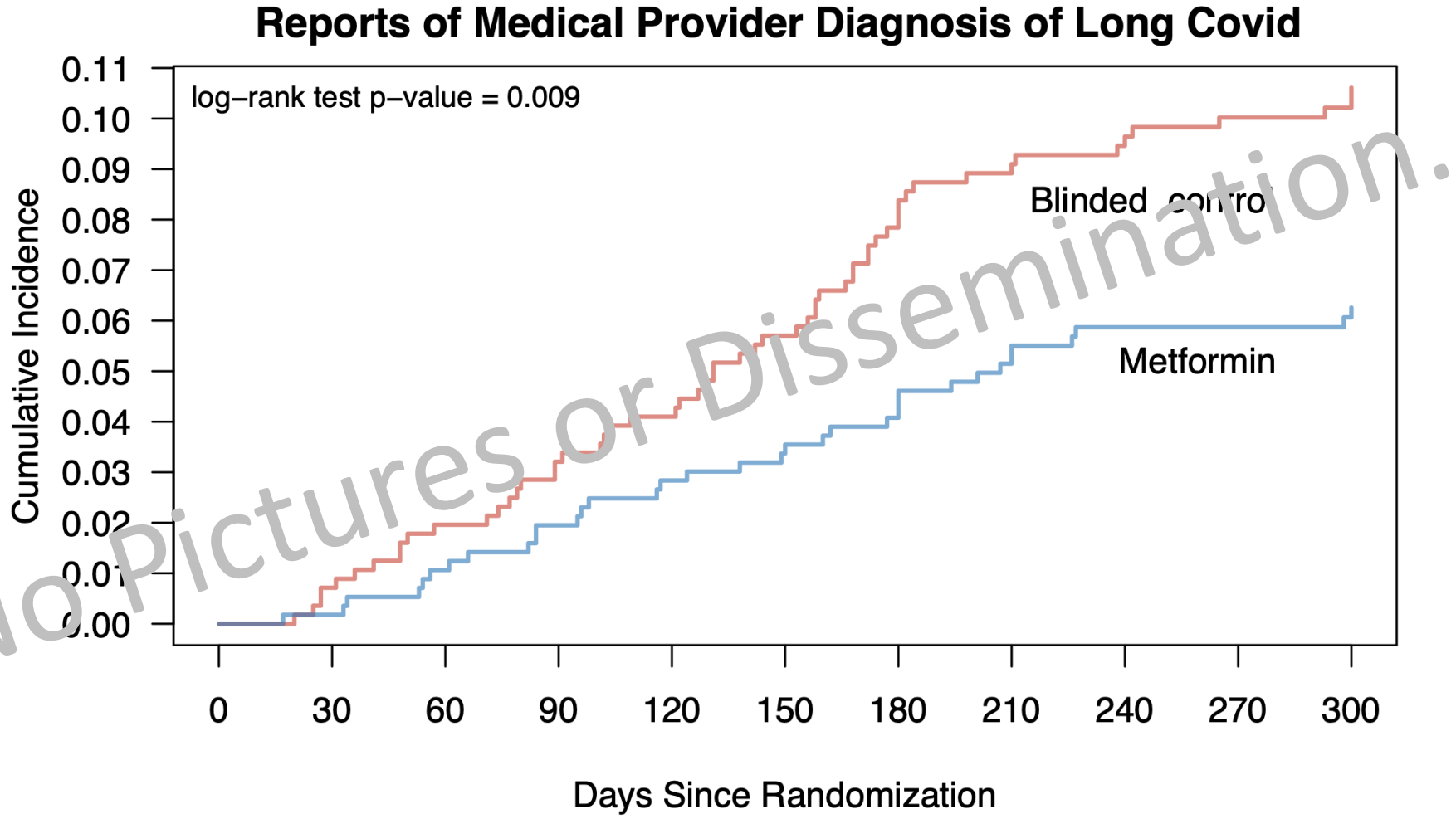
- Overall, 94/1125 (8.4%) responded Yes
  - Primary care providers, n=72 (73.4%)
  - Provider specializing in Long Covid, n=4 (4.3%)
  - Other specialists, n=8 (8.5%)
    - (cardiology n=3, neurology n=1, infectious disease n=1, otolaryngologist n=1, pulmonologist n=1)
  - Emergency department, n=3
  - Hospital, n=2
  - Urgent care, n=2
  - Chiropractor, n=1
  - Other, n=1
  - Missing, n=1

Few participants received treatment for Long Covid

Participants who responded Yes to having a clinician diagnosis of Long Covid were asked if they received treatment for Long Covid.

- 3.8% reported receiving treatment
  - 75% of this was at primary care provider
  - 10% from a cardiologist
  - Other: Blood Ozone, and telemedicine

Metformin versus placebo



Metformin versus placebo

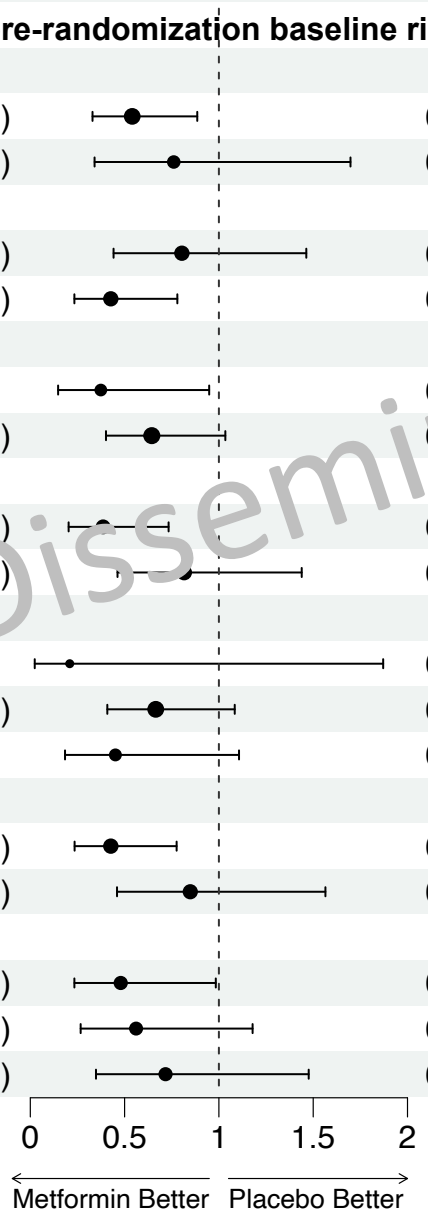
Table 2. Cumulative incidence of Long Covid, percent with 95% confidence intervals.

Day	Metformin	Blinded Control	Absolute Risk Reduction
60	1.1% (0.2% - 1.9%)	2.0% (0.8% - 3.1%)	0.9% (2.3% to -0.5%)
120	2.8% (1.5% - 4.2%)	4.1% (2.4% - 5.7%)	1.3% (3.4% to -0.9%)
180	4.6% (2.9% - 6.3%)	8.4% (6.1% - 10.6%)	3.8% (6.6% to 0.9%)
240	5.9% (3.9% - 7.8%)	9.6% (7.2% - 12.1%)	3.8% (6.9% to 0.7%)
300	6.3% (4.2% - 8.2%)	10.6% (8.0% - 13.1%)	4.4% (7.6% to 1.1%)

