



# Diabetes in the Time of COVID-19

Irl B. Hirsch, MD  
Professor of Medicine  
University of WA  
Seattle, WA

# Dualities

- Research: Medtronic Diabetes, Insulet, Beta Bionics
- Consulting: Abbott Diabetes Care, Bigfoot, Roche, GWave



## New Data, ADA Scientific Sessions, June 2021

---

- 40% of Americans who have died from COVID-19 had diabetes
- 1 in 10 hospitalized from COVID-19 with diabetes die within one week
- 1 in 5 Americans with diabetes report that due to increased financial constraints of the pandemic, they had to choose between buying food or medications

# Doing the Math: % of *Total Population* With Both Diabetes and Not Vaccinated.

- WA State: 4.6%
- Missouri: 5.5%
- West Virginia: 6.0% (highest diabetes prevalence at 15.3%)
- Louisiana: 7.2%
- Mississippi: 8.4%



# COVID-19 and Diabetes

- Large body of evidence: DM (T2D) results in a 2-3-fold increase risk of mortality
- UK (NHS): 10,926 deaths linked to COVID-19, 4089 with DM (37%) (Nature 2020;584:430-436)
  - HbA1c > 7% had double the mortality risk
  - Independently, obesity resulted in a 2-fold increase risk of mortality
- Independent of both diabetes and obesity, minorities consistently shown to confer increased risk of mortality (HR = 1.78 in the UK study)

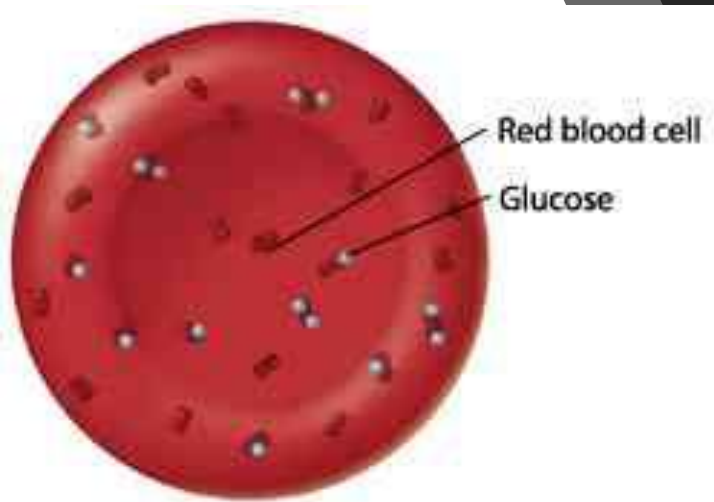


A photograph of a busy hospital ward. In the foreground, a patient is lying in a bed, partially covered by a white sheet. To the left, a medical cart with various supplies is visible. In the background, several other beds are occupied by patients, and medical staff in blue scrubs are attending to them. The ward is well-lit with overhead lights, and there are curtains and medical equipment visible throughout the room.

Fundamental Question: What is  
the Impact of Preinfection  
Glucose Control With SARS-CoV-2  
Infection?

# COVID19, Influenza, and CAD Mortality: UK Biobank (N=501,884)

- CAD: diabetes was associated with a 64% greater excess risk in women compared with men
- Higher levels of HbA1c were not associated with greater risk of COVID-19 or influenza/pneumonia death in *women*
- In *men*, an HbA1c >7.5% was associated with a greater risk of COVID-19 or influenza/pneumonia death





# Preadmission Diabetes-Specific Risk Factors for Mortality in Hospitalized Patients With Diabetes and Coronavirus Disease 2019

Shivani Agarwal,<sup>1</sup> Clyde Schechter,<sup>2</sup>  
Will Southern,<sup>3</sup> Jill P. Crandall,<sup>1</sup> and  
Yaron Tomer<sup>1</sup>

*Diabetes Care* 2020;43:2339–2344 | <https://doi.org/10.2337/dc20-1543>

N=1126 w DM, 98% T2DM

“HbA1c levels were not associated with mortality in unadjusted or adjusted analyses”



# Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study



*Naomi Holman, Peter Knighton, Partha Kar, Jackie O'Keefe, Matt Curley, Andy Weaver, Emma Barron, Chirag Bakhai, Kamlesh Khunti, Nicholas J Wareham, Naveed Sattar, Bob Young, Jonathan Valabhji*

- T1D: N = 264,390
  - Increased mortality with HbA1c > 10% (HR 2.23)
- T2D: N = 2,874,020
  - Increased mortality with HbA1c > 7.6% (HR 1.22), > 8.9% (HR 1.36)

Male sex, older age, renal impairment, non-white ethnicity, socioeconomic deprivation, and previous stroke and heart failure were associated with increased COVID-19-related mortality in both type 1 and type 2 diabetes

# What is the Evidence for Pre-COVID Glucose Control and SARS-CoV-2 Outcomes?



1. We don't have definitive data from numerous observational studies (all together including thousands of patients).
2. This is not a reason to practice outpatient poor glucose control!

