NEJM Journal Watch

NEJM Journal Watch Infectious Diseases Top Stories of 2021.

Bibliográfica Febrero-22

JL Mostaza

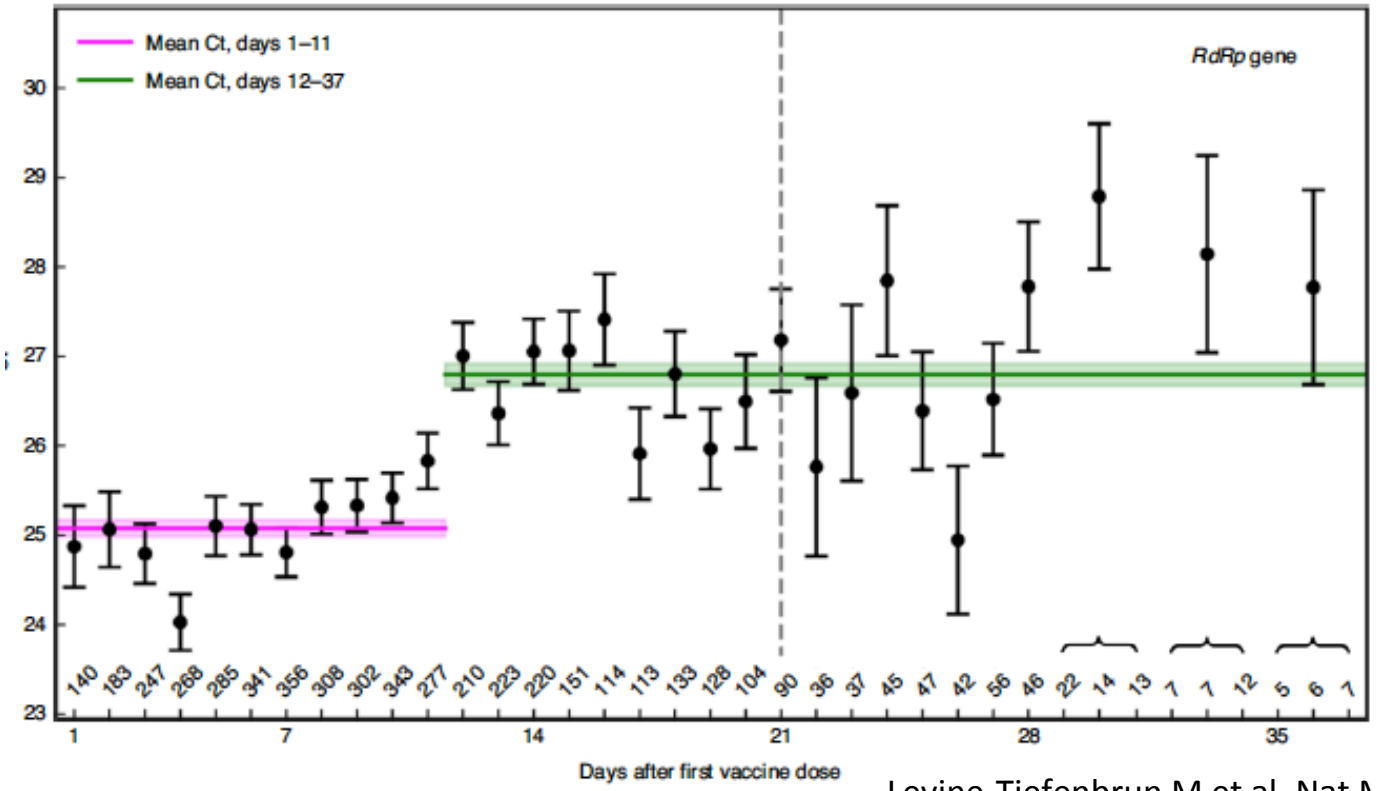
Medicina Interna. CAULE.

Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine.

Viral Load in Breakthrough Infection After Receiving the Pfizer-BioNTech COVID-19 Vaccine

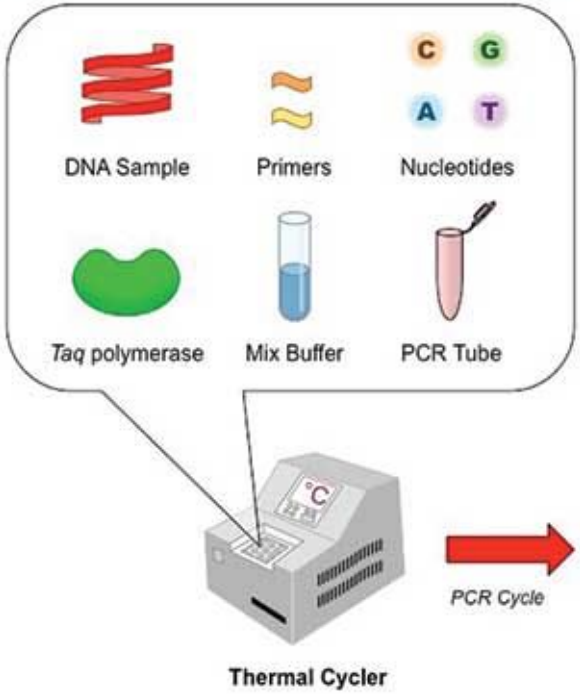
- 4938 vaccinated and subsequently infected individuals (Israel).
- We compared the Ct values of post-vaccination infections with Ct values of positive tests of unvaccinated patients.

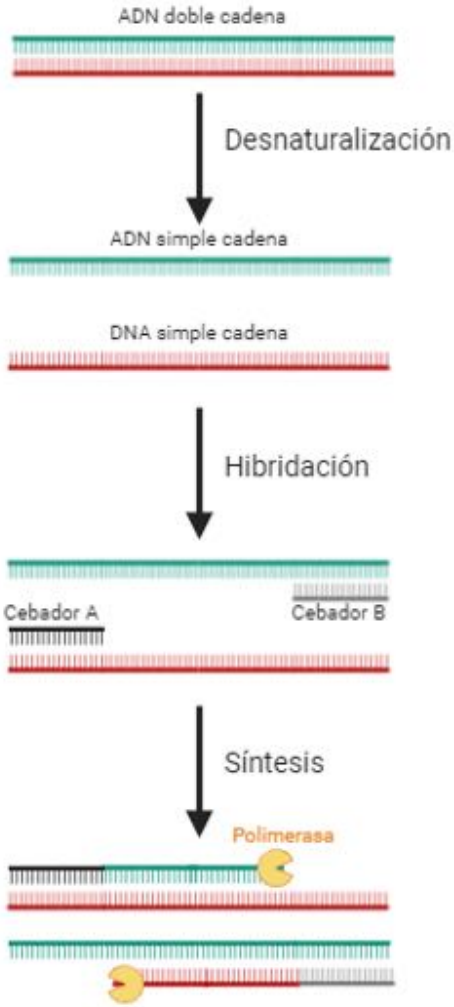
Decreased SARS-CoV-2 viral load after 12 d post-vaccination.