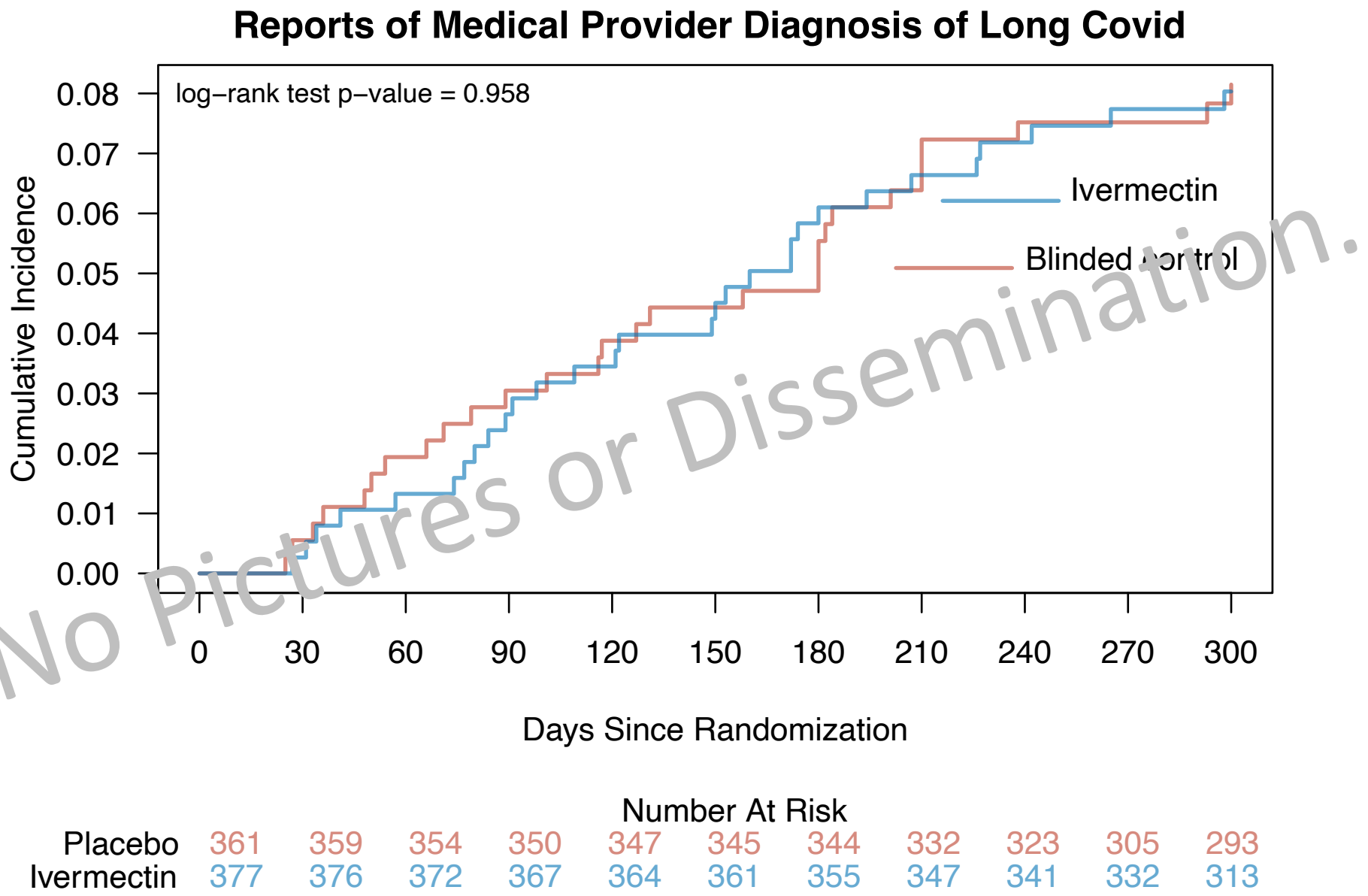
Hazard Ratio = 0.576 (95% CI 0.379 to 0.875)

Metformin versus placebo

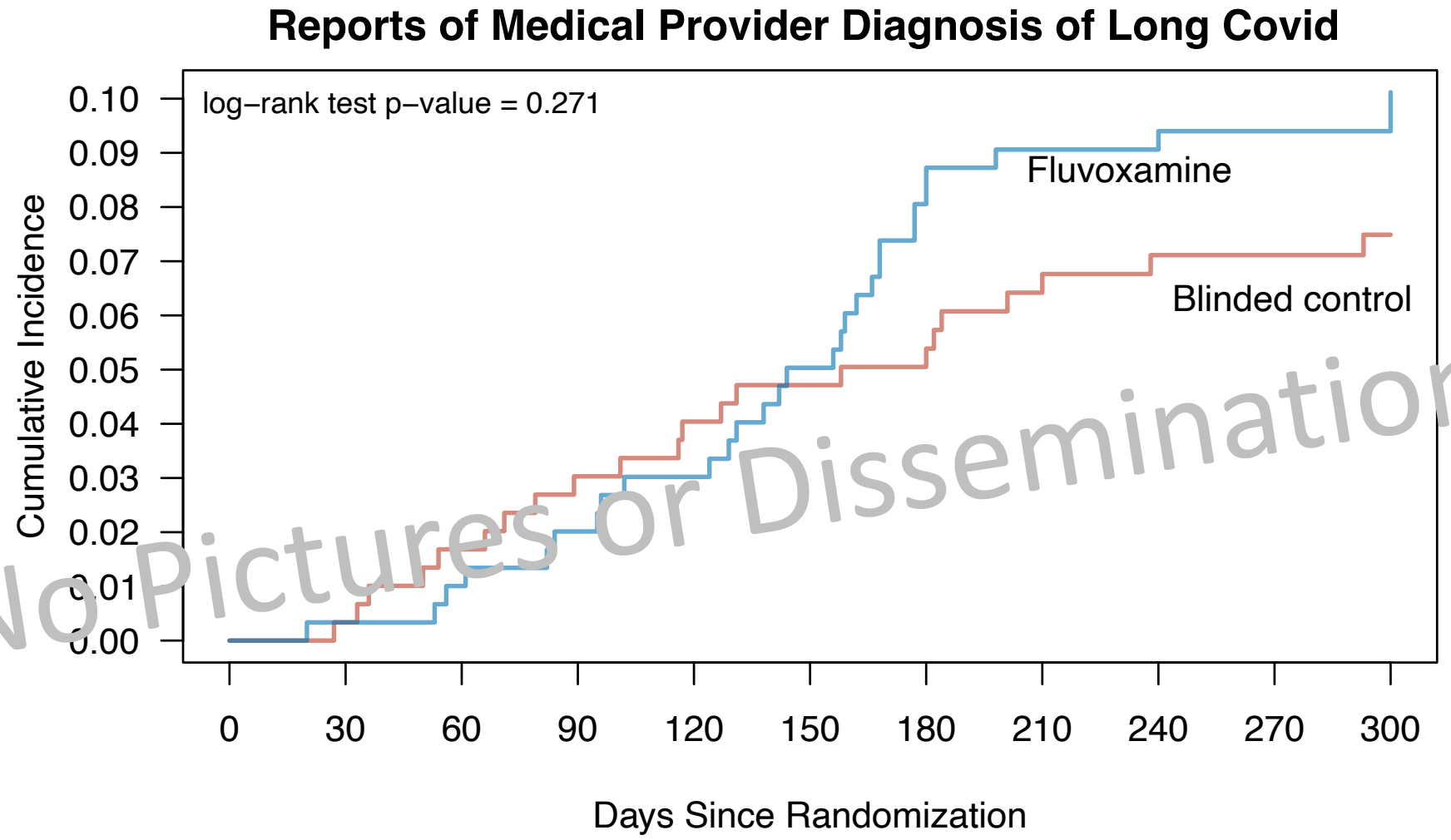
	Placebo	Metformin	Hazard Ratio (95% CI)
Assessment of treatment across a priori subgroups of pre-randomization baseline risk factors:			
Biologic sex			
Female	46/326 (14.1%)	24/305 (7.9%)	0.54 (0.33 to 0.89)
Male	13/235 (5.5%)	11/259 (4.2%)	0.76 (0.34 to 1.70)
BMI			
<30 kg/m2	23/279 (8.2%)	20/298 (6.7%)	0.80 (0.44 to 1.46)
>=30 kg/m2	36/282 (12.8%)	15/266 (5.6%)	0.43 (0.23 to 0.78)
Days since symptom onset			
<=3 days	17/143 (11.9%)	6/130 (4.6%)	0.37 (0.15 to 0.95)
>=4 days	42/407 (10.3%)	29/427 (6.8%)	0.64 (0.40 to 1.03)
Age			
<45 years	33/272 (12.1%)	13/265 (4.9%)	0.39 (0.20 to 0.73)
>=45 years	26/289 (9.0%)	22/299 (7.4%)	0.82 (0.46 to 1.44)
Dominant variant			
Alpha	4/29 (13.8%)	1/34 (2.9%)	0.21 (0.02 to 1.87)
Delta	40/401 (10.0%)	27/399 (6.8%)	0.67 (0.41 to 1.08)
Omicron	15/131 (11.5%)	7/131 (5.3%)	0.45 (0.18 to 1.11)
Vaccination status			
Not Vaccinated	38/269 (14.1%)	15/238 (6.3%)	0.43 (0.23 to 0.78)
Vaccinated	21/292 (7.2%)	20/326 (6.1%)	0.85 (0.46 to 1.56)
Additional study drug			
Nothing/Placebo	23/229 (10.0%)	11/221 (5.0%)	0.48 (0.23 to 0.98)
Ivermectin	19/188 (10.1%)	11/189 (5.8%)	0.56 (0.27 to 1.18)
Fluvoxamine	17/144 (11.8%)	13/154 (8.4%)	0.72 (0.35 to 1.48)