# My Opinion



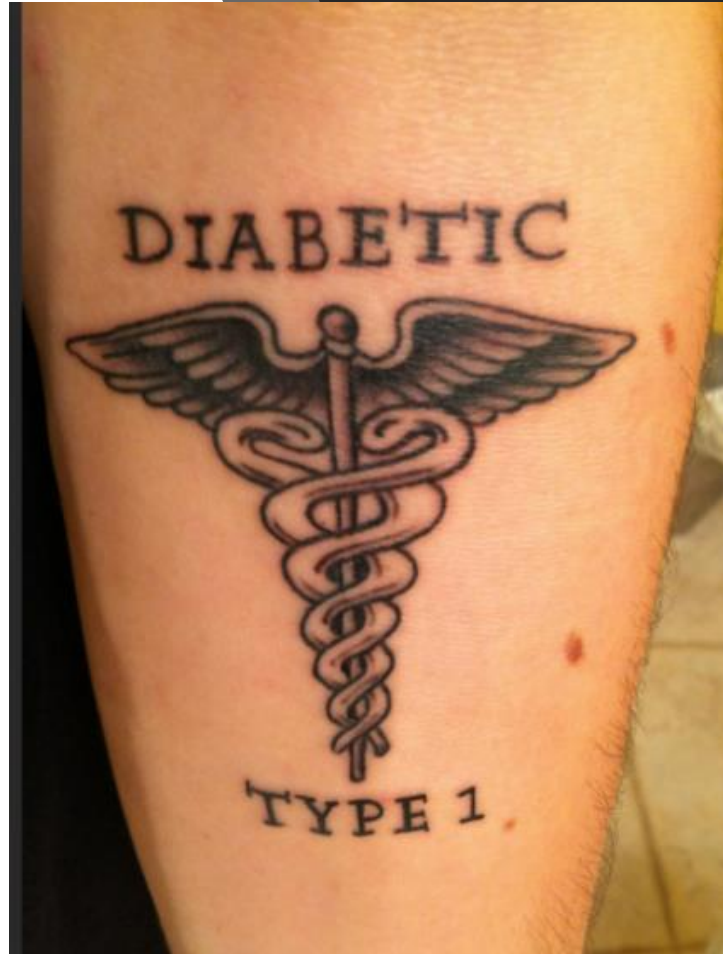
- 1. The science would suggest pre-existing glucose control should impact COVID-19 outcomes but the data as of now are inconclusive.
- 2. I suggest complete transparency about this point with your patients, especially those who are not vaccinated



# Type 2 Diabetes Presentation in Children: ADA Sci Sessions, 2021

- New-onset T2D in children requiring hospitalization increased 2.3X at tertiary pediatric hospital (Baton Rouge, LA)
- 2019: HbA1c 12.4% admission glucose 441 mg/dL
- 2020: HbA1c 13.1%, admission glucose 669 mg/dL