Levine-Tiefenbrun M et al. Nat Med 2021.

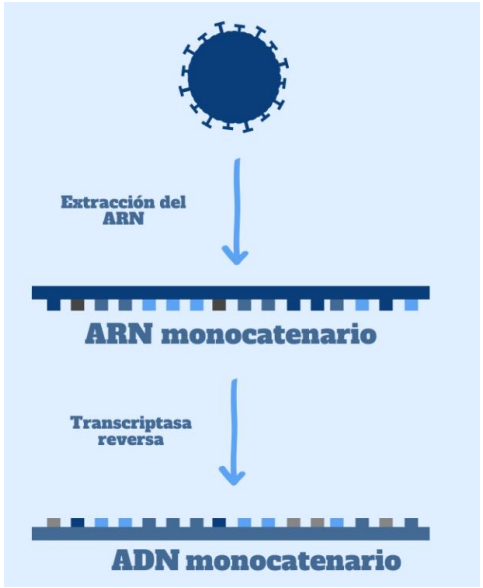
Reacción en cadena de la polimerasa (PCR)

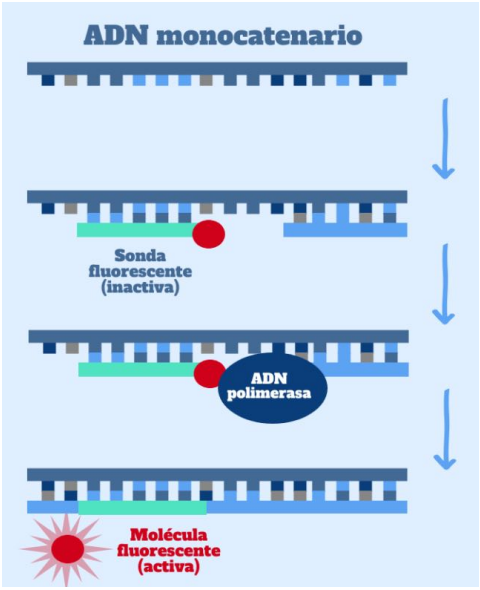


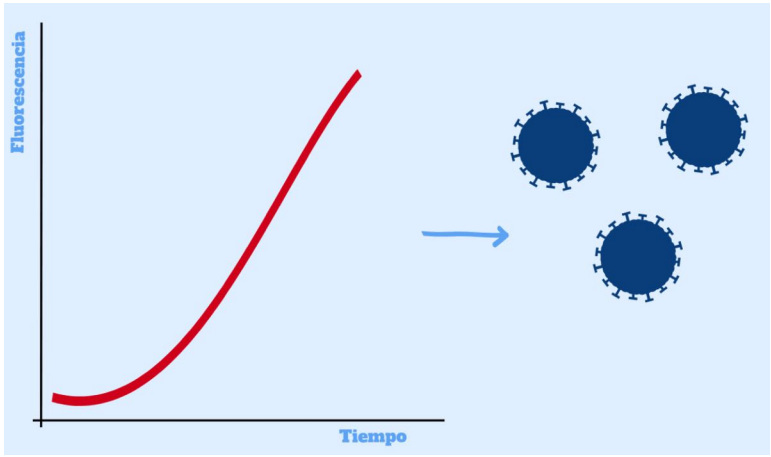


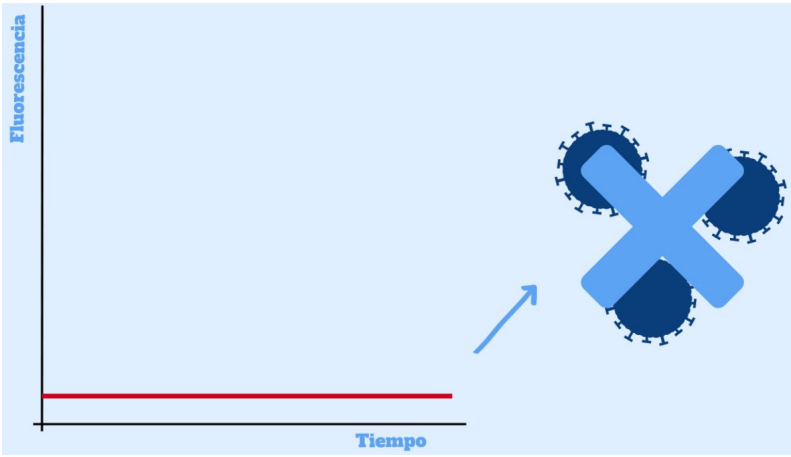
Created in BioRender.com

RT-PCR en tiempo real









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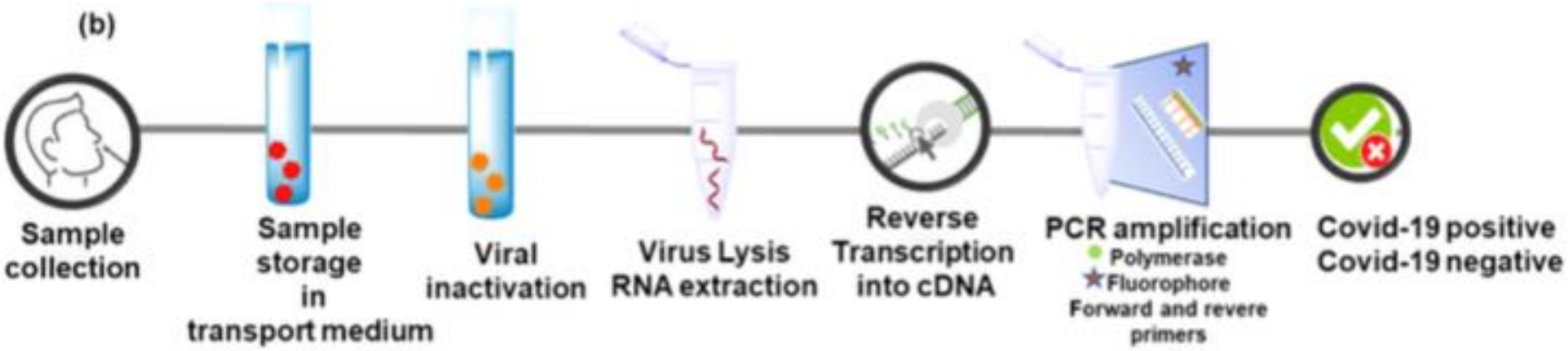

