Passive Immunotherapy for COVID-19

The 3rd Webinar in the INA-RESPOND COVID-19 Series: COVID-19 Treatment

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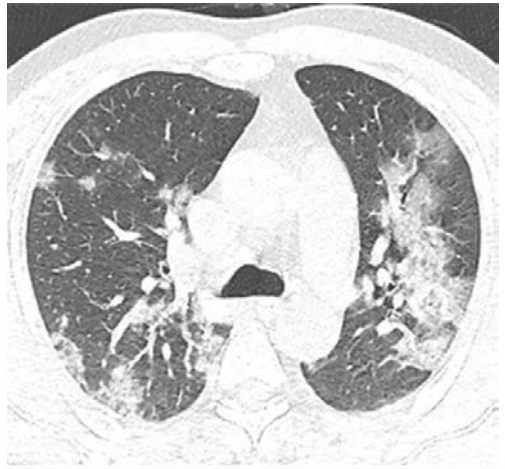
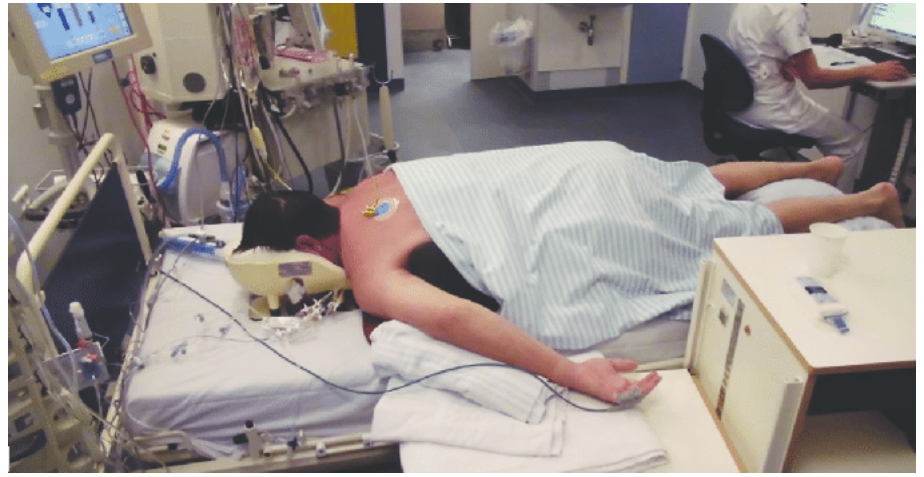
Different Stages of COVID-19 Illness

COVID-19+ Disease Progression

No Symptoms → Outpatient, Mild Symptoms → Inpatient, No Oxygen → Inpatient, Low-flow Oxygen → Inpatient, High-flow Oxygen → Mechanical Ventilation





Anti-viral Strategies

Immunomodulatory Strategies

Anti-coagulation Strategies

Passive Antibody Therapy in COVID-19

- Convalescent plasma 
  - Emergency Use Authorization (EUA) in the US for hospitalized patients; minimal supportive data
- Immune IVIg 
  - Failed to show benefit in a RCT in hospitalized patients
  - Soon to be studied in ambulatory patients
- Monoclonal Antibodies 
  - Available under EUA for ambulatory patients at high-risk of serious disease.
  - Thus far no benefit demonstrated in hospitalized patients

Single Donor Convalescent Plasma

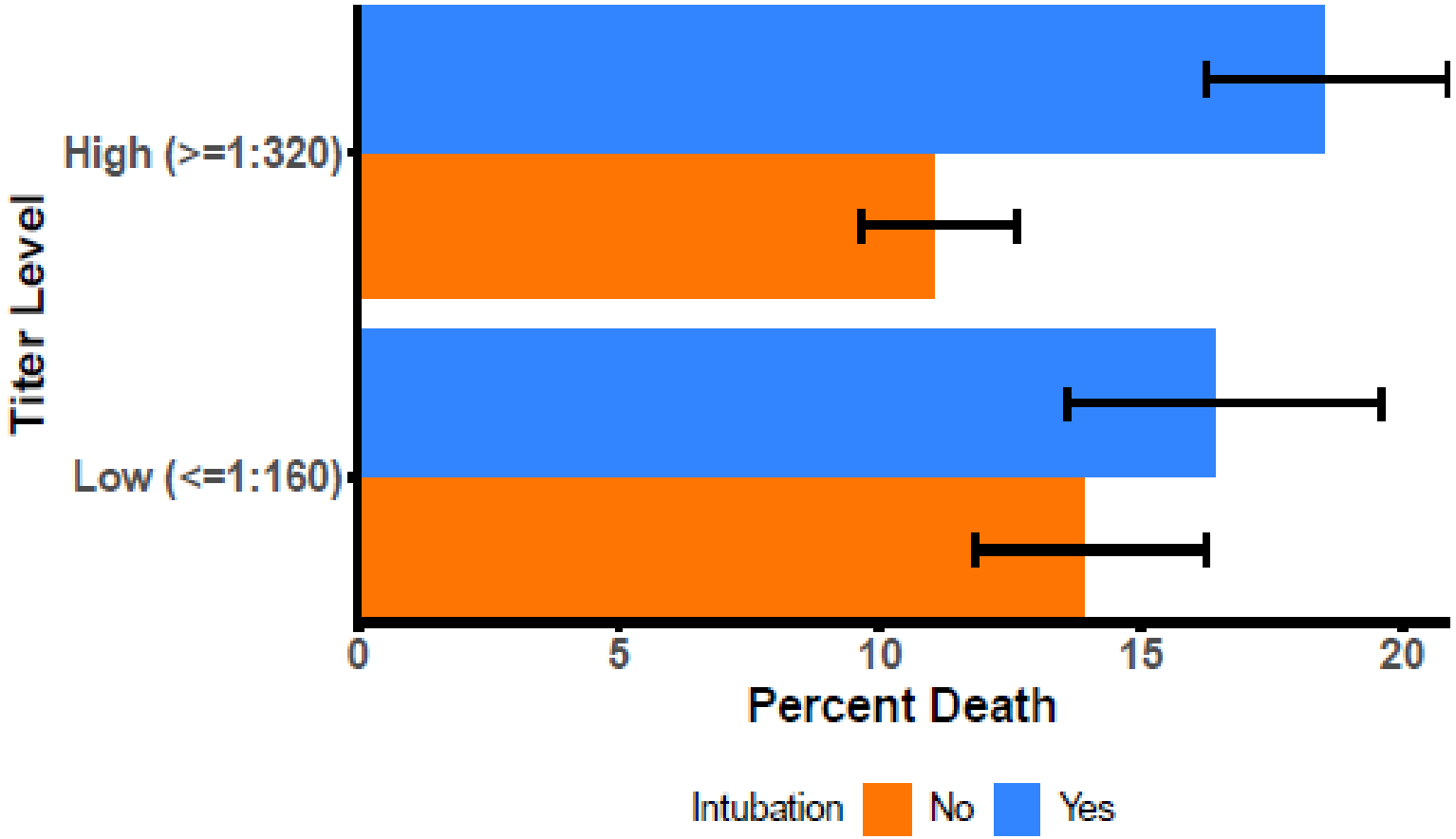
- A perennial favorite in the setting of a new outbreak dating back to the 1918 influenza pandemic; 19th century treatment for diptheria and tetanus
- Multiple anecdotes of success in diseases ranging from influenza to SARS to Ebola
- Only one randomized, controlled trial with efficacy:
  - 1979 – Improved survival in patients with Argentine Hemorrhagic Fever (16.5% vs. 1.1%)
  - Had to be given within 8 days of symptom onset
  - Associated with a delayed neurologic syndrome

Convalescent Plasma in COVID-19

- Promoted early in the outbreak: available in 3 waves
  - Single patient access via emergency IND (eIND)
  - Expanded Access Program (EAP) via the Mayo Clinic (89,850 units infused)
  - Emergency Use Authorization (EUA)
- Promising data from above observational studies not supported by emerging RCT data

Exploratory Inpatient Efficacy
Mayo Expanded Access Program

Initial Cohort (n=4330)