# Summary of T1D Incidence and COVID-19



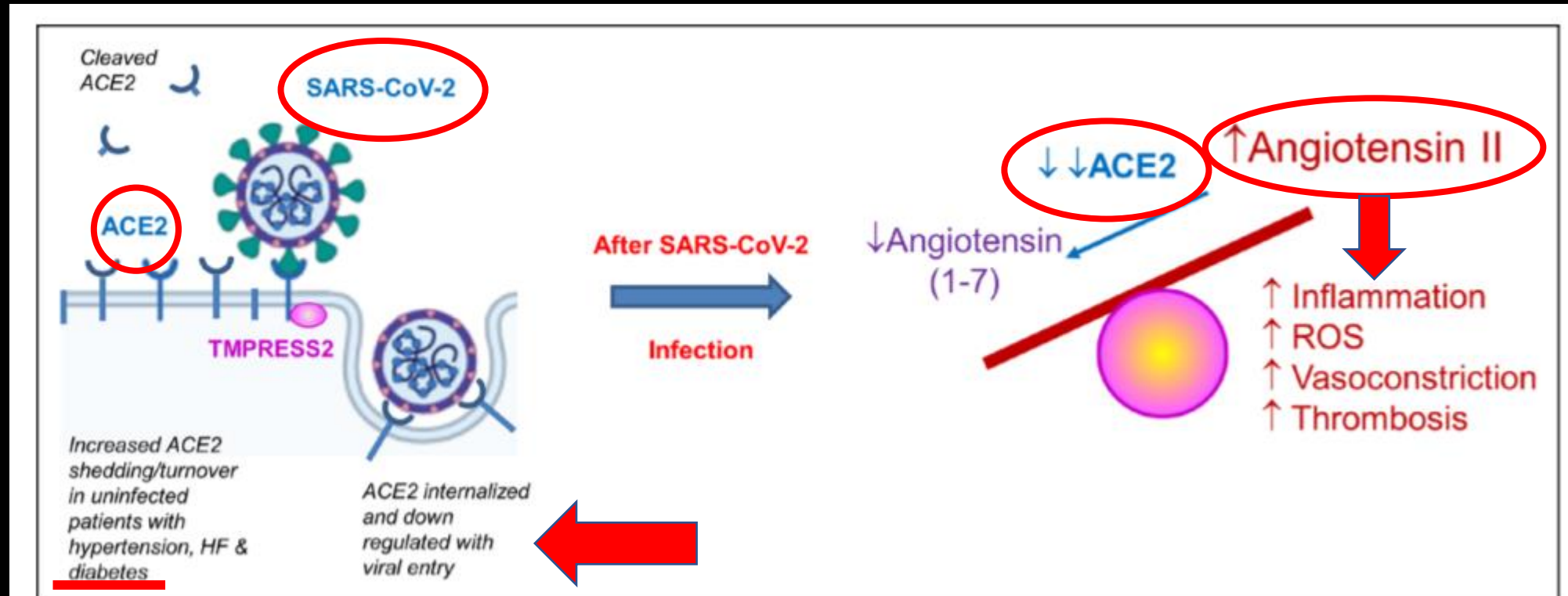
- Has T1D incidence changed during the pandemic?
  - Data from Germany, Italy, and US are mixed
- Frequency and severity of DKA increased in most but not all reports
- Non-Hispanic Blacks and Hispanics with T1D develop more DKA with COVID-19 than Non-Hispanic Whites in US

Endo Diab Obese 2021;28:35-42

JCEM 2021; 106:e1755-e1762

# What Do We Know About ACE2 and Diabetes?

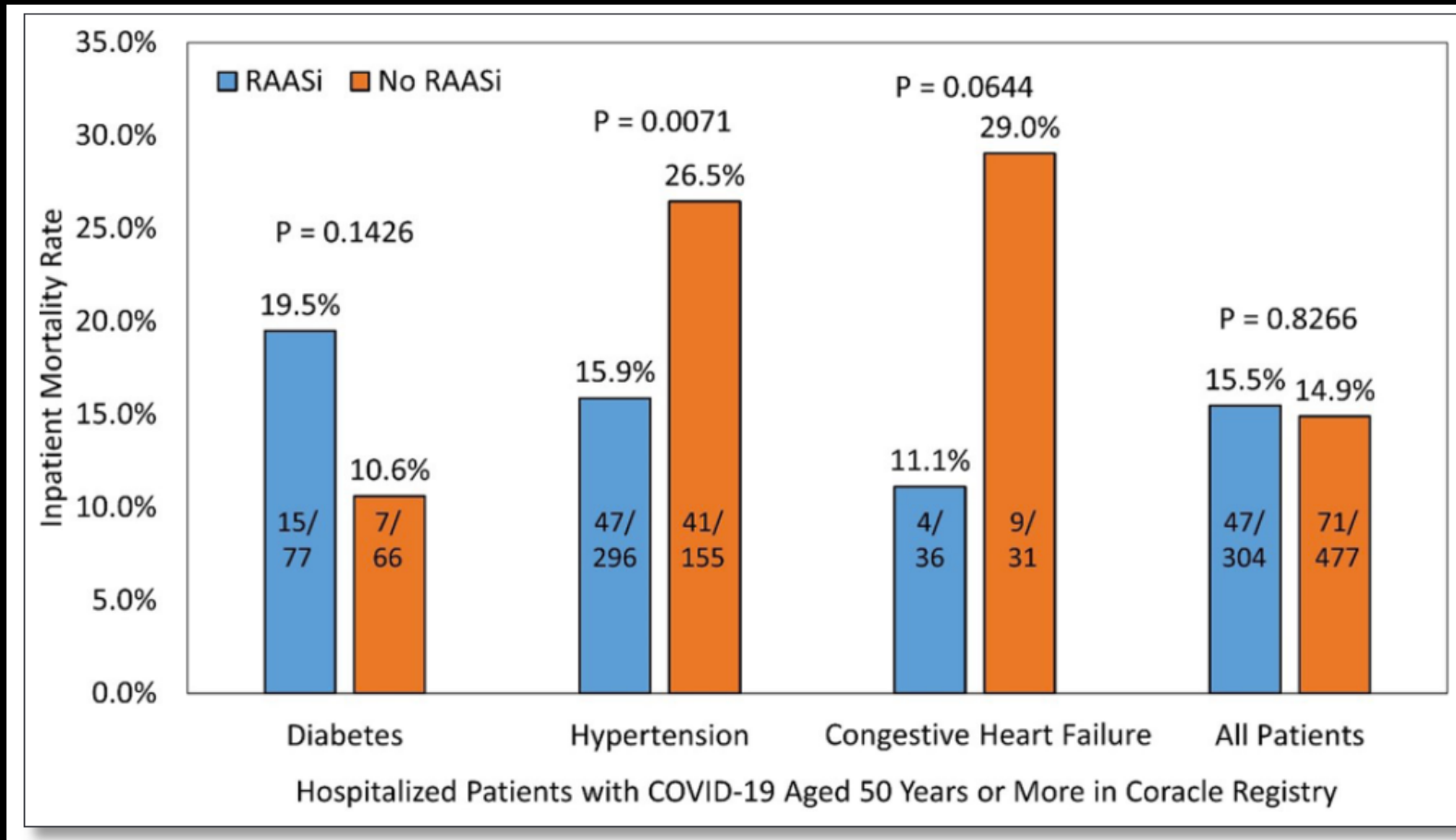
- Angiotensin-converting enzyme2 (ACE2) is a site of entry of the virus into cells
- ACE2 is increased in people with HTN, HF, and DM; downregulated after viral entry