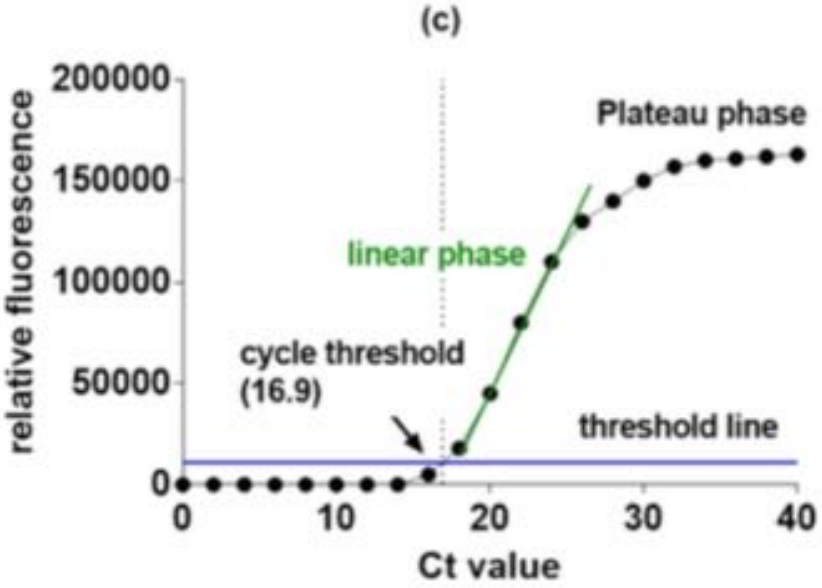

https://hal.archives-ouvertes.fr/hal-03196337/document

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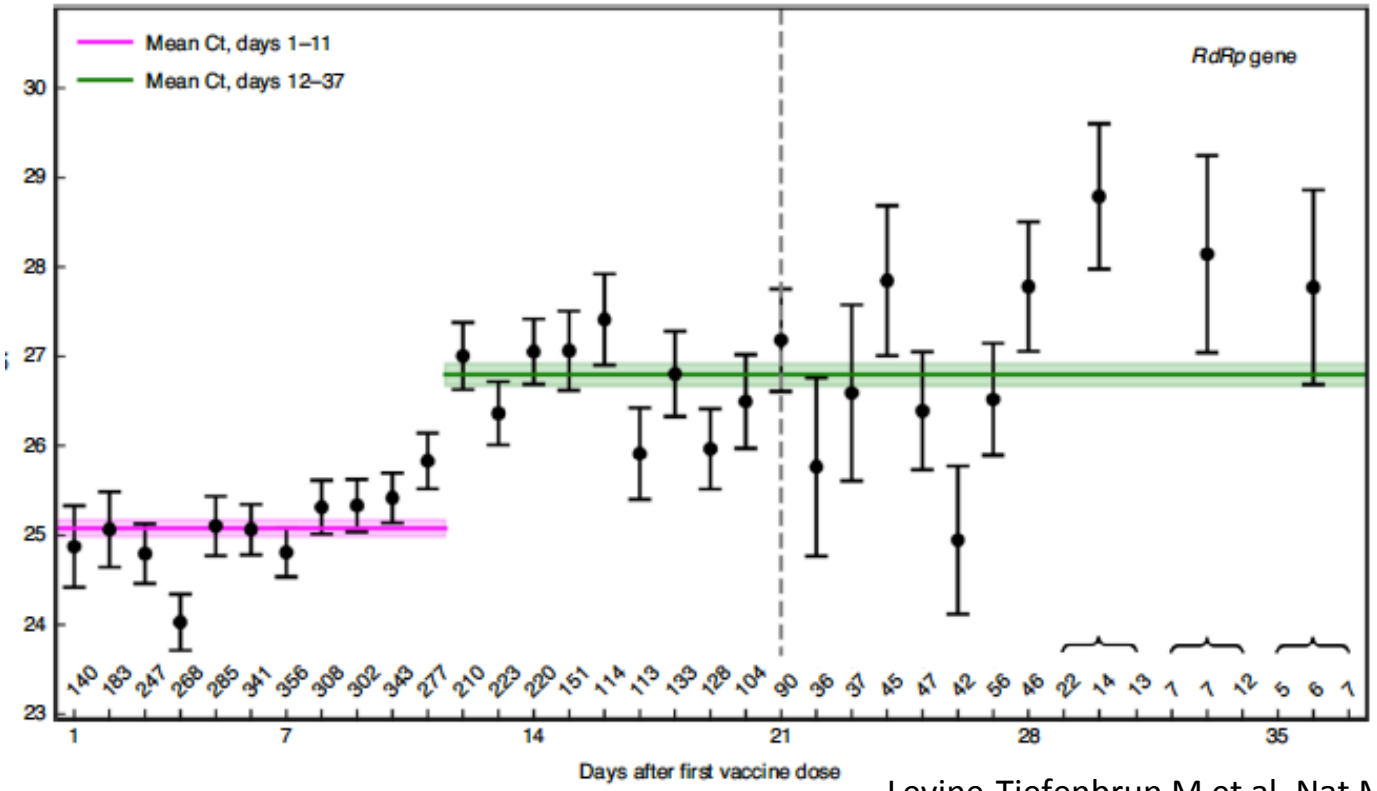