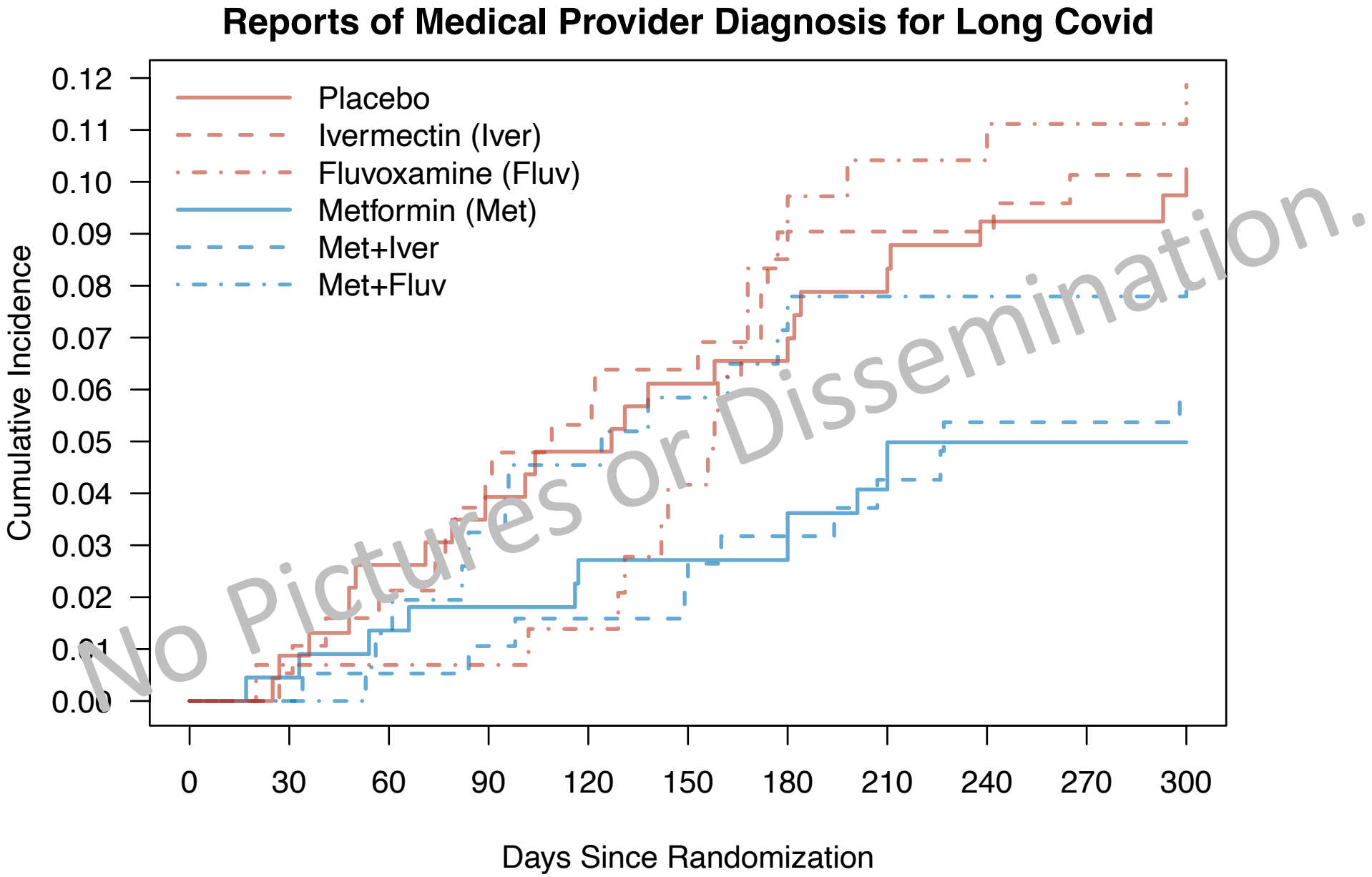
Ivermectin versus control



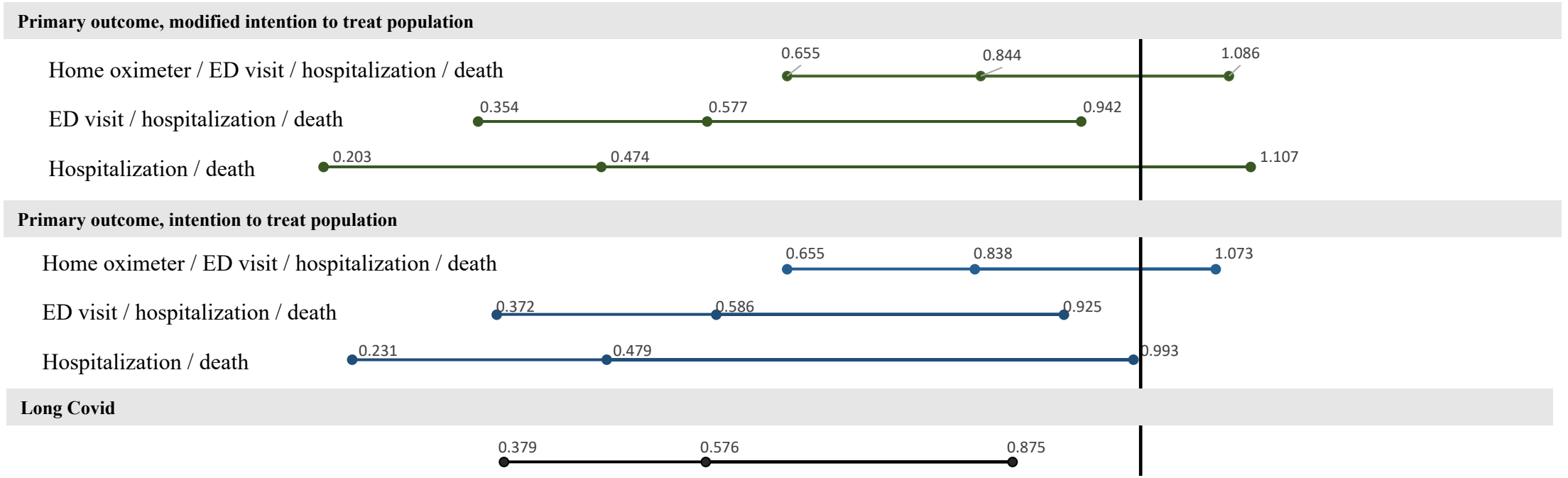
Fluvoxamine versus control



6 randomization arms



Consistent with outcomes during acute period



Overview

- Overview of COVID-OUT Trial
  - Scientific rationale for these agents
  - Design, Study population
  - Results of acute Covid outcomes
- Overview of Long Covid Outcome
- Statistical Considerations
- Results
  - **How these results Compare to other trials and data**
  - New pre-clinical Data
  - New observational data
  - Viral load
- Review of metformin's safety
- Next Steps

New observational data

Covid and Diabetes, Colliding in a Public Health Train Wreck

New York Times, April 2021

"Studies suggest that 30 to 40% of all coronavirus deaths in the United States have occurred among people with diabetes."