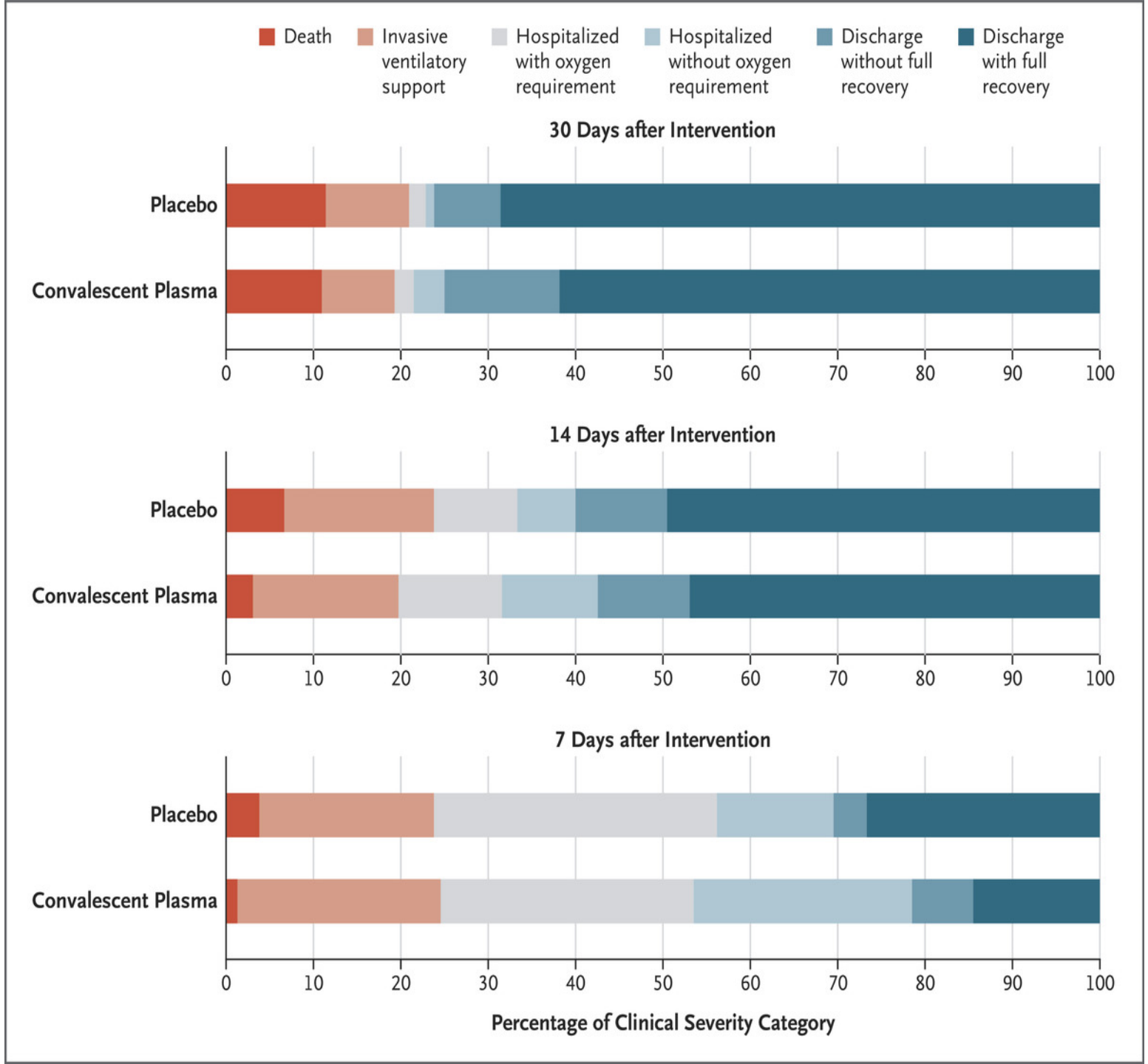
Higher titer plasma administered to patients not intubated resulted in a reduction in 7-day mortality from 14% to 11% (p=0.03)

COVID-19 Convalescent Plasma In Hospitalized Patients (PlasmAr) Study (n=333)

- Multi-center, randomized placebo-controlled trial
  - Plasma with a median titer of 1:3200 (>1:800)
- Patients with evidence of COVID-19 pneumomia
- Primary Endpoint: clinical status at 30 days as defined by a 6-category ordinal scale
- Conducted by 12 clinical sites in Argentina and coordinated by the Hospital Italiano de Buenos Aires

PlasmAr– Primary Endpoint

OR = 0.83
95% CI = 0.52 – 1.35
p=0.46



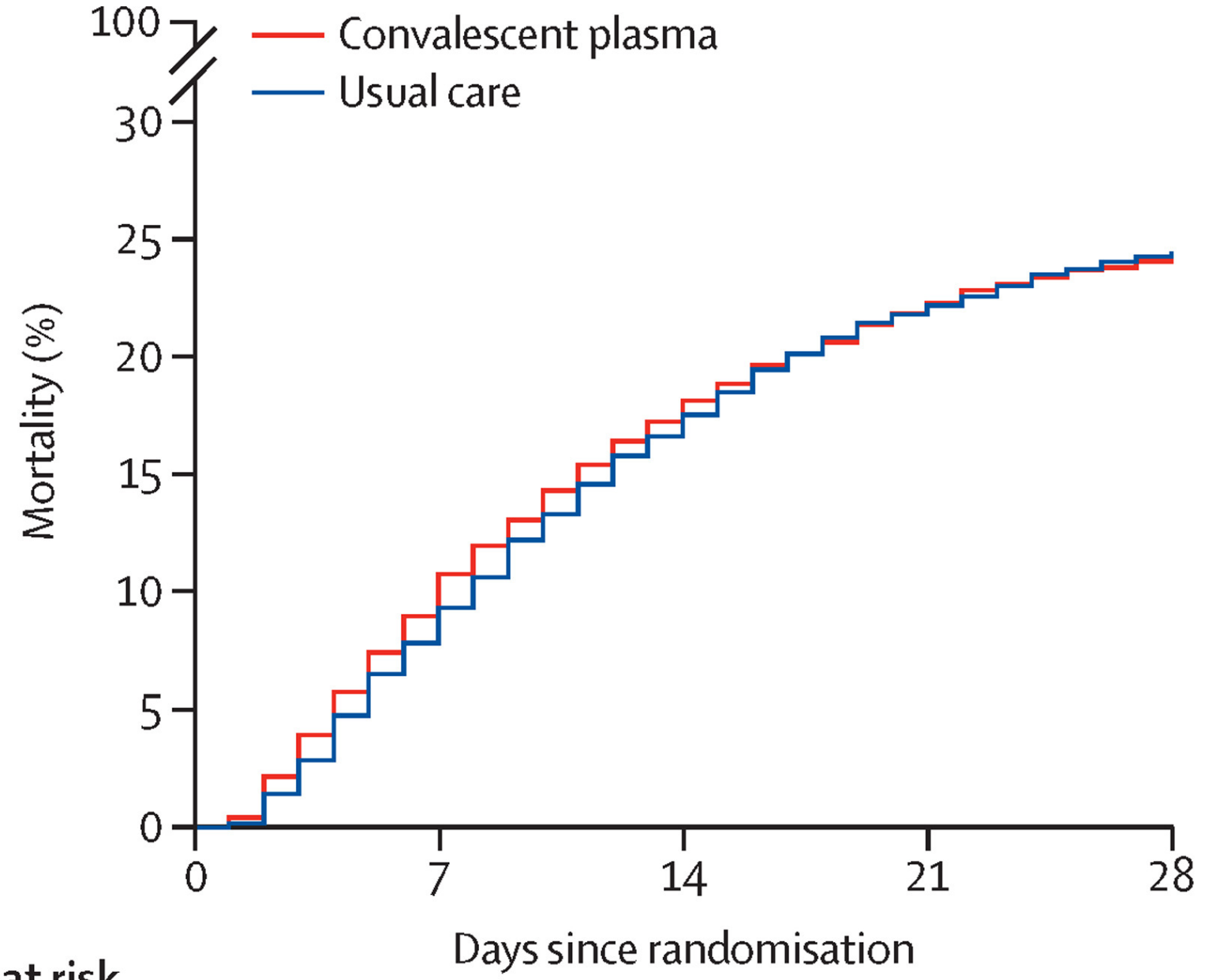
VA Simonovich et al.
N Engl J Med 2021;384:619-629.