# Diabetes, and renin-angiotensin-aldosterone system inhibitors (N=781, unadjusted)

Long-standing administration of angiotensin-converting enzyme inhibitors (ACEI) and or angiotensin II receptor antagonists/blockers (ARB) leads to an upregulation of ACE-2 on the surface of vascular endothelial cells



Are RAASi protective or harmful with COVID-19 infection? Note the small numbers

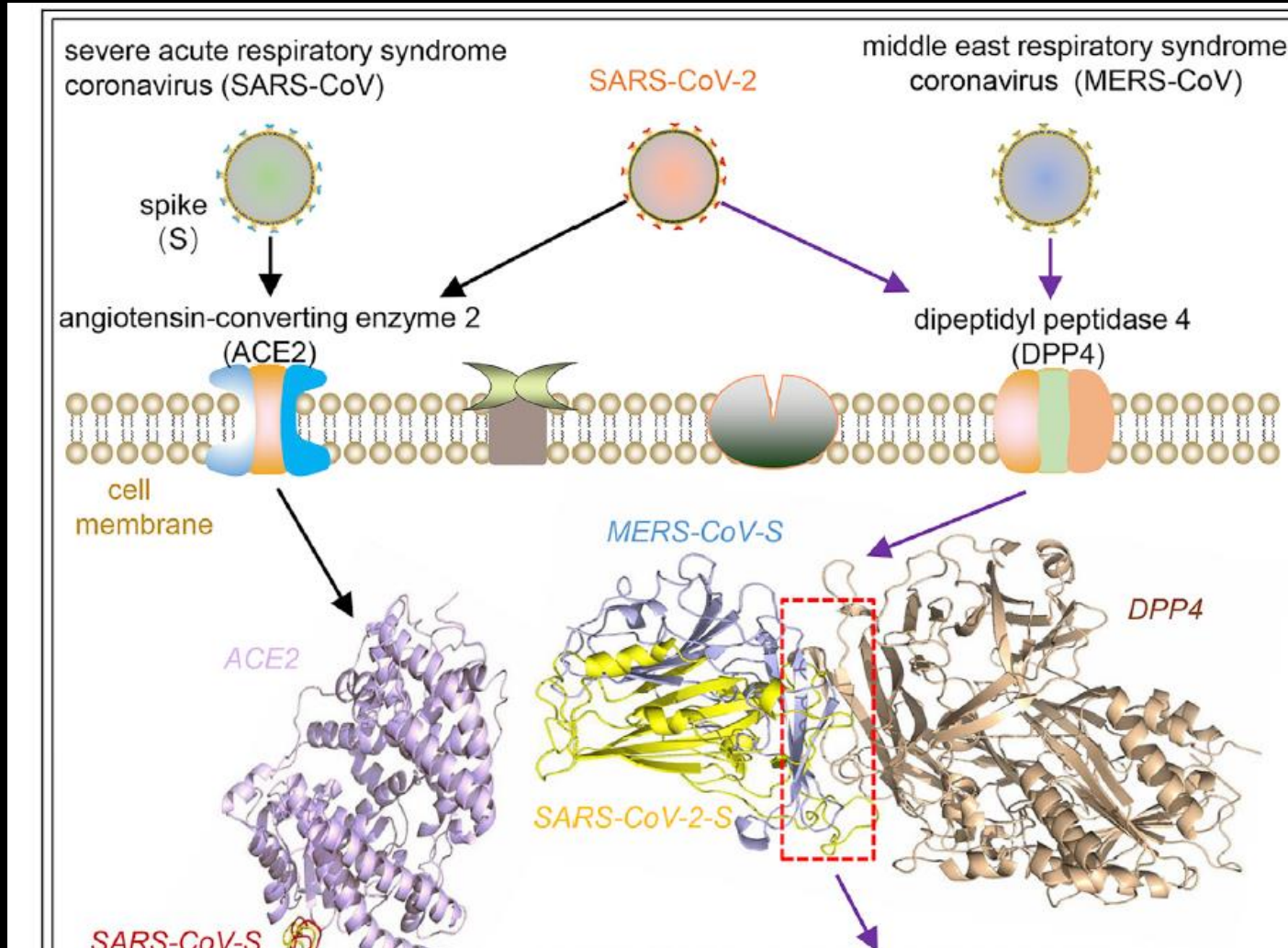
# Cohort Study: Premier Healthcare Data Base (N=64,781 patients, 54.5% inpatient, endpoint = mortality)