- That is the approximate prevalence of diabetes in seniors

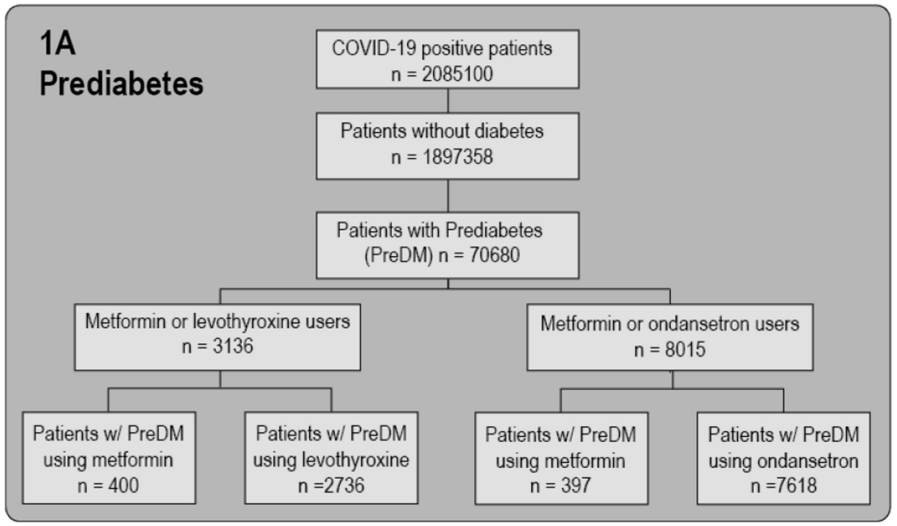
1) The first source: a two-year old report from the CDC that explained that underlying conditions was not known for over 55% of decedents

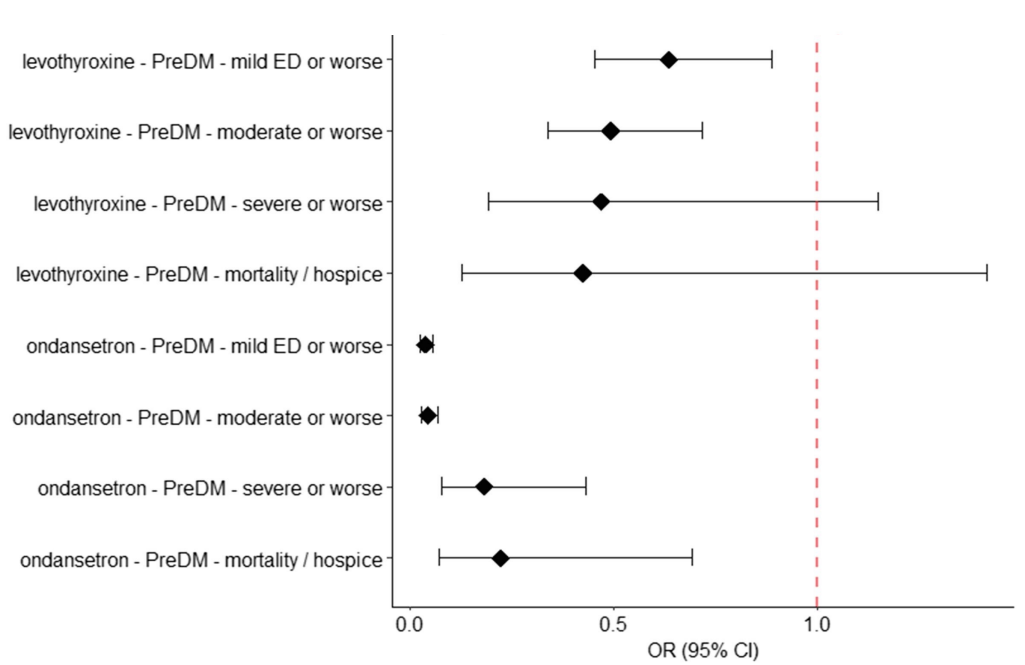
2) The 2nd source reported that diabetes, hypertension, obesity and smoking combined contributed to nearly 30% of COVID-19 deaths.

- When looking at each comorbidity separately the proportion of COVID-19 related deaths attributable to diabetes was 8%.

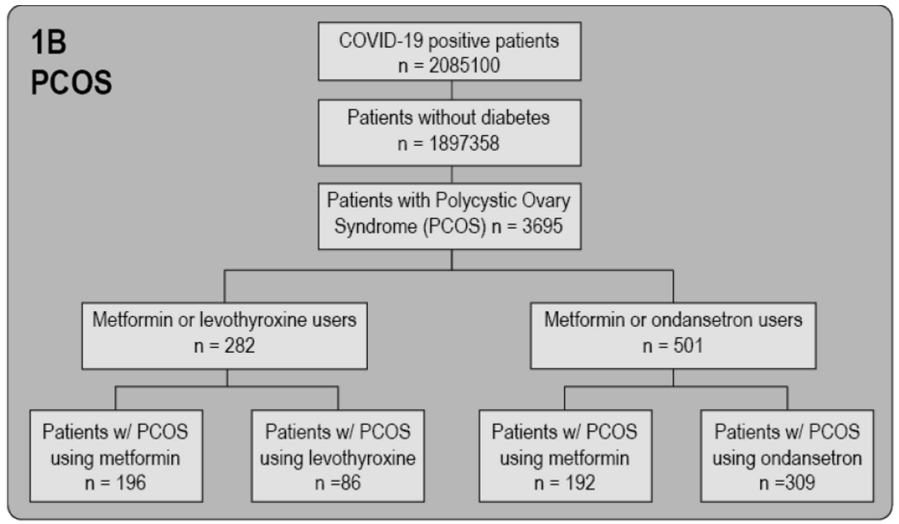
2016 Medicare data, among those dying of influenza, 48.8% had diabetes.
2017 Medicare data, among those dying of influenza, 44.9% had diabetes.

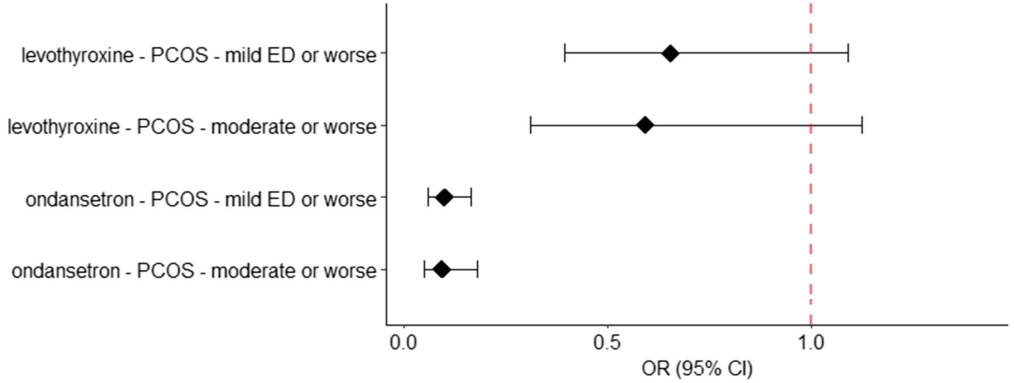
New observational data





	OR (95% CI)	p-value
levothyroxine - PreDM - mild ED or worse	0.636 (0.455-0.888)	0.03154
levothyroxine - PreDM - moderate or worse	0.493 (0.339-0.718)	0.00091
levothyroxine - PreDM - severe or worse	0.47 (0.192-1.15)	0.39247
levothyroxine - PreDM - mortality / hospice	0.426 (0.128-1.416)	0.65495
ondansetron - PreDM - mild ED or worse	0.039 (0.026-0.057)	0
ondansetron - PreDM - moderate or worse	0.045 (0.03-0.069)	0
ondansetron - PreDM - severe or worse	0.183 (0.077-0.431)	0.00041
ondansetron - PreDM - mortality / hospice	0.223 (0.071-0.694)	0.03852