The UK Randomization of COVID-19 Therapy (RECOVERY) Trial

- A “real-world” randomized, controlled trial facilitated by the UK National Health System
- Physicians throughout the UK able to randomize hospitalized patients to standard care or standard care + intervention (~2000/arm):
- Agents shown to be of benefit:
  - Dexamethasone
  - Tocilizumab
  - Casirivimab / Imdevimab in antibody-negative patients

RECOVERY: Convalescent Plasma Arm – 28-day Mortality n=11,558

RR = 1.0
95% CI = 0.93– 1.07
p=0.95

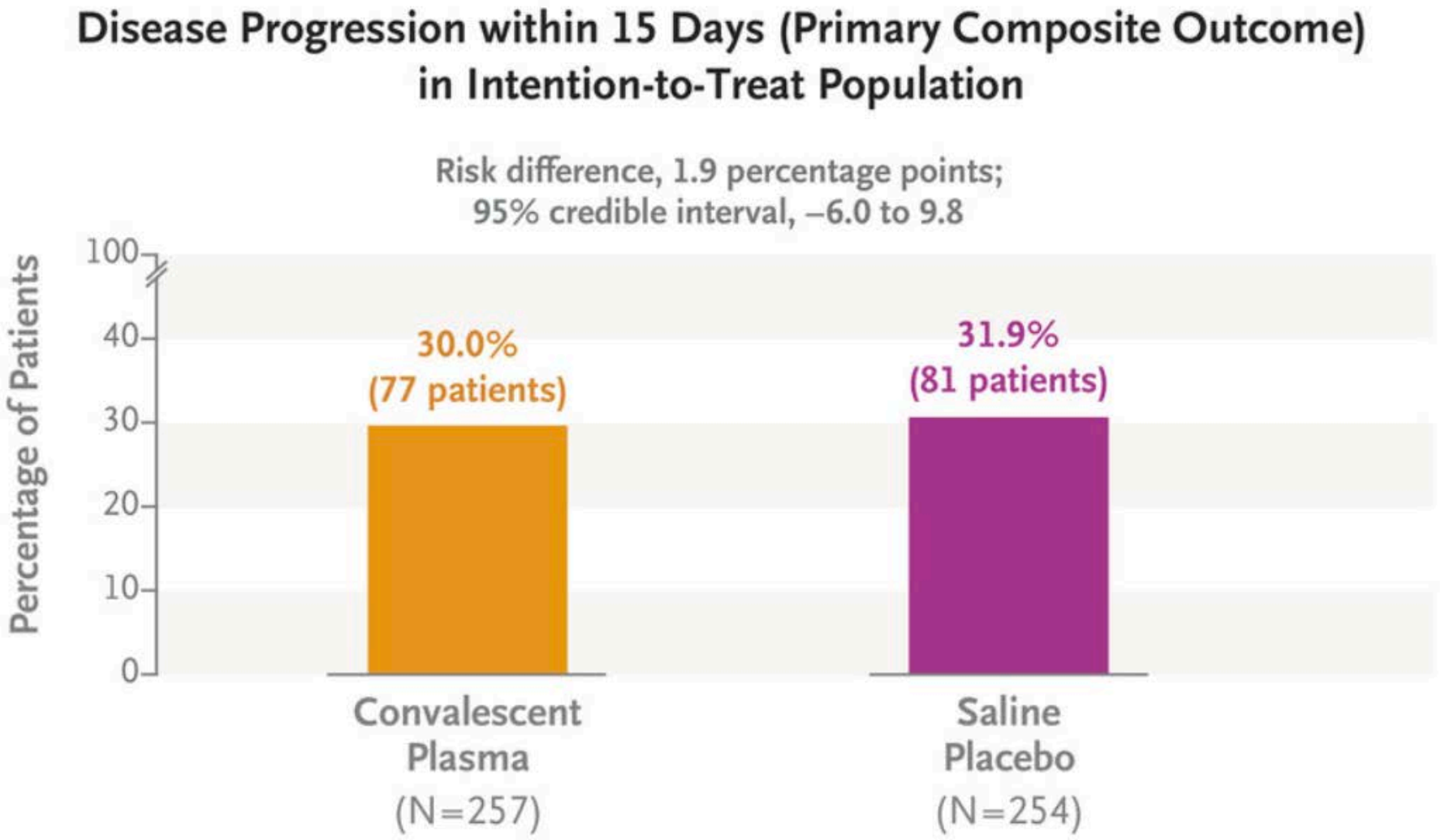


Number at risk					
Convalescent plasma	5795	5152	4725	4484	4373
Usual care	5763	5215	4740	4472	4339

COVID-19 Convalescent Plasma In Outpatients (C3PO) Study (n=511)

- Phase 3, multi-center, placebo-controlled trial
  - Plasma with an ID_{50} >1:250 vs. saline
- Patients at high risk (age ≥50 and/or co-morbidities)
- Symptoms ≤7 days
- Primary Endpoint a composite of ER visit, hospital admission or death within 15 days
- Conducted by the SIREN Network (NHLBI and NINDS)

C3PO Study – Primary Endpoint



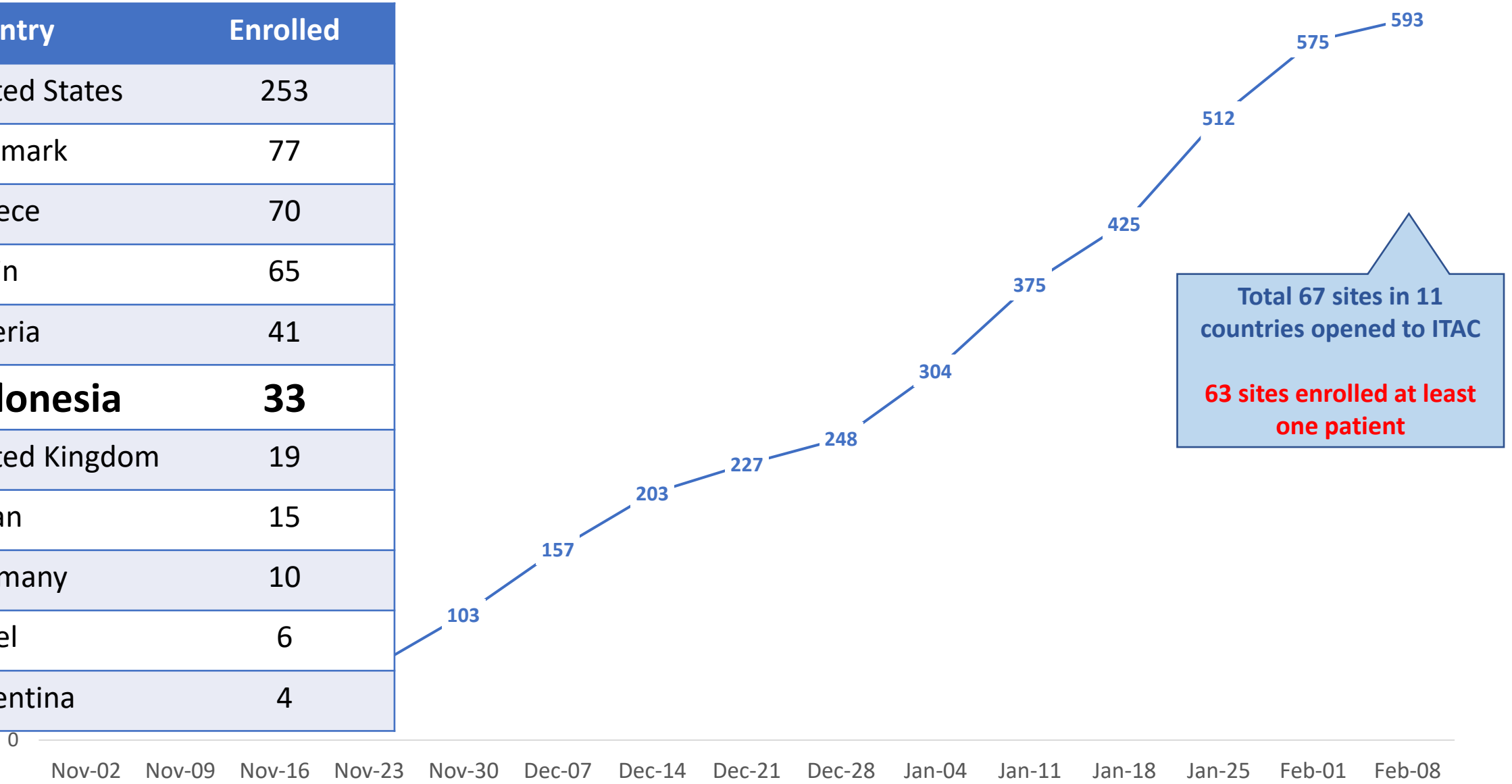
FK Korley et al. N Engl J Med 2021;385:1951-1960.

Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC) INSIGHT Protocol 013 (n=93)

- Phase 3, multi-center, placebo-controlled trial
  - One of 4 Immune IVIg products vs. saline
- Patients hospitalized for COVID-19 without end-organ failure
- Symptoms ≤12 days
- Primary Endpoint: clinical status at day 7 using a 7-category ordinal scale

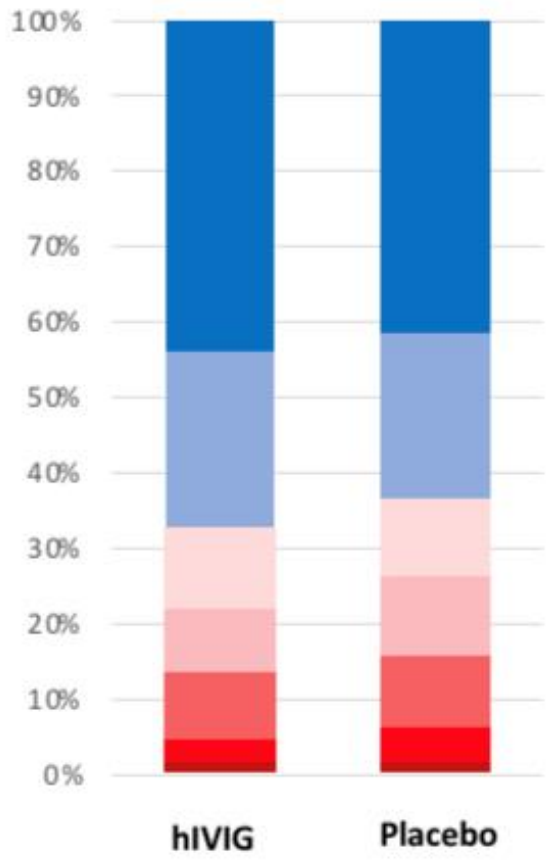
Enrollment

Country	Enrolled
United States	253
Denmark	77
Greece	70
Spain	65
Nigeria	41
Indonesia	**33**
United Kingdom	19
Japan	15
Germany	10
Israel	6
Argentina	4



Primary Efficacy Outcome at Day 7

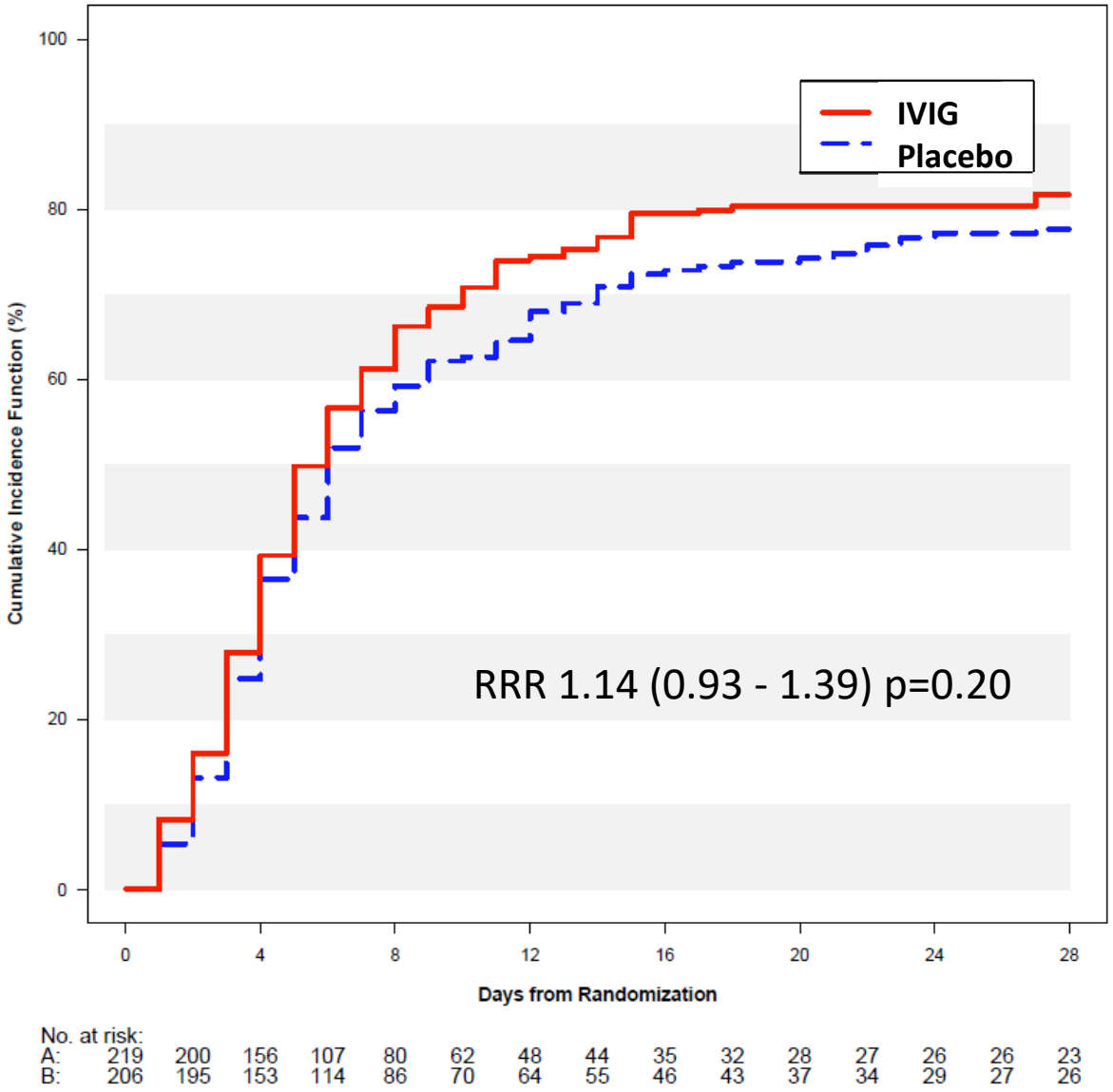
Category		hIVIG	Placebo
		No. of patients (%)	
Better	1	129 (44.0%)	116 (41.6%)
	2	66 (23.2%)	61 (21.9%)
	3	31 (10.6%)	28 (10.0%)
	4	25 (8.5%)	30 (10.8%)
	5	26 (8.9%)	26 (9.3%)
	6	9 (3.1%)	13 (4.7%)
Worse	7	5 (1.7%)	5 (1.8%)