	Multivariable Regression	
Diabetes	1.20 (1.12-1.28)	P< 0.001
ACEi	0.53 (0.46-0.60)	P< 0.001
Statin	0.60 (0.56-0.65)	P<0.001

JAMA Network Open. 2020;3(12):e2029058

Conclusions from retrospective data in 2021 for COVID-19 infection and mortality: diabetes (type 2) is a risk factor while the totality of the data suggests ACEi's and statins *may be* protective

# What Has Not Received As Much Attention

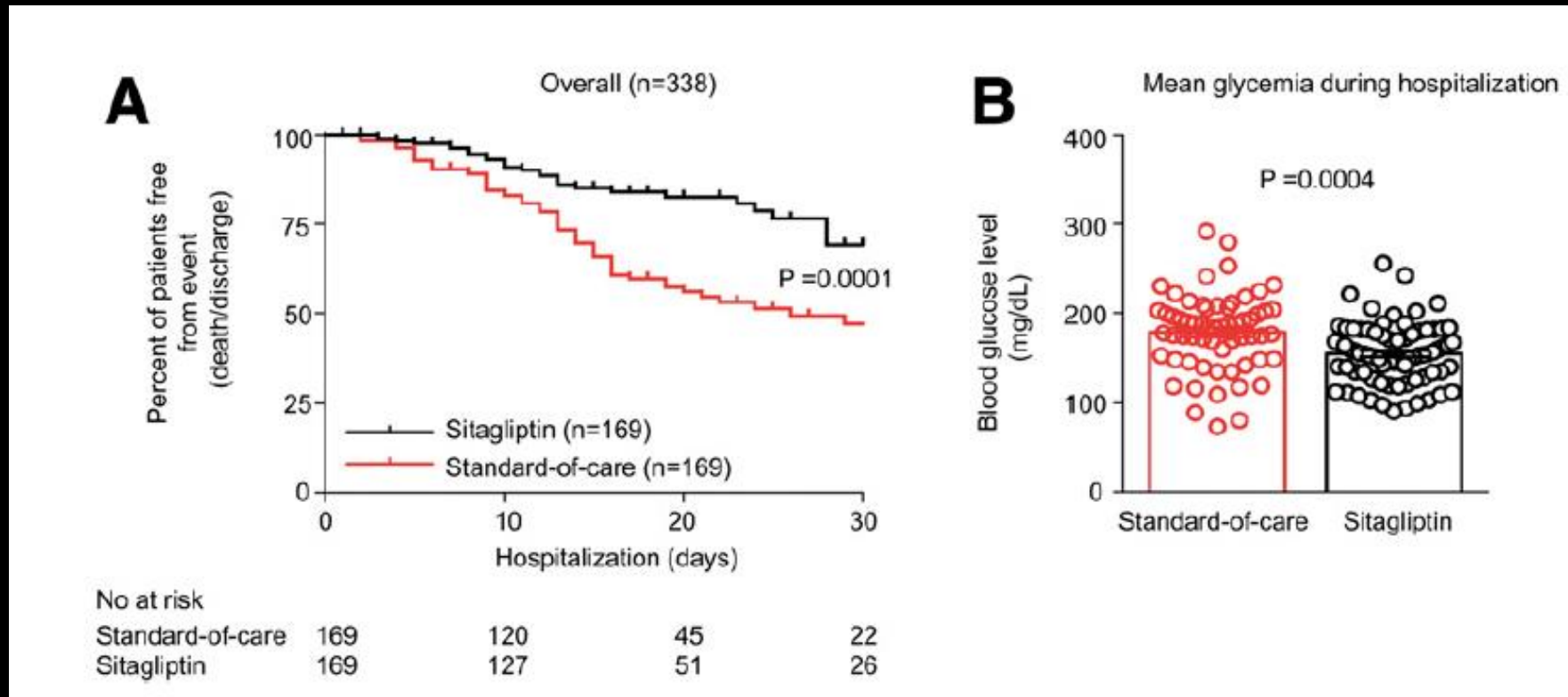


- 2 outbreaks: SARS (2003), MERS (2012)
- MERS-CoV uses DPP4 as the primary receptor
- New studies suggest SARS-CoV2 may also bind DPP4