	OR (95% CI)	p-value
levothyroxine - PCOS - mild ED or worse	0.655 (0.394-1.089)	0.20514
levothyroxine - PCOS - moderate or worse	0.593 (0.312-1.126)	0.21987
ondansetron - PCOS - mild ED or worse	0.1 (0.061-0.166)	0
ondansetron - PCOS - moderate or worse	0.094 (0.049-0.18)	0

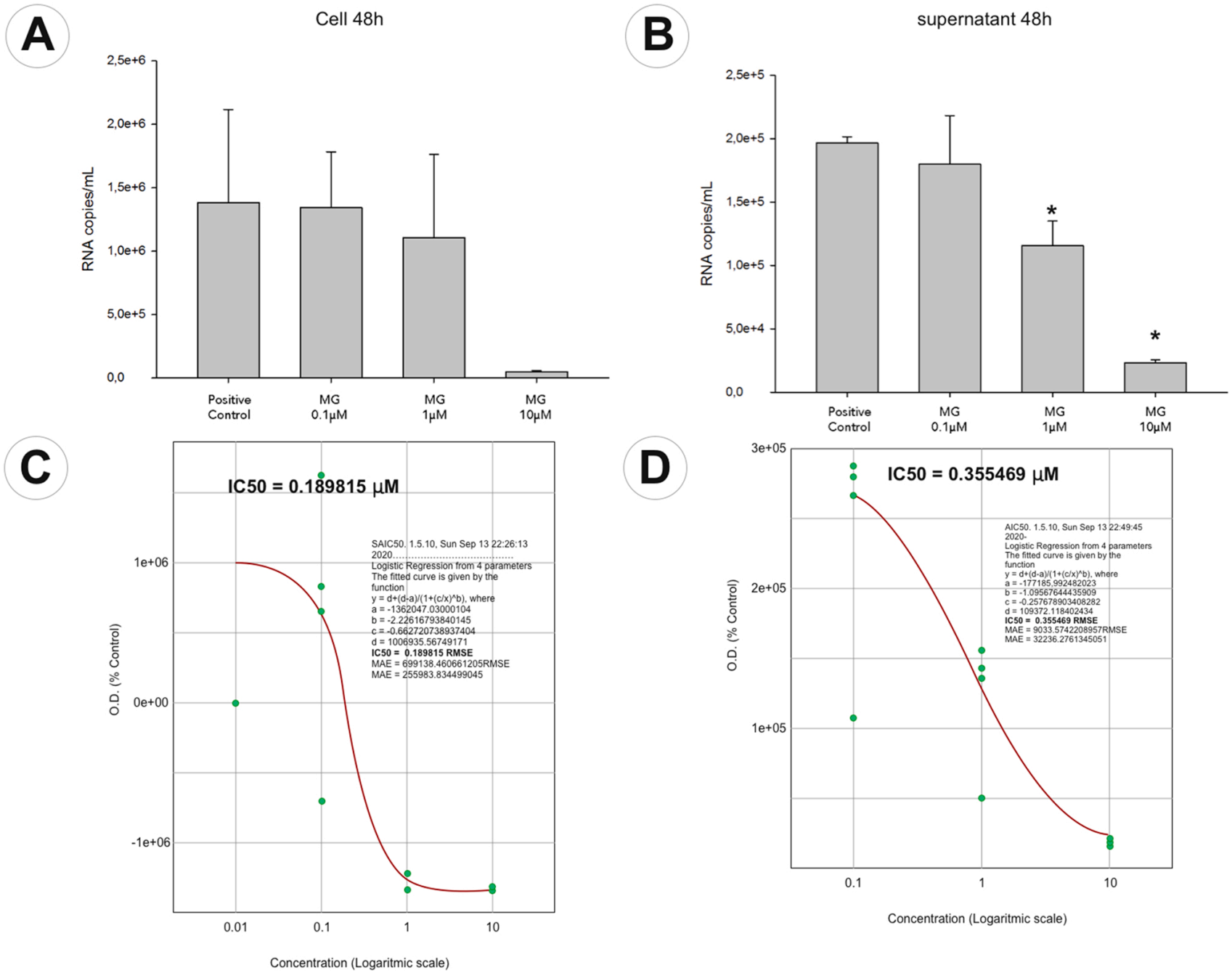
Metformin is associated with reduced COVID-19 severity in patients with prediabetes. [In the N3C database]
Chan, Lauren E. et al. *Diabetes Research and Clinical Practice,* Volume 194, 110157

New Preclinical data

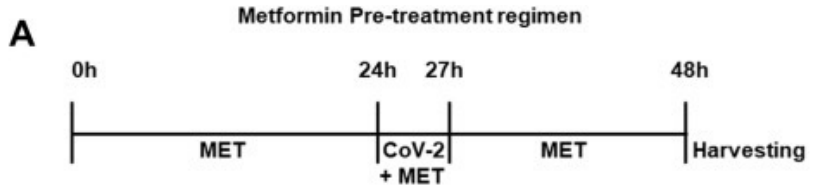
Fig. 1. Metformin glycinate (MG) Inhibition effect on SARS-CoV-2 clinical isolated (MX/BC1/2020).

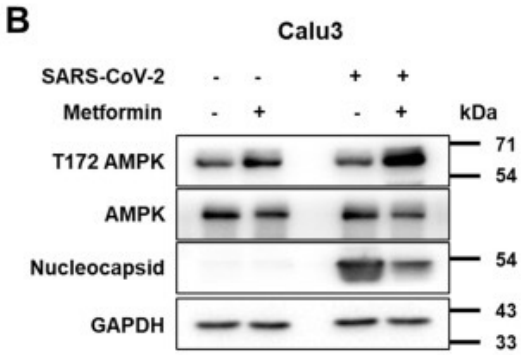
Metformin Glycinate effect on the SARS-CoV-2 (MOI = 100) viral load (RNA copies per mL) determined 48 h after infection in
(**A**) supernatant and
(**B**) whole cells (carcinoma; non-small cell lung cancer; Cell line H1299).

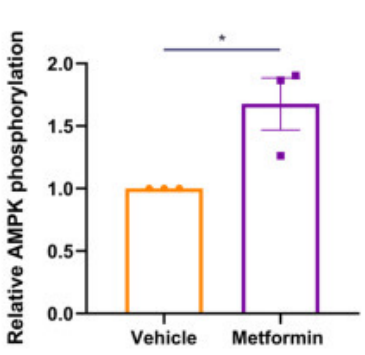
Half-maximal inhibitory concentration (IC50) of MG on cell viability in
(**C**) whole cells and
(**D**) supernatant.