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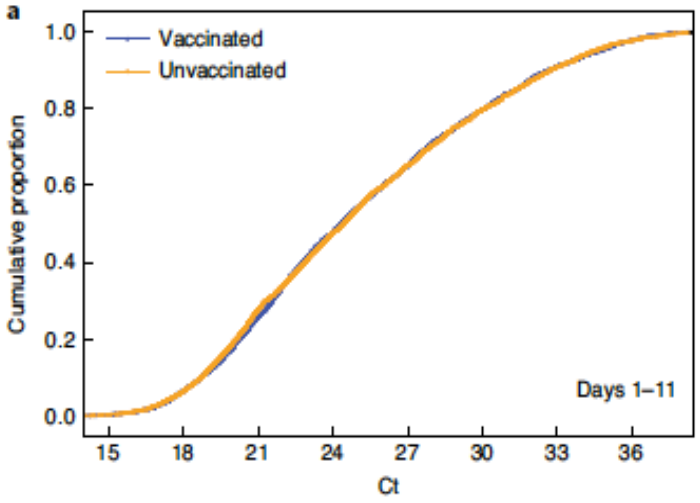
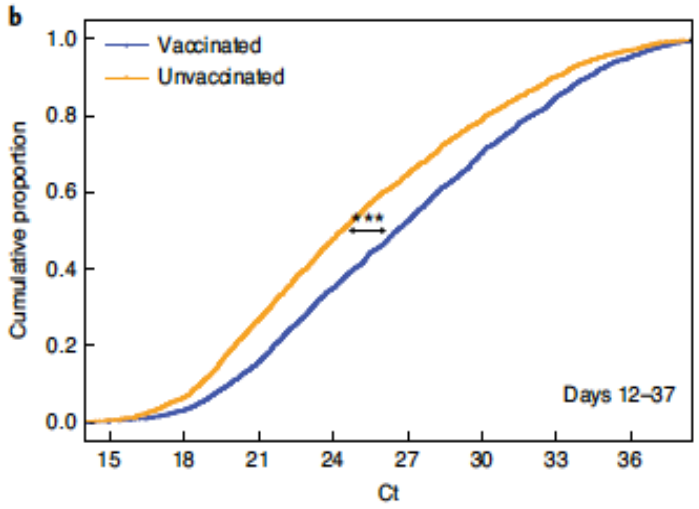
Comparison of SARS-CoV-2 viral loads among vaccinated and unvaccinated patients.

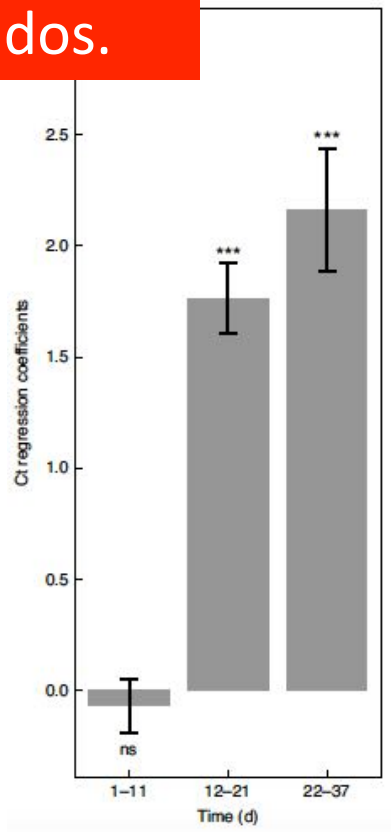
Los vacunados infectados tienen menor riesgo de transmitir la infección que los no vacunados.



1–11 d after vaccination



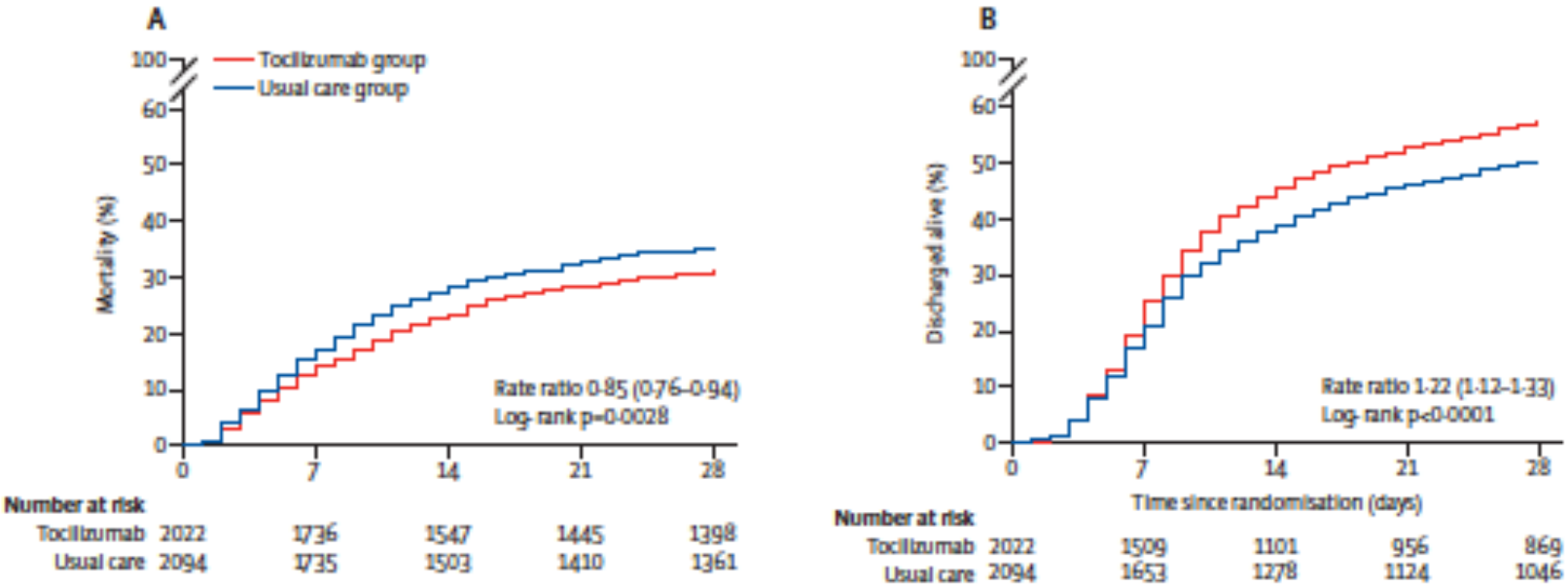
12–37 d after vaccination



Levine-Tiefenbrun M et al. Nat Med 2021.

Largest Randomized Tocilizumab Trial Shows Mortality Reduction (*RECOVERY* trial).

- 4116 patients randomly assigned between tocilizumab and usual care alone
- Progressive COVID-19:
  - O2 Sat <92% (room air or receiving oxygen therapy).
  - CRP ≥75 mg/L.