# Ok, if SARS-CoV2 Binds DPP4 As a Receptor (Entry Point), What is the Impact of DPP4-Inhibitors?

- Multicenter, case-control, retrospective, observational study receiving sitagliptin or not (N=338 with T2D)



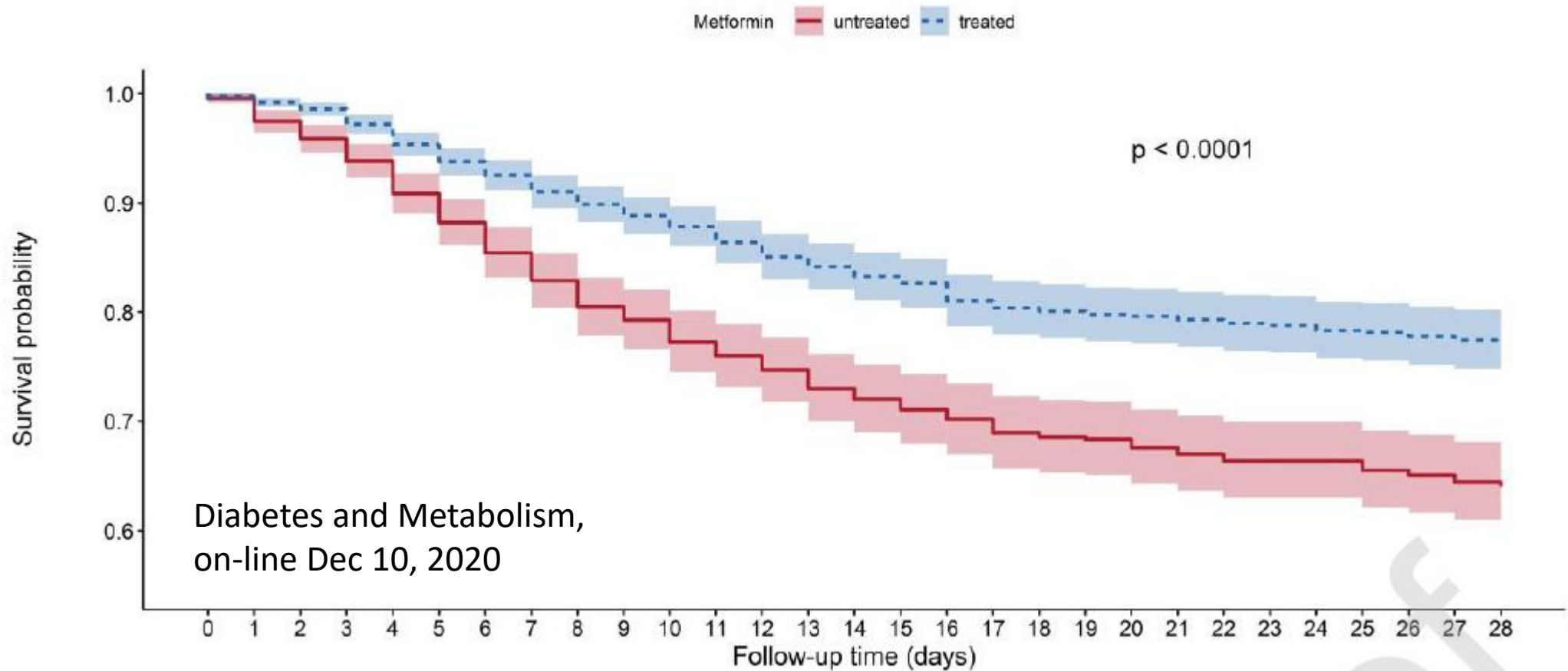
This association is worthy of an RCT

# What is the Impact of COVID-19 Outcomes for Those Already Taking Metformin

- Pubmed search for “metformin” and “COVID-19” on January 2, 2021 reveals 62 articles and all studies retrospective
- Potential mechanism: metformin has many immunosuppressive and anti-inflammatory effects, (including sex-specific effects on  $\text{TNF}\alpha$ )
- For now, totality of data of this retrospective data are mixed and inconclusive
- Some examples...