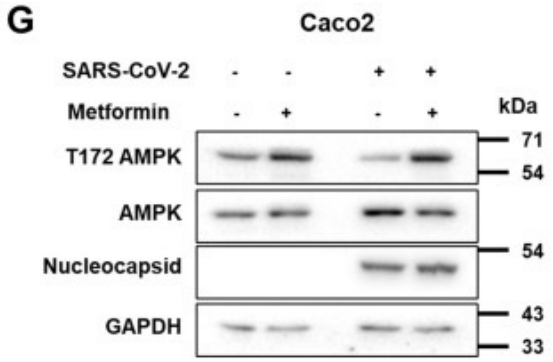


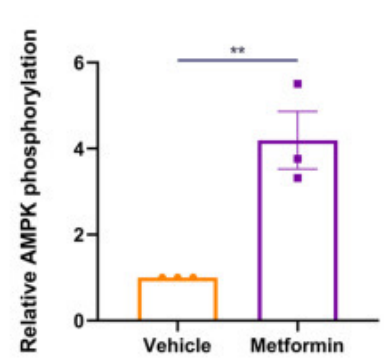
New preclinical data

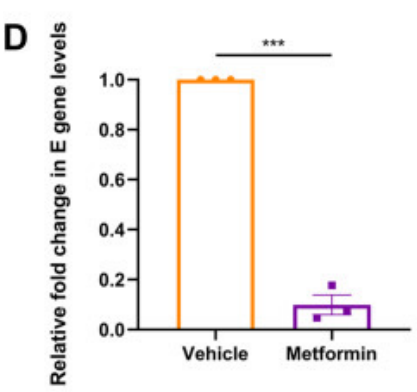


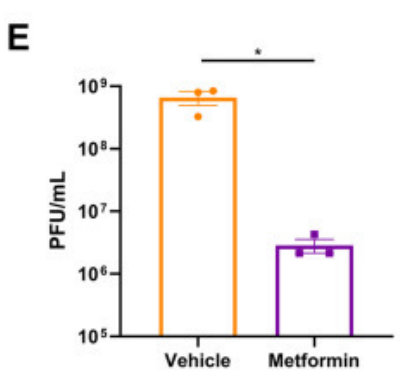


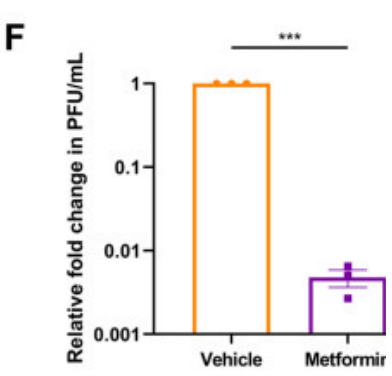


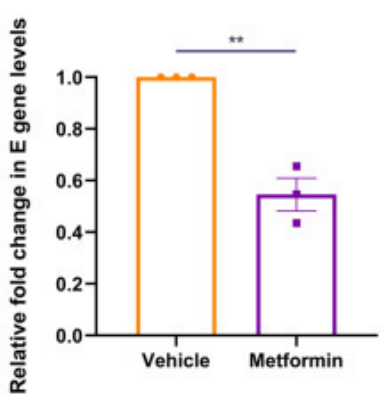


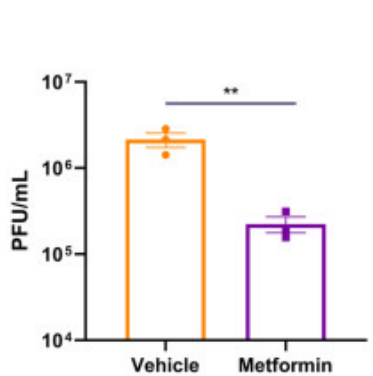


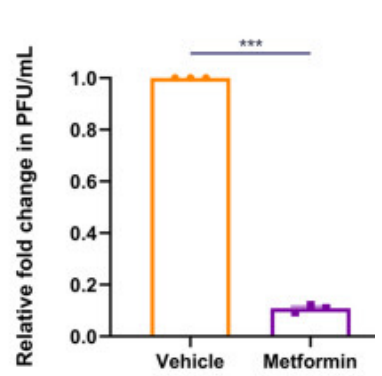








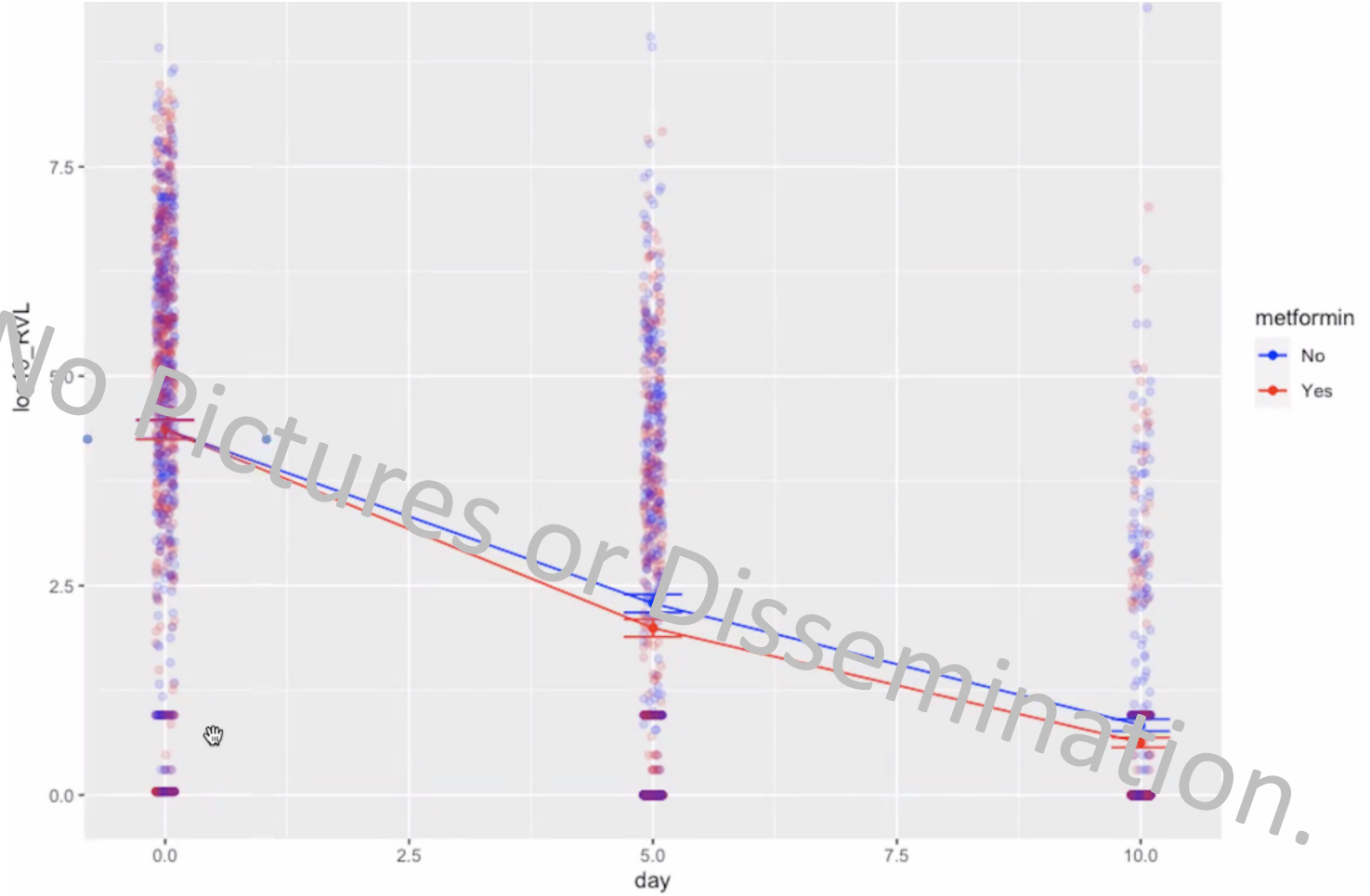




H. Parthasarathy, D. Tandel, A. H. Siddiqui, K. H. Harshan, Metformin Suppresses SARS-CoV-2 in Cell Culture. *Virus Res*, 199010 (2022)