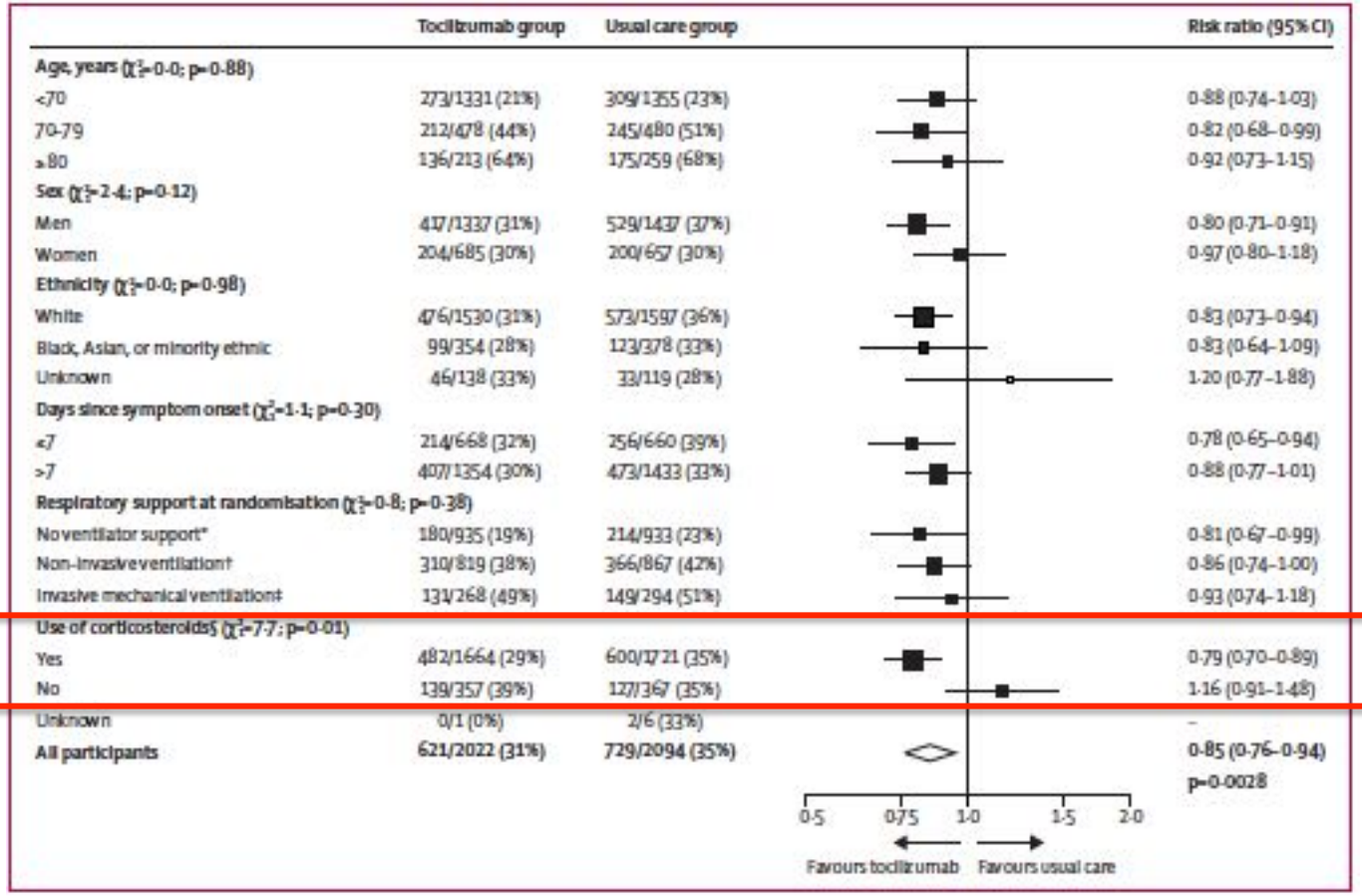


Effect of allocation to tocilizumab on 28-day mortality (A) and discharge from hospital within 28 days of randomisation (B).

RECOVERY Collaborative Group. Lancet 2021

Largest Randomized Tocilizumab Trial Shows Mortality Reduction (*RECOVERY* trial).

Effect of allocation to tocilizumab on 28-day mortality by baseline characteristics.

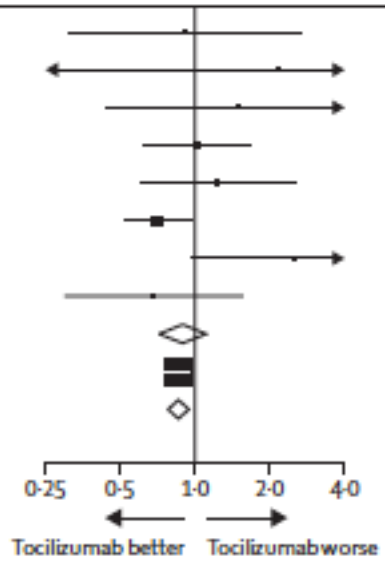


RECOVERY Collaborative Group. Lancet 2021

Largest Randomized Tocilizumab Trial Shows Mortality Reduction (*RECOVERY* trial).

Meta-analysis of mortality in randomised, controlled trials of tocilizumab in patients hospitalised with COVID-19

	Deaths/patients randomly assigned (%)		Observed minus expected deaths*		Ratio of death rates, rate ratio (95% CI)
	Tocilizumab group	Usual care group	(O–E)	Var (O–E)	
CORIMUNO–TOCI[10]	7/64 (11%)	8/67 (12%)	–0·3	3·3	0·91 (0·31–2·65)
RCT–TCZ–COVID-19[11]	2/60 (3%)	1/66 (2%)	0·6	0·7	2·17 (0·22–21·3)
BACC Bay[12]	9/161 (6%)	(3/82) ×2† (4%)	1·0	2·6	1·51 (0·44–5·13)
COVACTA[9]	58/294 (20%)	(28/144) ×2† (19%)	0·3	15·3	1·02 (0·62–1·68)
EMPACTA[13]	26/249 (10%)	(11/128) ×2† (9%)	1·6	7·5	1·23 (0·60–2·52)
REMAP–CAP[15]	98/353 (28%)	142/402 (35%)	–14·2	40·8	0·71 (0·52–0·96)
TOCIBRAS[8]	14/65 (22%)	6/64 (9%)	3·9	4·3	2·51 (0·97–6·50)
COVINTOC[14]	11/91 (12%)	15/89 (17%)	–2·1	5·6	0·68 (0·30–1·56)
Subtotal: eight trials	**225/1337 (17%)**	**256/1396 (18%)**	**–9·3**	**80·1**	**0·89 (0·72–1·11)**
RECOVERY	621/2022 (31%)	729/2094 (35%)	–54·4	330·6	0·85 (0·76–0·94)
All trials	**846/3359 (25%)**	**985/3490 (28%)**	**–63·7**	**410·7**	**0·86 (0·78–0·94)**
					p=0·0017



RECOVERY Collaborative Group. Lancet 2021

Baricitinib for Management of Severe COVID-19 (COV-BARRIER study).