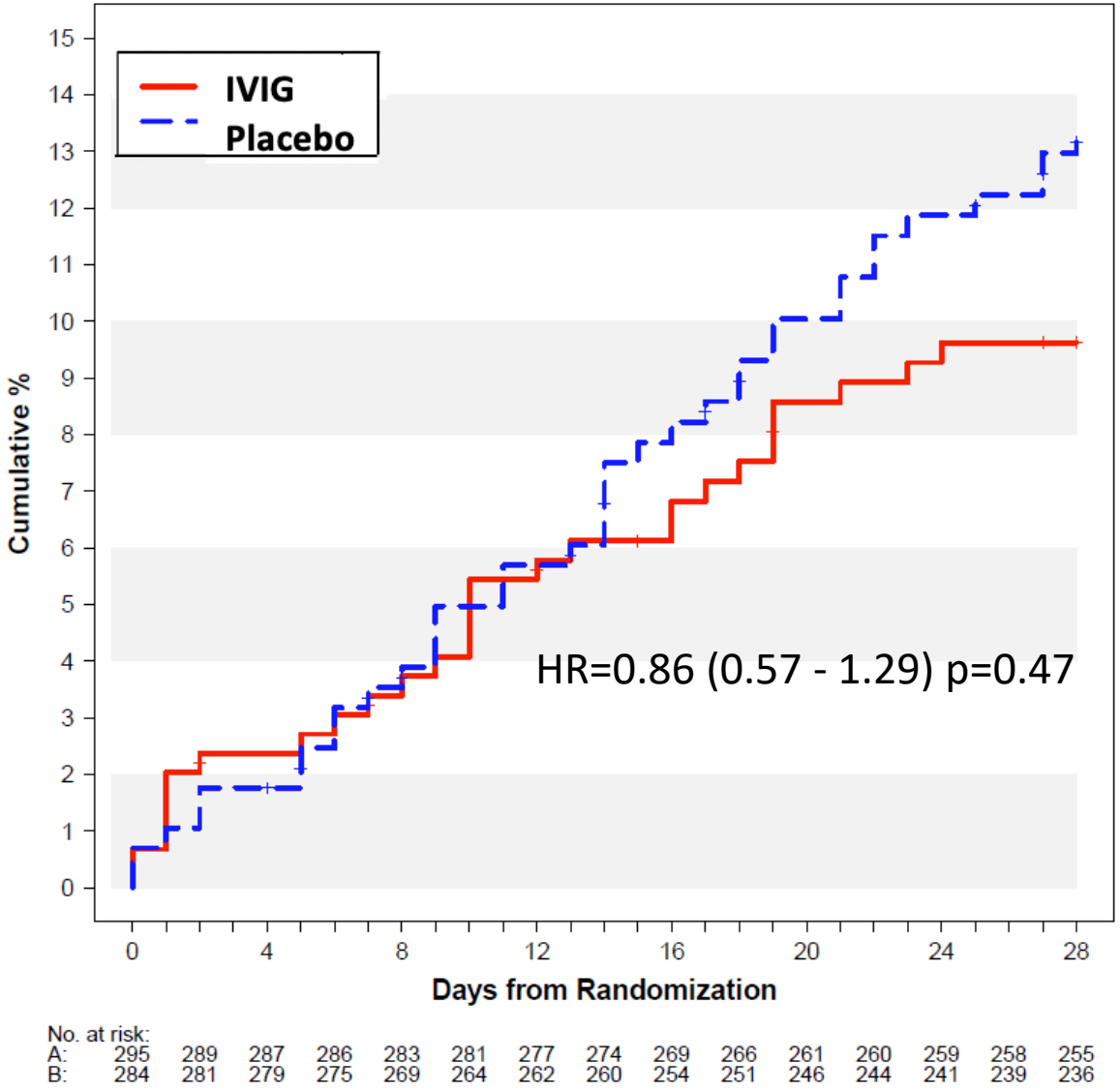
- Can independently undertake usual activities with minimal/no symptoms
- No supplemental oxygen; symptomatic and unable to independently undertake usual activities
- Supplemental oxygen < 4 liters/min
- Supplemental oxygen ≥ 4 liters/min or symptoms/signs of extra-pulmonary conditions
- Non-invasive ventilation, high flow oxygen or symptoms and signs of acute stroke (NIHSS > 14)
- Invasive ventilation, ECMO, mechanical circulatory support, vasopressor therapy or renal replacement therapy
- Death

Summary OR 1.08 (95% CI 0.79 – 1.48) p = 0.63

Time to Two Most Favorable Ordinal Categories (Recovery)



Time to Serious Adverse Event or Death



Conclusions from ITAC

- **No evidence of a beneficial effect of SARS-CoV=2 IVIG in individuals hospitalized with COVID-19.**
- **Aligns with other recent findings for convalescent plasma and MoAbs in similar patient populations.**
- **Role for immune IVIG in non-hospitalized individuals with earlier infection requires evaluation (OTAC)**

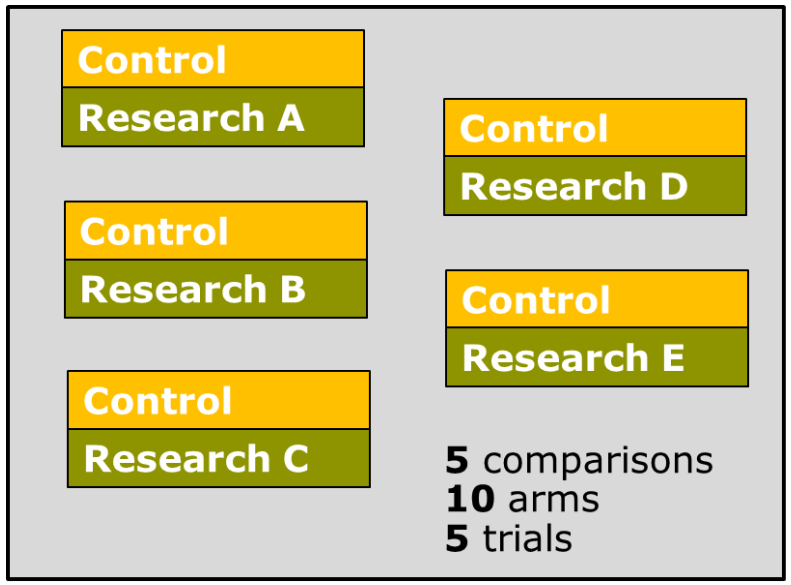
Monoclonal Antibodies to the Spike Protein of SARS-CoV-2

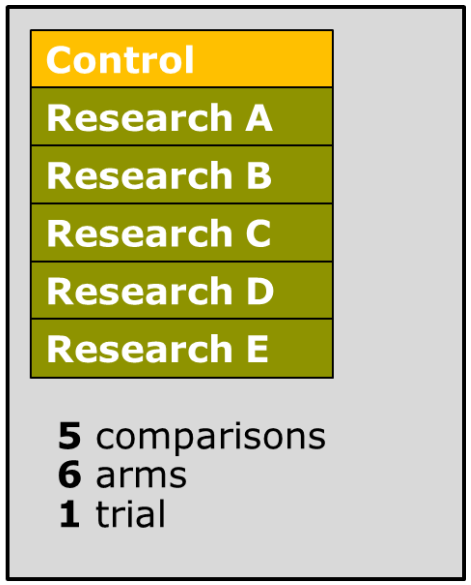
- Have been shown to be of benefit in decreasing the 5-7% rate of progression to severe disease in high-risk individuals by 2-6% absolute; 70-85% relative
- Have been shown to be of benefit in a post-exposure setting
- Have not been shown to be of benefit overall in hospitalized patients

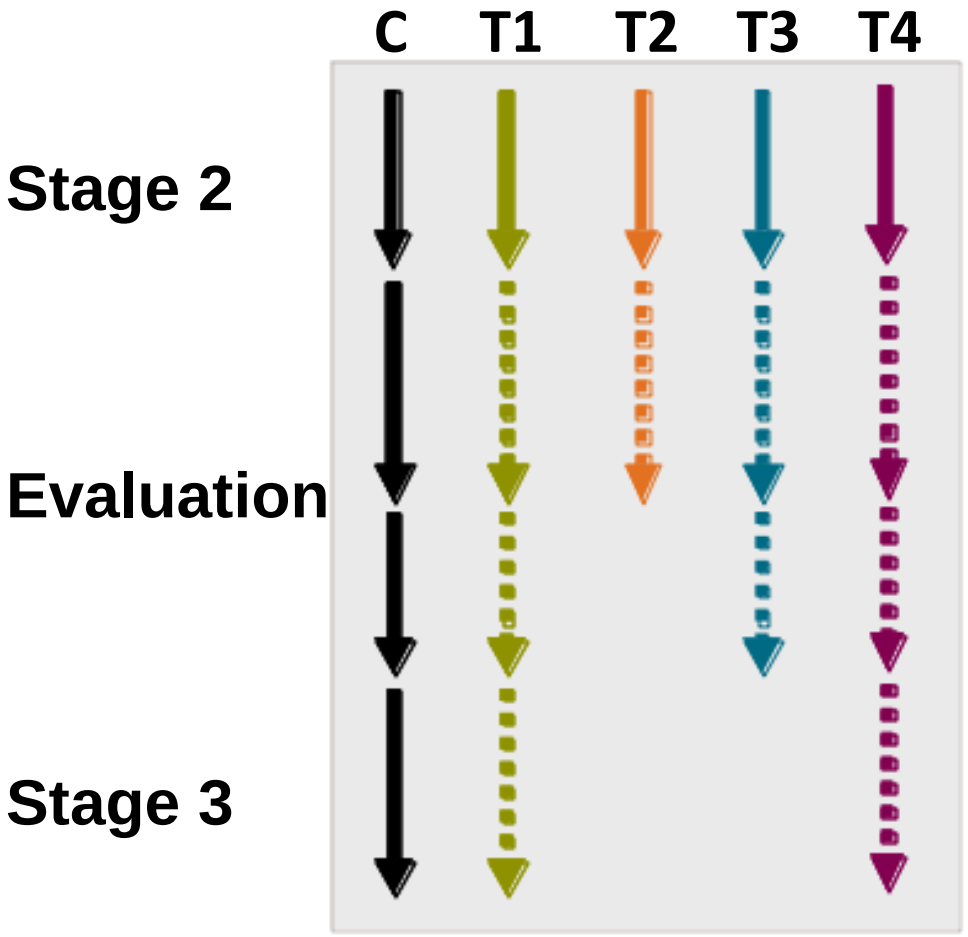
Monoclonal Antibodies Available in the US Under Emergency Use Authorization