# CORONADO Trial

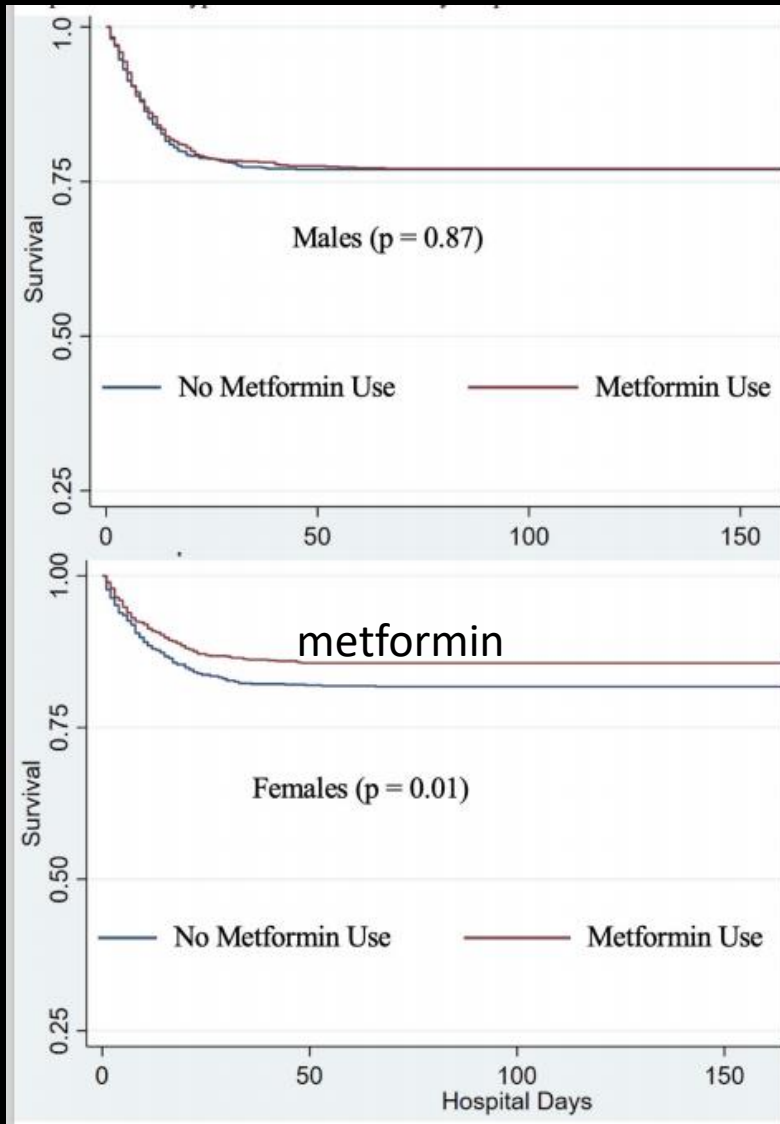
- Observatory study of 2449 subjects, 1496 receiving metformin





# Metformin and COVID-19

- N=6256, 53% women, mean age 75 years using United Health Group data base



“Metformin was significantly associated with reduced mortality in women with obesity or T2DM in observational analyses of claims data from individuals hospitalized with Covid-19. This sex-specific finding is consistent with metformin’s reduction of TNF $\alpha$  in females over males”

# What About SGLT2 Inhibitors in the Era of COVID-19? Pros and Cons

- Pros:
  - Reduces inflammatory markers, cardiac and renal endpoints
  - Reduces myocardial oxygen consumption
  - Reduces lactate which can reduce entry of virus into cells
  - Increases ACE 2 (when enzyme TMPRSS2 not available) which increases AT 1-7 which is a potent vasodilator, anti-oxidant, and anti-fibrotic (reduce ARDS?)
- Cons
  - Concerns of volume depletion and hypotension
  - Numerous cases of eDKA reported associated with COVID-19 infection

# Update on the DARE-19 Phase III trial for Farxiga in COVID-19

12 April 2021 07:00 BST

AstraZeneca and Saint Luke's Mid America Heart Institute today announced high-level results of the primary analysis from the DARE-19 Phase III trial assessing the potential of *Farxiga* (dapagliflozin) to treat patients hospitalised with COVID-19 who are at risk of developing serious complications.

The trial did not achieve statistical significance for the primary endpoint of prevention measuring organ dysfunction and all-cause mortality, and the primary endpoint of recovery measuring a change in clinical status (from early recovery to death), at 30 days.