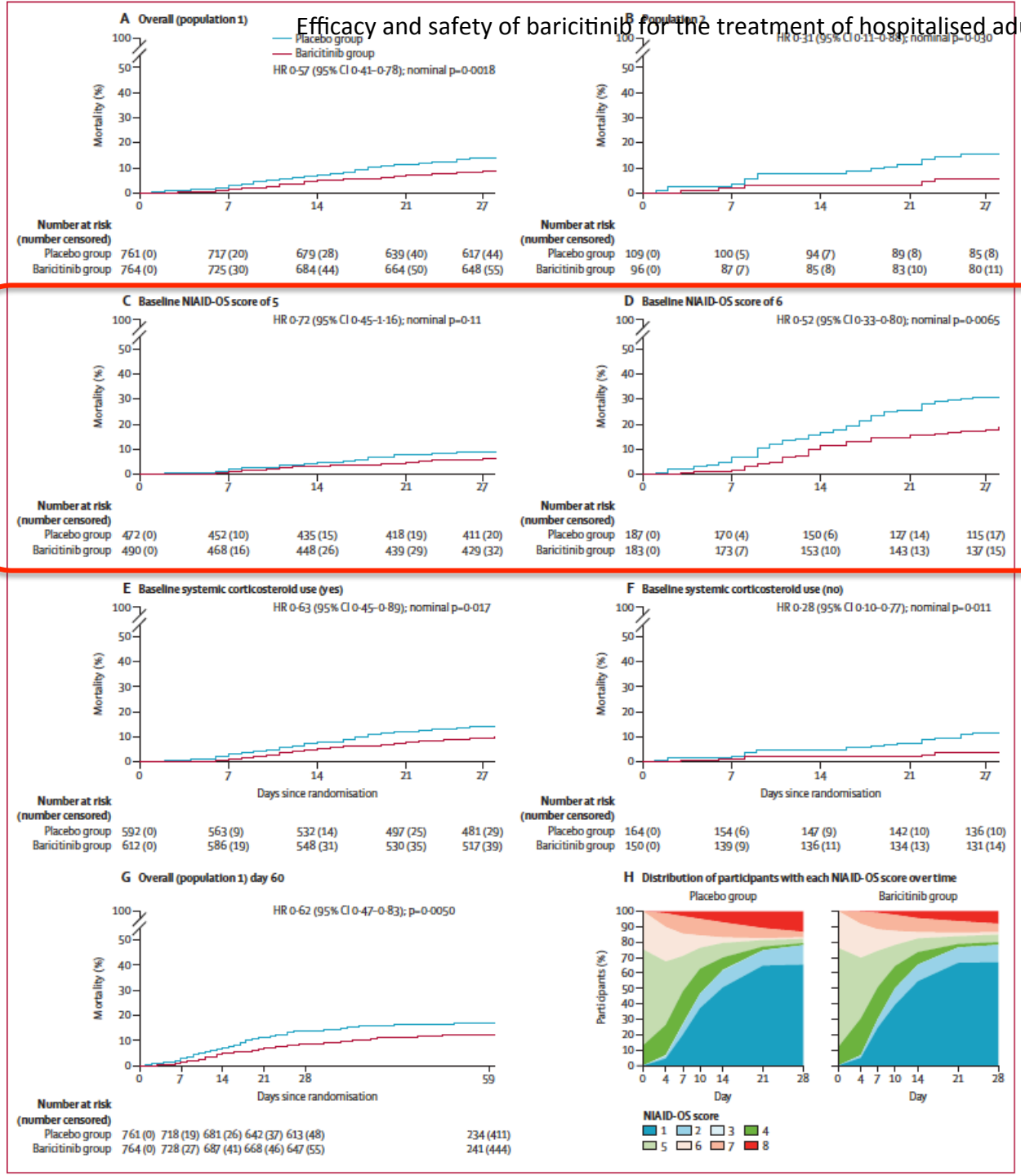
- 1525 patients hospitalized with COVID-19.
  - Randomized to baricitinib or placebo.
  - ≥1 elevated inflammatory marker: C-reactive protein, D-dimer, LDH, or ferritin.
- Composite primary endpoint: Proportion who progressed to…
  - High-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or death by day 28 (intention-to-treat population).
- 79% were receiving systemic corticosteroids.
- 19% were receiving remdesivir.
- Progressed to meet the primary endpoint:
  - 27·8% with baricitinib and 30·5% with placebo
    - (OR 0·85 [95% CI 0·67 to 1·08], p=0·18).

28-day mortality: 8% with baricitinib and 13% with placebo (38% relative reduction). (HR 0,57 [95% CI 0·41–0·78]; p=0·0018)

Marconi VC et al. Lancet Respir Med 2021.