- Bamlanivimab / Etesevimab (intravenous)
  - Human monoclonals; less effective against beta and gamma variants; ?omicron
- Casirivimab / Imdevimab (intravenous or SQ)
  - Human and humanized mouse
  - Authorized for treatment and post-exposure
- Sotrovimab (intravenous)
  - Human monoclonal to SARS-CoV-1

Therapeutics for Inpatients with COVID-19 (TICO; INSIGHT 014; ACTIV-3) A Multi-Arm, Multi-Stage Trial



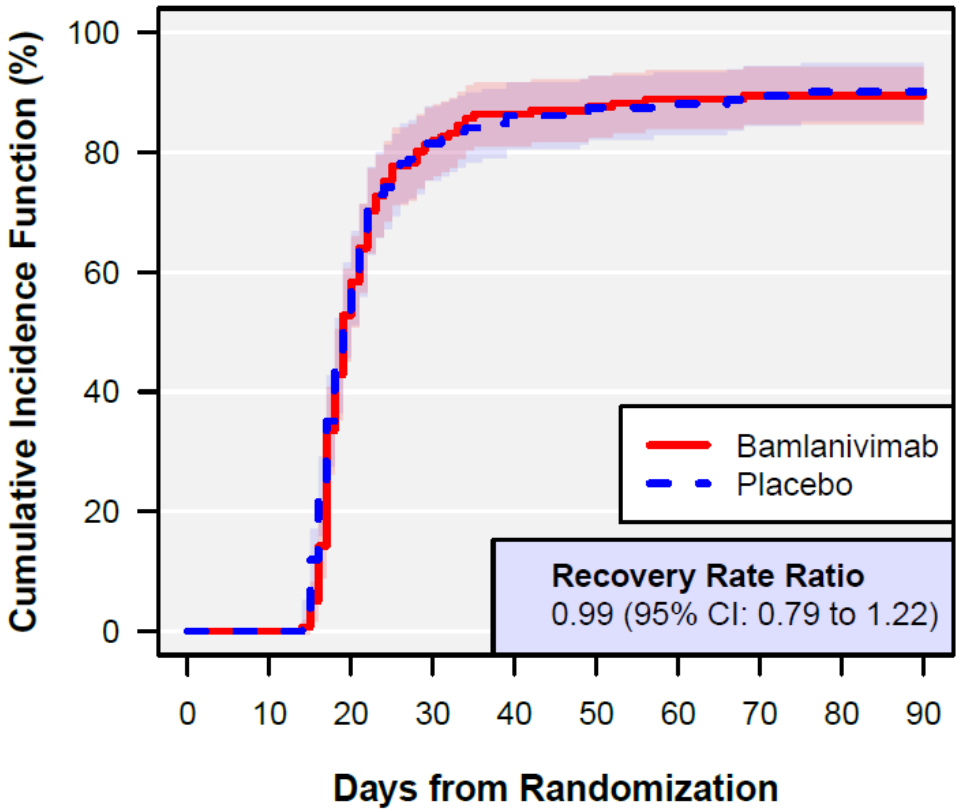




Mahesh Parmar, UK MRC, UCL

Bamlanivimab in Hospitalized Patients (TICO) Sustained Recovery* & Hospital Discharge

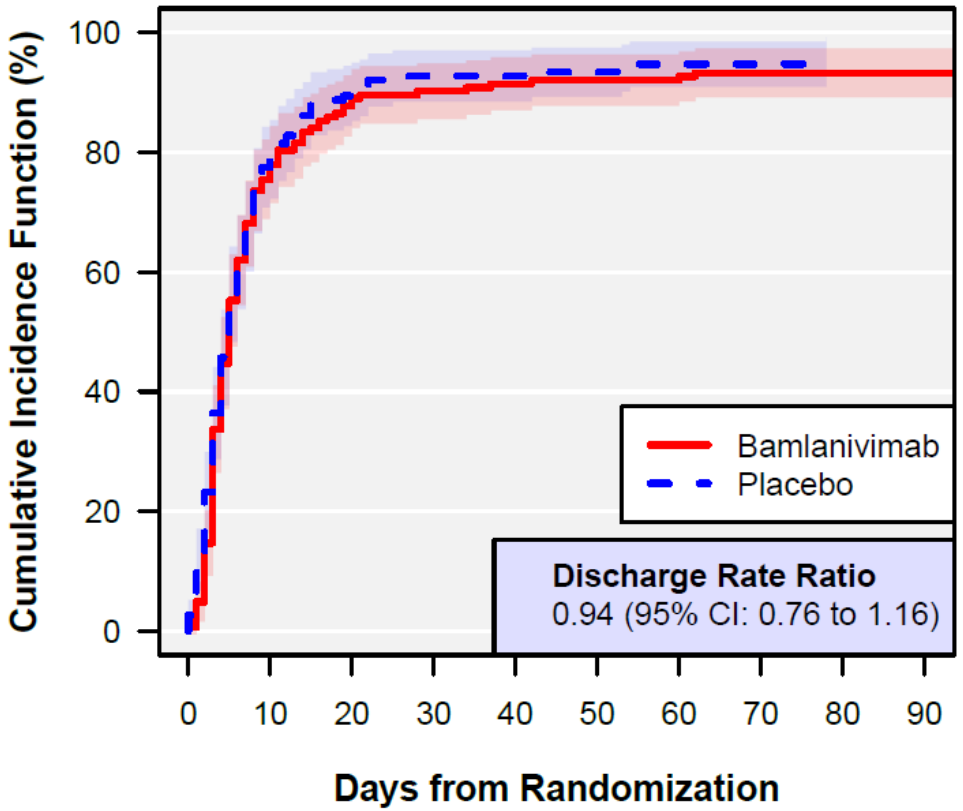
Time to Sustained Recovery*



Number at Risk:

Bam.:	163	160	72	22	11	9	6	5	4	4
Placebo:	151	150	65	21	13	10	9	7	4	4

Time to Hospital Discharge



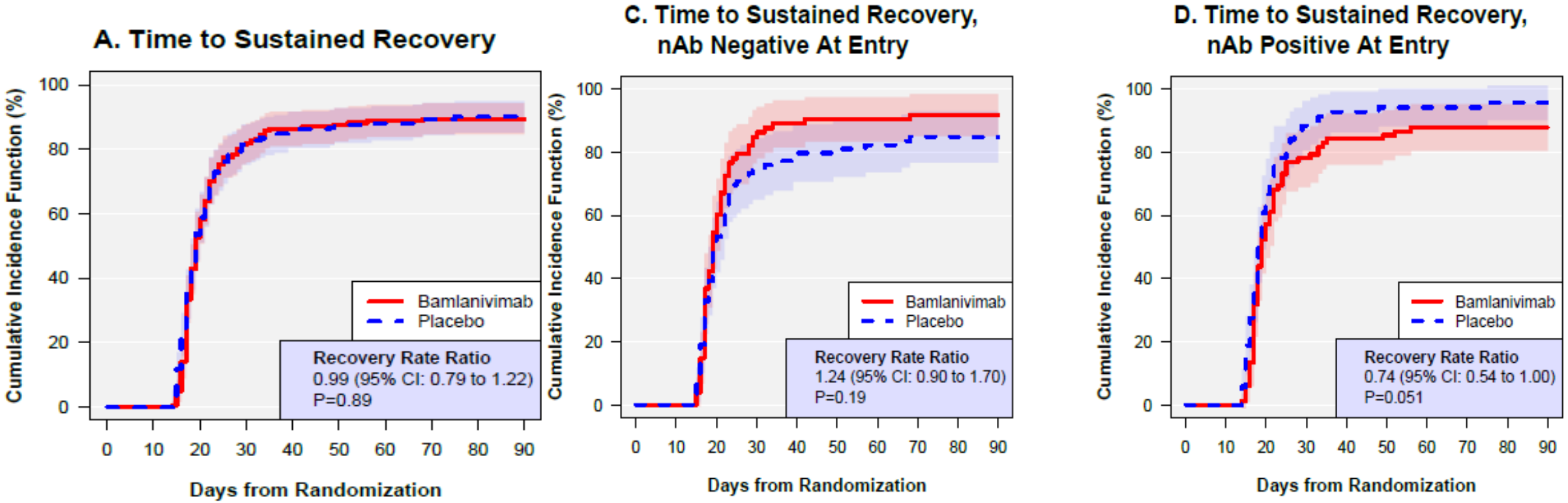
Number at Risk:

Bam.:	163	38	16	10	5	4	3	1	1	1
Placebo:	151	34	14	7	6	4	2	2	0	0

***Sustained recovery** = return to pre-hospitalization residence for ≥14 consecutive days.

Lundgren, et al.
N Engl J Med 2021; 384:905-914

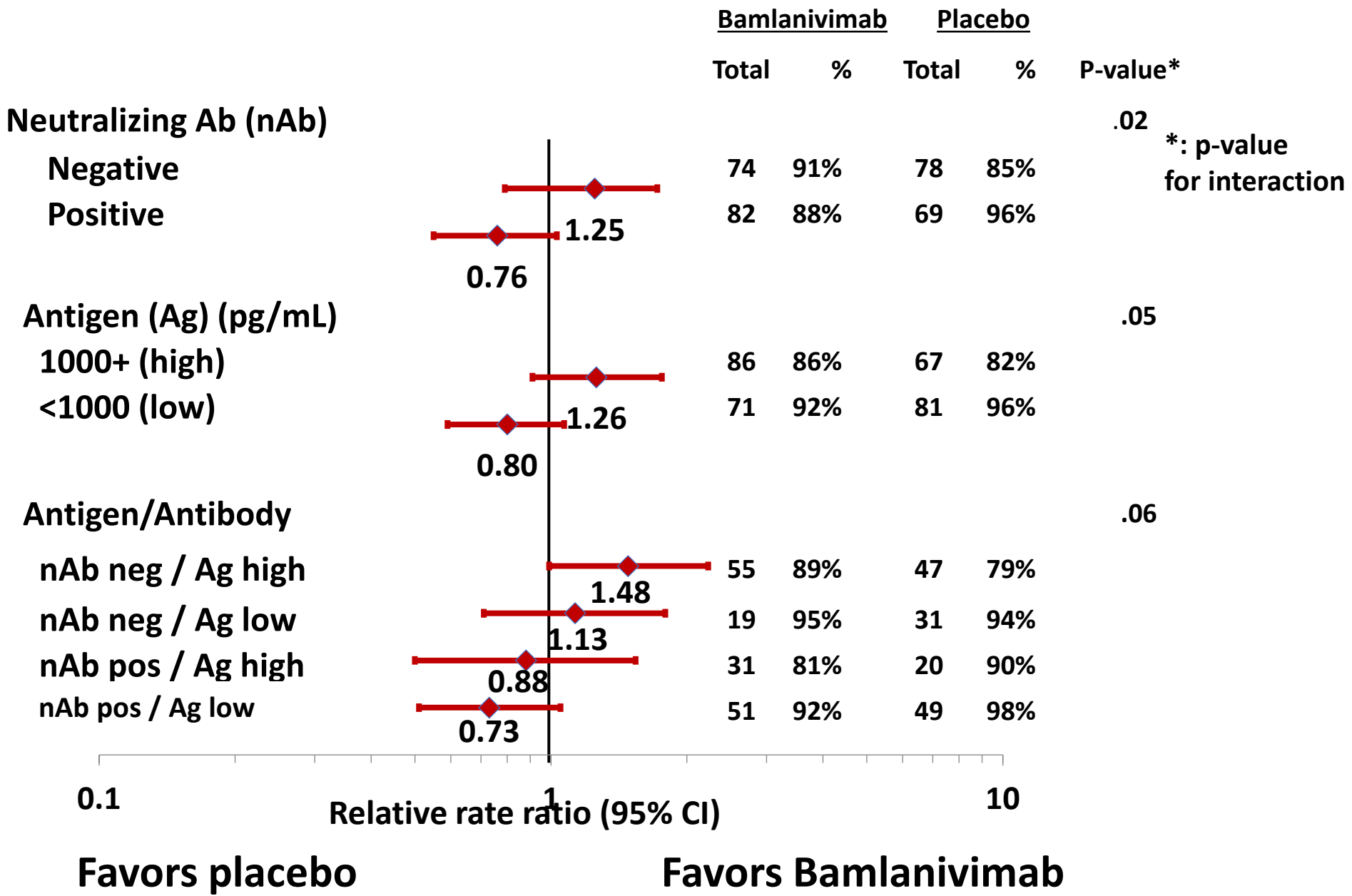
Bamlanivimab: Time to Sustained Recovery by Baseline Serostatus



P value = 0.02 for interaction between baseline nAb status and treatment effect

ACTIV-3/TICO Bamlanivimab Study Group. Clinical and Virological Response to a Neutralizing Monoclonal Antibody for Hospitalized Patients with COVID-19. MedRxiv 2021. https://doi.org/10.1101/2021.07.19.21260559

Sustained Recovery for Bamlanivimab vs Placebo by Baseline Antigen and Antibody Levels



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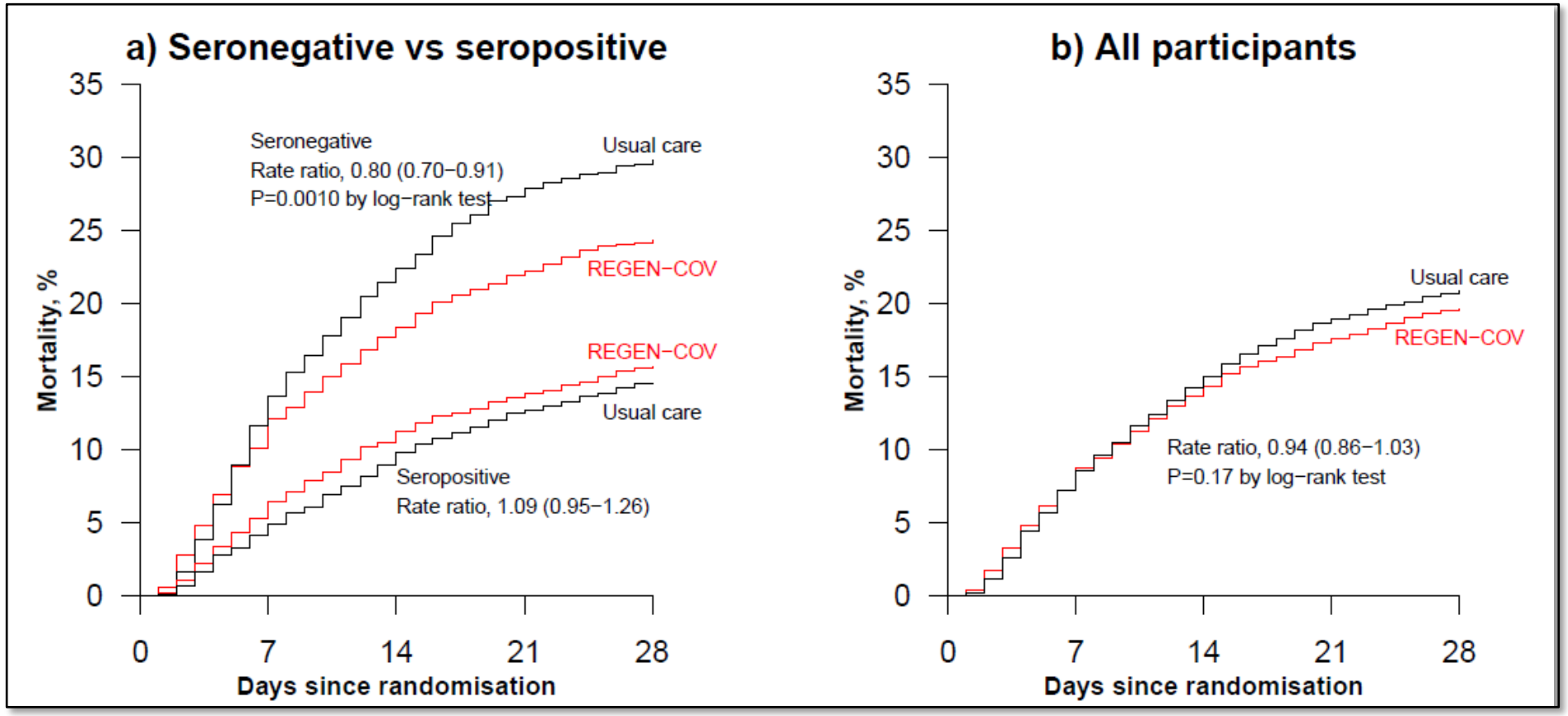
- A “real-world” randomized, controlled trial facilitated by the UK National Health System
- Physicians throughout the UK able to randomize hospitalized patients to standard care or standard care + intervention (~2000/arm):
- Agents shown to be of benefit:
  - Dexamethasone
  - Tocilizumab
  - Casirivimab / Imdevimab in antibody-negative patients