Metformin decreased viral load in our trial

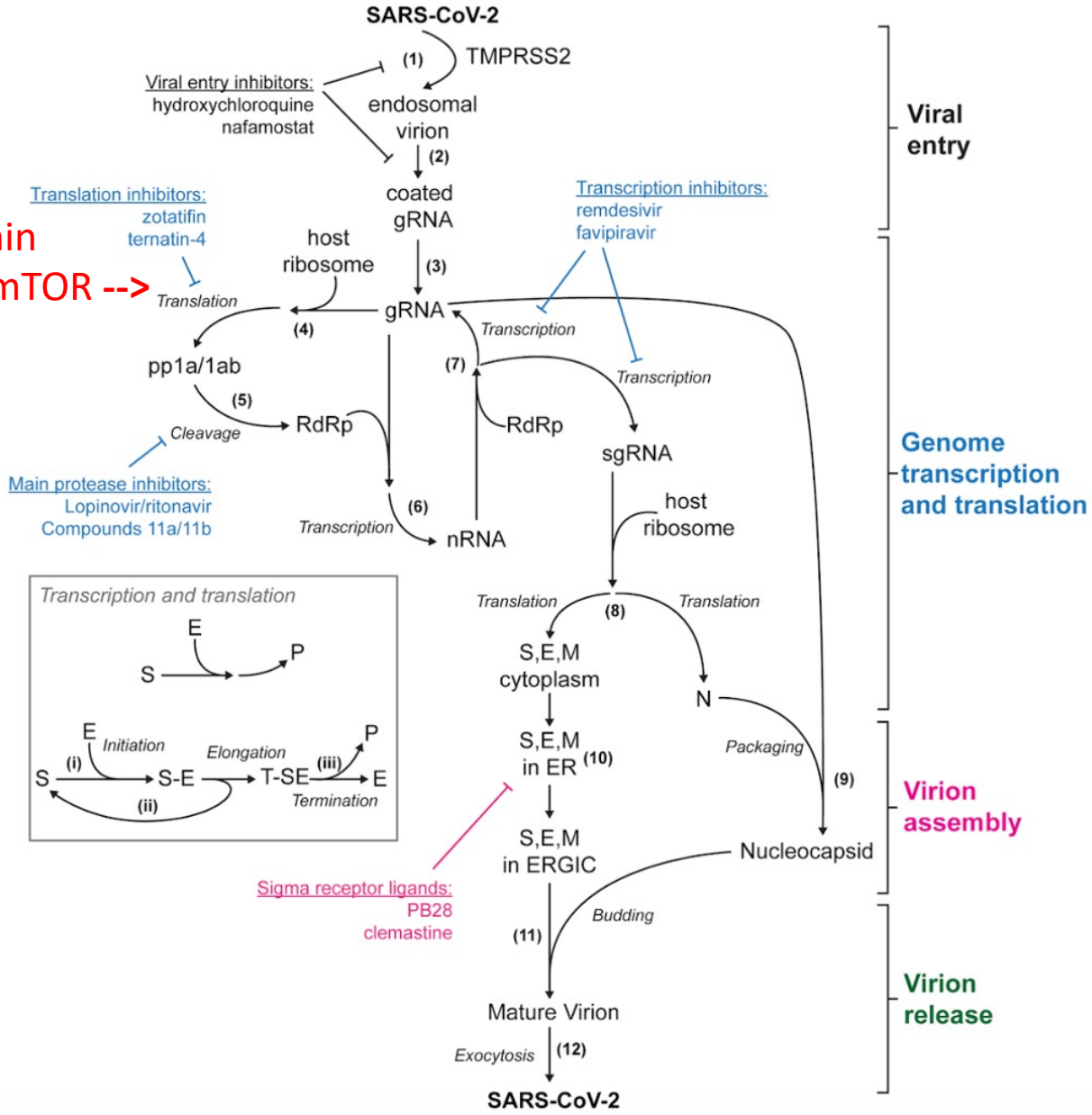
Analyzing Viral Load Data



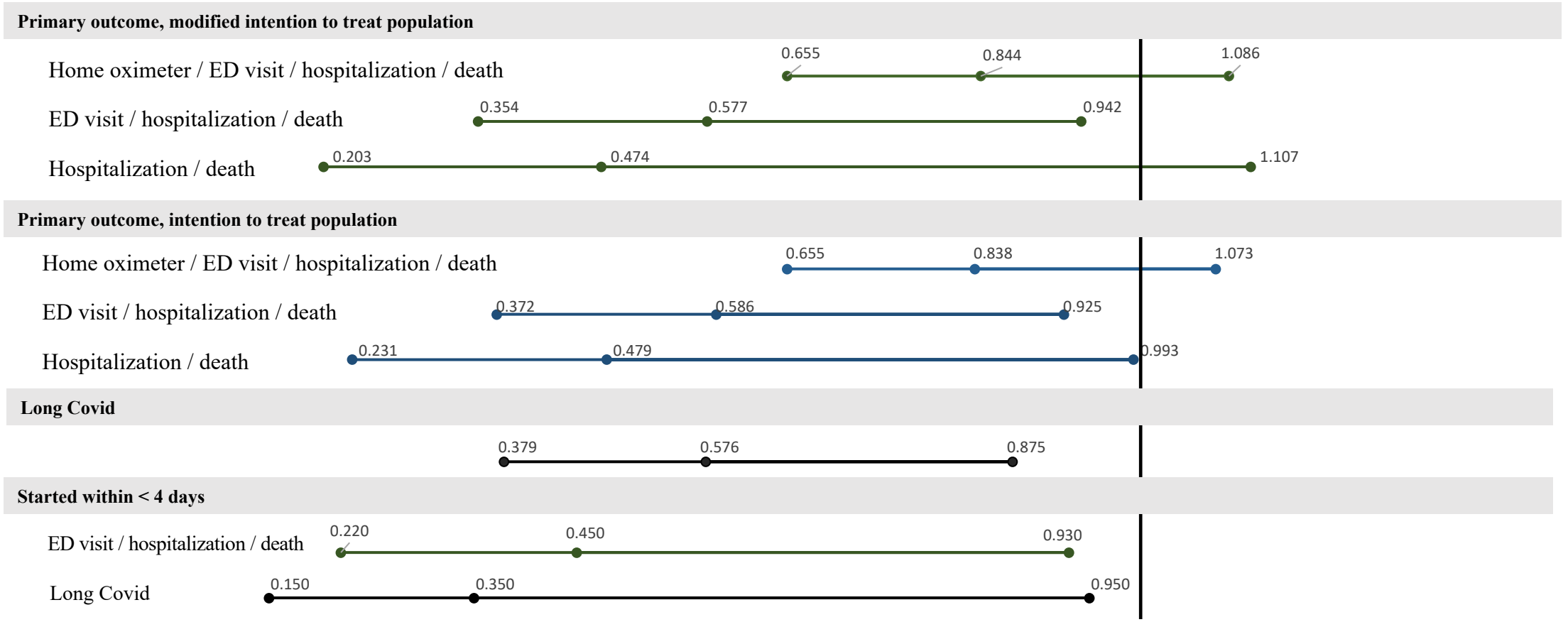
Mechanism for decreasing viral load

Activity against host mechanisms may
be less likely to cause selective pressure on the virus