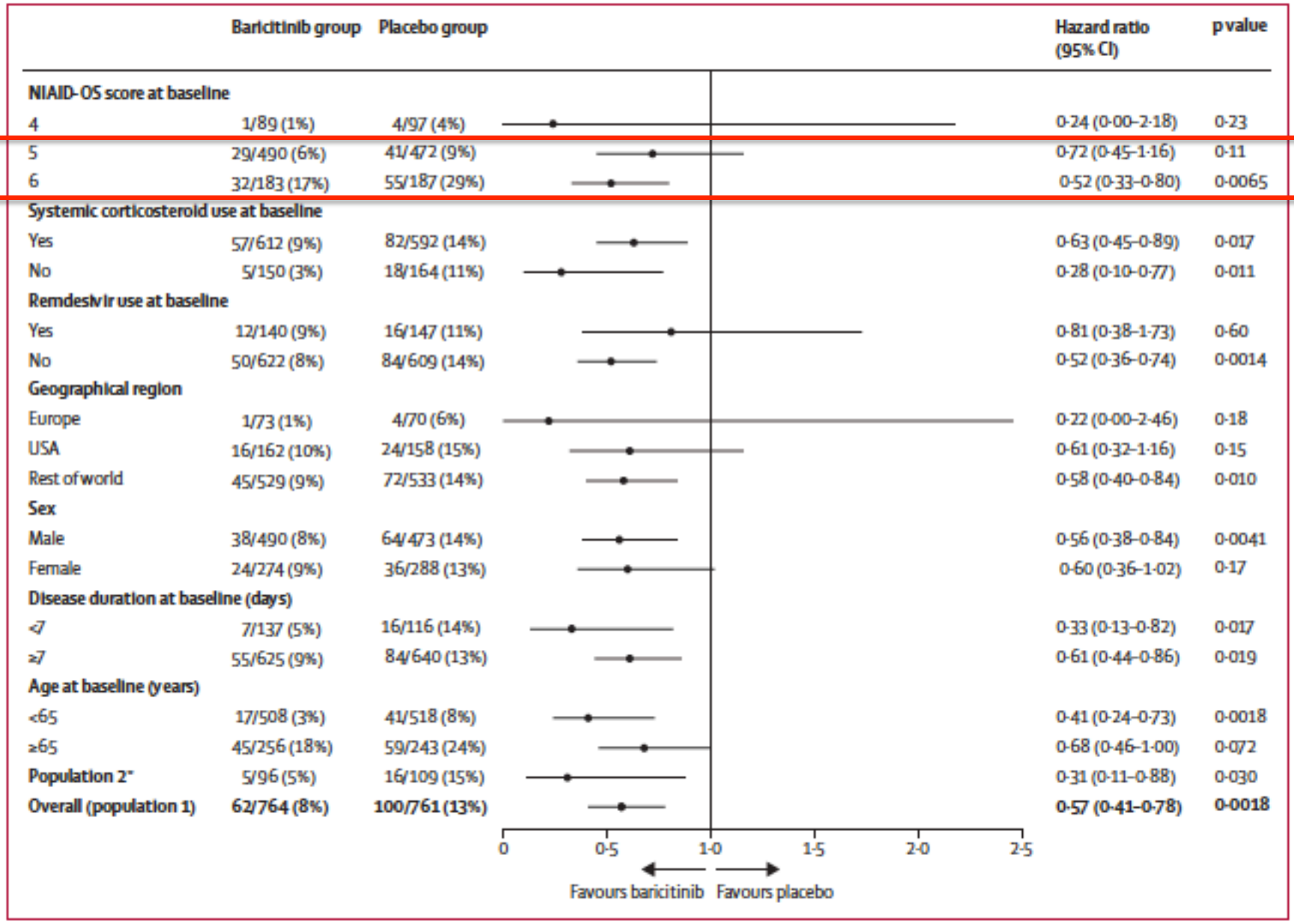
NIAID-OS (National Institute of Allergy and Infectious Disease Ordinal Scale)	
SCORE	**Descriptor**
OS 1	Not hospitalized, no limitations on activities
OS 2	Not hospitalized, limitation on activities and/or requiring home O2
OS 3	Hospitalized, no supplemental O2 – no longer requires ongoing medical care
OS 4	Hospitalized, no supplemental O2 – requiring ongoing medical care
OS 5	Hospitalized, requiring supplemental O2
OS 6	Hospitalized, on non-invasive ventilation or high-flow oxygen devices
OS 7	Hospitalized, on invasive mechanical ventilation or ECMO
OS 8	Death

Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER):



Marconi VC et al.
Lancet Respir Med 2021.

28-day all-cause mortality by subgroup



	Baricitinib group	Placebo group	Hazard ratio (95% CI)	p value
NIAID-OS score at baseline				
4	1/89 (1%)	4/97 (4%)	0·24 (0·00–2·18)	0·23
5	29/490 (6%)	41/472 (9%)	0·72 (0·45–1·16)	0·11
6	32/183 (17%)	55/187 (29%)	0·52 (0·33–0·80)	0·0065
Systemic corticosteroid use at baseline				
Yes	57/612 (9%)	82/592 (14%)	0·63 (0·45–0·89)	0·017
No	5/150 (3%)	18/164 (11%)	0·28 (0·10–0·77)	0·011
Remdesivir use at baseline				
Yes	12/140 (9%)	16/147 (11%)	0·81 (0·38–1·73)	0·60
No	50/622 (8%)	84/609 (14%)	0·52 (0·36–0·74)	0·0014
Geographical region				
Europe	1/73 (1%)	4/70 (6%)	0·22 (0·00–2·46)	0·18
USA	16/162 (10%)	24/158 (15%)	0·61 (0·32–1·16)	0·15
Rest of world	45/529 (9%)	72/533 (14%)	0·58 (0·40–0·84)	0·010
Sex				
Male	38/490 (8%)	64/473 (14%)	0·56 (0·38–0·84)	0·0041
Female	24/274 (9%)	36/288 (13%)	0·60 (0·36–1·02)	0·17
Disease duration at baseline (days)				
<7	7/137 (5%)	16/116 (14%)	0·33 (0·13–0·82)	0·017
≥7	55/625 (9%)	84/640 (13%)	0·61 (0·44–0·86)	0·019
Age at baseline (years)				
<65	17/508 (3%)	41/518 (8%)	0·41 (0·24–0·73)	0·0018
≥65	45/256 (18%)	59/243 (24%)	0·68 (0·46–1·00)	0·072
Population 2*	5/96 (5%)	16/109 (15%)	0·31 (0·11–0·88)	0·030
Overall (population 1)	**62/764 (8%)**	**100/761 (13%)**	**0·57 (0·41–0·78)**	**0·0018**