ADA Sci Sessions, June 2021: “numerically fewer patients treated with dapagliflozin experienced organ failure and death, and this was consistent across the components — respiratory, cardiovascular, kidney complications and death”

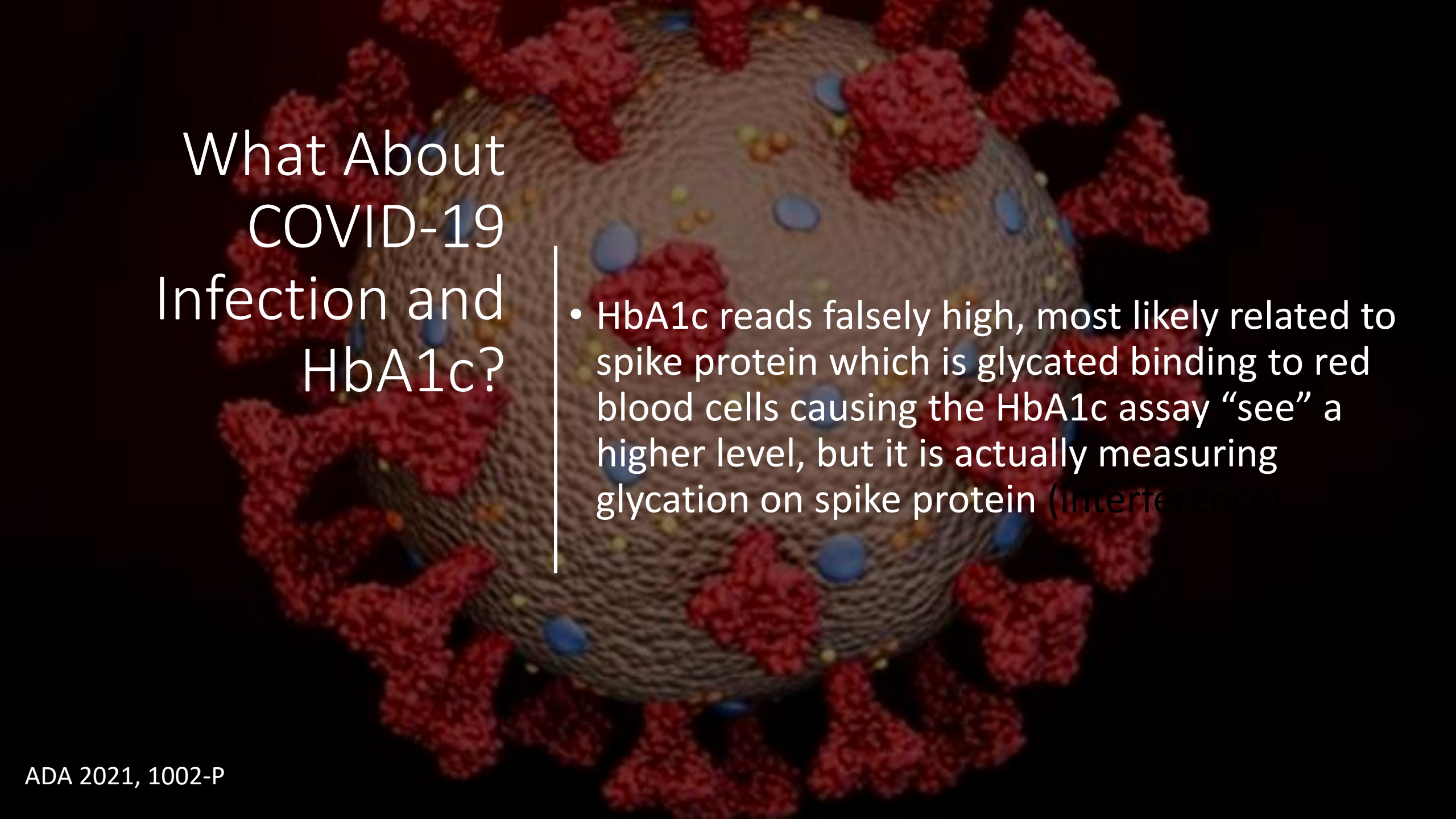
# What To Expect with Diabetes Drugs and COVID-19

- SYMPATICO: RCT using SC semaglutide to reduce myocardial injury in patients with COVID-19



More data on DPP-4 inhibitors?





# What About COVID-19 Infection and HbA1c?

- HbA1c reads falsely high, most likely related to spike protein which is glycated binding to red blood cells causing the HbA1c assay “see” a higher level, but it is actually measuring glycation on spike protein (interference)

# Conclusions: COVID-19 and Diabetes, July 2021

- 40% of American mortality from COVID-19 has been from people with diabetes
- Unvaccinated Americans with diabetes is a major public health problem
- The data are mixed with the association between outpatient glycemic control and mortality in T2D
- The totality of evidence suggests RAAS inhibitors either have no effect or may be beneficial to COVID-19 outcomes

# Conclusions: COVID-19 and Diabetes, July 2021

- There are interesting theoretical reasons DPP4 inhibitors may improve outcome and as of now they appear to be safe and may be beneficial.
- SGLT2 inhibitors do not have data to support their routine use for the treatment of COVID-19 infection.
- COVID-19 is yet another reason resulting in HbA1c discordance.

Thank You



12/24/2020