Metformin
inhibits mTOR -->



Point estimate moves Left when metformin is started earlier

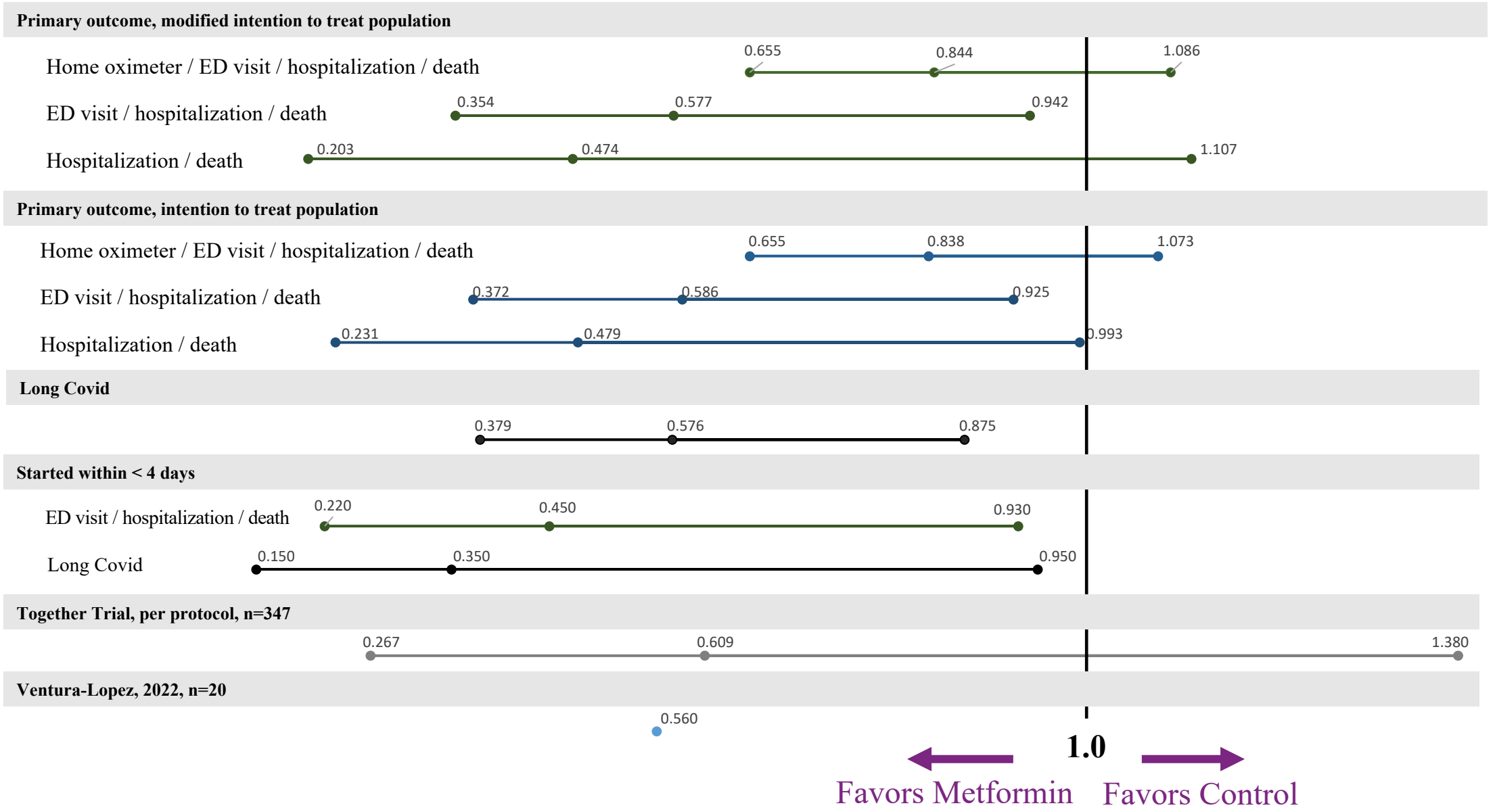


Sabizabulin is an oral, novel microtubule disruptor that has dual antiviral and anti-inflammatory activities in preclinical models

1.0

Favors Metformin Favors Control

Consistent with other trial data



Metformin is Safe

- Recent studies have shown a lower risk of lactic acidosis in those not on metformin
- Used in advanced heart, liver, kidney failure
- Now being continued when patients are admitted to the hospital
- Providers are familiar with prescribing it
- Few drug interactions
- Few contra-indications
- Safe in children
- No follow-up monitoring needed (for 12 months or more)
- Well tolerated in most people, especially at <2,000mg/day

Limitations

Covid-Out Trial overall:

- Generalizability (82% white)
- Self-report of medication adherence
- Internal validity of oxygen data reduces the internal validity of the primary outcome
- Definition of intention to treat
- Low number of pregnant women

Long Covid follow-up:

- Long Covid ascertainment may under- or over-ascertain Long Covid

In Summary

Summary of Data on Metformin & SARS-CoV-2	
Effect against SARS-CoV-2	
In vitro	✓✓ (α, **Δ**, ***O***)
In vivo	✓✓ (α, **Δ**, ***O***)
Observational	✓✓✓✓✓✓✓✓✓✓✓✓
Phase 2 trial, prevents need for supplemental O2	✓
Phase 3 trial, primary outcome with $p<0.05$	
Phase 3 trial, prevents ED visit, hospitalization, death	✓✓(α, **Δ**, ***O***)
Phase 3 trial, prevents Long Covid	✓(α, **Δ**, ***O***)
Phase 3 trial in high risk adults	✓✓(α, **Δ**, ***O***)
Phase 3 trial in moderate risk adults	✓✓(α, **Δ**, ***O***)
Phase 3 trial in average risk adults	✓(α, **Δ**, ***O***)
Phase 3 trial in the US	✓(α, **Δ**, ***O***)
Phase 3 trial in vaccinated adults	✓(α, **Δ**, ***O***)
Favorable aspects of metformin	
Safe, safe in pregnancy, tested in pregnant women	✓(α, **Δ**, ***O***)
Inexpensive and widely available	
Few interactions	
Mechanism may be less likely to cause mutations	

Next Steps

- All findings should be replicated
- Inpatient study
- Treatment of Long Covid

Thank you

Participants

Patient Advisory board

- KL2 and Learning Health System training, to guide research around obesity
- They discussed this trial with me from the beginning
- They reviewed every aspect of patient-facing material, consent, protocol
- Gave important feedback on recruitment and consent approach
- Long Covid is a huge priority

Thank you

Funders

Co- investigators
John B. Buse
David Liebovitz
Jacinda Nicklas
Michael A. Puskarich
Ken Cohen
Hrishikesh Belani
Blake Anderson
Jared D. Huling
Christopher Tignanelli
Jennifer Thompson
Matthew Pullen
Lianne Siegel
Jennifer Proper
David Odde
Nichole Klatt
Nancy Sherwood
Kenny Beckman
David R. Boulware

Surgery CTO: Lisa Rogers, Dave Ankarlo, Mary Farnsworth

FDA Prep: Harvey Arbit, Wrenda Temple

Pharmacists: Darlette Luke, Theresa Christiansen, Derek LaBar

Statisticians: Jennifer Proper, Lianne Siegel, Sara Lindberg

ADRL: Bob Janicke, Jamie Lavalle

Fairview Research: Jill Cordes, Andrew Snyder, Pa Chia Yang, Melissa Schedler, Sarah Zwagerman, Erik Kuehl, Madeline Zolik

BME: Bo Connelly

DOM: Sara Eischen, Leslie Kennedy, Alicia Callahan, Ashlee Janecke

CPOM: Cameron Naughton, Juanita Jenson, Lucas Simmons

GIM: Kate Brekke, Jill Charles, HR

CTSI: Casey Dahl, Study Monitor

SPA: contracts

Study Staff, Students

Participating Sites

Samuel Lee
Jannis Brea
Naveen Reddy
Bristol Pavol
Gwen Carangi
Amber Voit
Amber Bretz

Audrey Hendrickson
Walker Tordsen
Lucas Brown
Olivia Kaus
Nicole Rudin
Radhika Edpuganti
Leah Stodieck
Jane Ude

Riannon Atwater
Nikita Deng
Alex Pedowitz
Rosario Machicado
Daniela Parra
Paula Campora

UMN

Grace Christensen
Kristi Fordyce
Regina Fricton
Gwen Griffiths
Aubrey Hagen

Barkha Patel
Via Rao
Manju Nayar
Mercury Wu

Students

Katrina Hartman
Hanna Saveraid
Tannon Tople
Arman Quraishi
Neha Reddy
Rumbidzai Ngonyama
Sarah Fenno
Megan Sxchramski
Spencer Erickson
Nandini Avula
Carissa Dock
Hanna Saveraide
Faith Fairborn
Daniel Fraser

Riannon Atwater
Jannis Brea

HEALTH FAIRVIEW
HennepinHealthcare
OPTUM Labs
EMORY UNIVERSITY SCHOOL OF MEDICINE
VANDERBILT School of Medicine
Northwestern Medicine
University of Colorado Anschutz Medical Campus
UCLA David Geffen School of Medicine

Thank You

- Questions, discussion