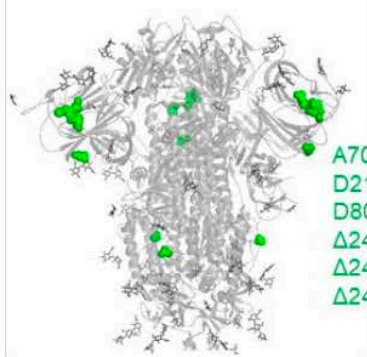
RECOVERY: casirivimab + imdevimab



- Serostatus determined by Oxford immunoassay: indirect ELISA, for serum IgG against trimeric spike protein

medRxiv preprint doi: https://doi.org/10.1101/2021.06.15.2125854

Spike Mutations in the Variants of Concern



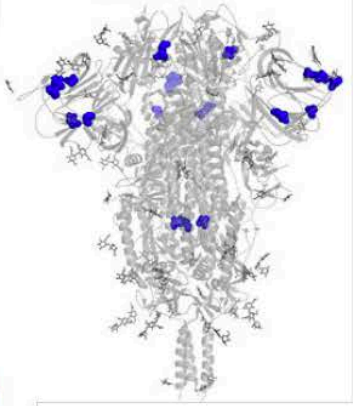
6 unique spike mutations in beta variant

A701V
D215G
D80A
Δ241
Δ242
Δ243

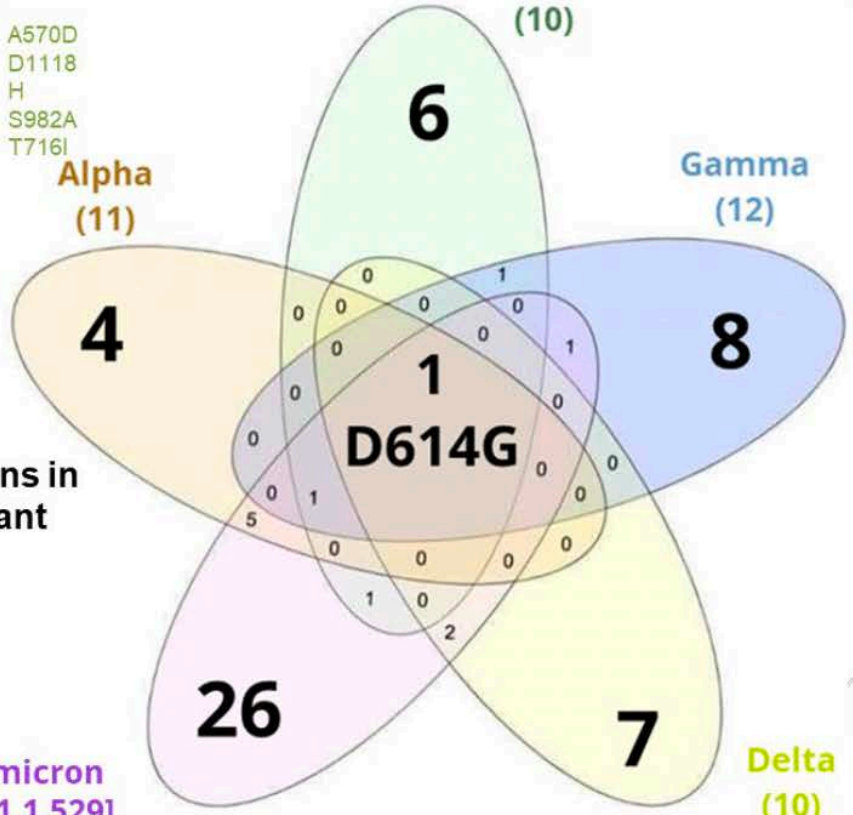
4 unique spike mutations in alpha variant

A570D
D1118H
S982A
T716I

8 unique spike mutations in gamma variant

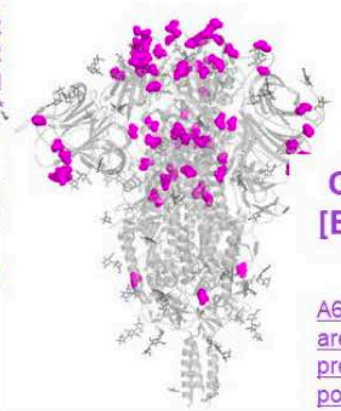


D138Y
K417T
L18F
P26S
R190S
T1027I
T20N
V1176F



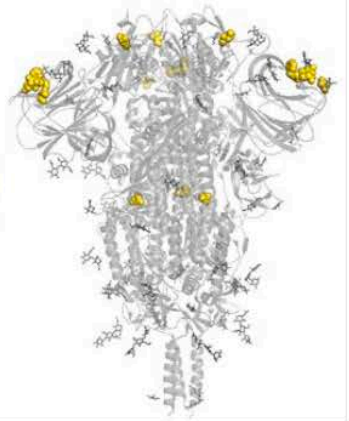
26 unique spike mutations in omicron (B.1.1.529) variant

A67V
D796Y
E484A
G339D
G446S
G496S
L212I
L981F
N440K
N679K
N764K
N856K
ins214EPE*
N969K
Q493R
Q498R
Q954H
S371L*
S373P
S375F
S477N
T547K
T95I
Y505H
Δ143
Δ211



A67V, S477N, T95I, Δ143 are associated with previous surges in PCR positivity

7 unique spike mutations in delta variant



D950N
E156G
L452R
P681R
T19R
Δ157
Δ158

*As of 12PM 11/29/21

National Institutes of Health
Turning Discovery Into Health

Tuesday, April 21, 2020

News Release

Expert U.S. Panel Develops NIH Treatment Guidelines for COVID-19

- www.covid19treatmentguidelines.nih.gov
- March 20 – request from HHS
- March 24 – initial meeting of 37 members;
  6 US government agencies; 8 professional societies
- April 7 – first release ready
- April 21 – final approval and first release
- Since then:
  - 25 major revisions; >15,000,000 page views

NIH Guidelines Panel Recommendations for Outpatients

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider During an ED, In-Person, or Telehealth Visit	Anti-SARS-CoV-2 mAb products are recommended for outpatients with mild to moderate COVID-19 who are at high risk of disease progression, as defined by the EUA criteria (treatments are listed in alphabetical order, and they may change based on circulating variants):[a] • **Bamlanivimab plus etesevimab**; *or* • **Casirivimab plus imdevimab**; *or* • **Sotrovimab** The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[b]
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen*[c]	There is insufficient evidence to recommend either for or against the continued use of remdesivir, dexamethasone, and/or baricitinib. Review the text below when considering the use of any of these agents after hospital discharge.
Discharged From ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured*[d]	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not** exceed 10 days) with careful monitoring for AEs **(BIII)**. There is insufficient evidence to recommend either for or against the use of remdesivir. When considering the use of remdesivir, review the text below for more information. The Panel **recommends against** the use of **baricitinib** in this setting, except in a clinical trial **(AIII)**.

NIH Guidelines Panel Recommendations for Inpatients

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone** (when combination with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIII)** For recently hospitalized[c] patients with rapidly increasing oxygen needs and systemic inflammation: • Add either **baricitinib (BIIa)** or **IV tocilizumab (BIIa)** to one of the two options above[d] • If neither baricitinib nor IV tocilizumab is available or feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** or **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.
Hospitalized and Requires IMV or ECMO	• **Dexamethasone (AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** • If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.