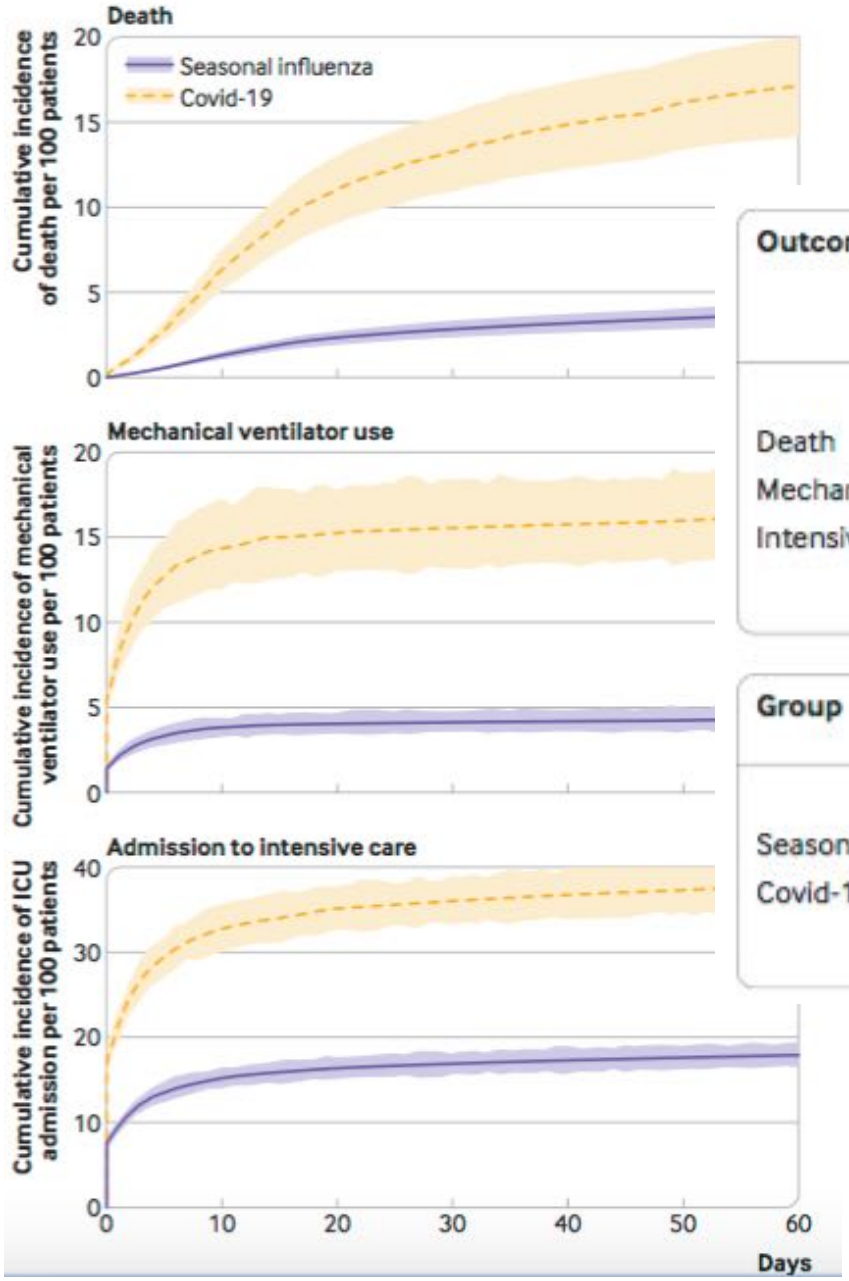
Marconi VC et al. Lancet Respir Med 2021.

COVID-19: Five Times More Deadly Than Seasonal Influenza.

- Analysis from:
  - 3641 hospitalized patients with COVID-19 (1 Febr 2020 - 17 June 2020).
  - 12,676 patients with seasonal influenza (2017 – 2019).
  - Propensity scores.
- COVID- 19 conferred significantly higher risk: (OR range, 1.5–7.8).
  - Acute renal failure, need for dialysis, septic shock, need for vasopressors, deep venous thrombosis and pulmonary embolism, stroke, myocarditis, arrythmias and sudden cardiac death, elevated troponin, elevated liver enzymes, and rhabdomyolysis.
- Hospital admissions for COVID-19 were also associated with significantly:
  - Higher mortality risk (adjusted hazard ratio, 5.0)
  - Greater likelihood of mechanical ventilation (HR, 4.0)
  - Treatment in an intensive care unit (HR, 2.4).
- The highest excess mortality was seen:
  - >75 years with chronic kidney disease or dementia.
  - Black patients with obesity, diabetes, or chronic kidney disease.
- Hospital stay was a median of 3 days longer in individuals with COVID- 19.

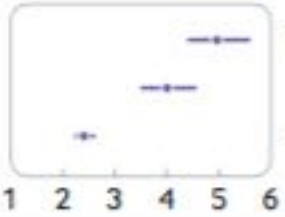
Xie Y et al. BMJ. 2020 Dec 15

Comparative evaluation of clinical manifestations and risk of death in patients admitted to hospital with covid-19 and seasonal influenza.



Risks of death and healthcare resource

Outcome	Covid-19 *v* seasonal influenza Adjusted hazard ratio (95% CI)	Excess outcomes per 100 patients (95% CI)
Death		16.85 (14.85 to 18.99)
Mechanical ventilator use		11.29 (9.62 to 13.14)
Intensive care unit admission		19.80 (17.81 to 21.87)



Group	Adjusted length of stay (days)	Additional length of stay (days) (95% CI)
Seasonal influenza		3.00 (2.20 to 3.80)
Covid-19		

Can Organs from SARSCoV-2 Positive Donors Be Safely Transplanted?

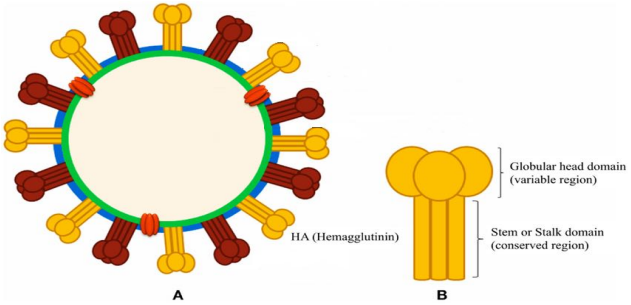
- Transplant of 10 kidneys from 5 SARS-CoV-2–infected deceased donors.
- Causes of death were unrelated to COVID-19 in all donors.
  - Nobody had symptoms of COVID-19 prior to or during hospital admission.
- No documented transmission of SARS-CoV-2 occurred.
  - No recipient developed COVID-19 symptoms.

Koval CE et al. Am J Transplant 2021 Jul 13

A chimeric hemagglutinin-based universal influenza virus vaccine approach induces broad and long-lasting immunity.

On the Path Toward a Universal Influenza Vaccine

- Inactivated influenza vaccines target the head domain of the viral hemagglutinin (HA).
  - Highly mutable region.
- HA stalk domain is more conserved
  - It does not induce a strong Ab response.
- Randomized, placebo-controlled trial involving 65 adults (P I).
- Live vaccine containing cHA with the hemagglutinin 8 head and hemagglutinin 1 stalk (cHA8/1HA).
  - Followed 85 days later by inactivated vaccine expressing the hemagglutinin 5 head and the hemagglutinin 1 stalk (cHA5/1HA) along with adjuvant.



Nachbagauer R et al. Nat Med 2020 Dec 7.

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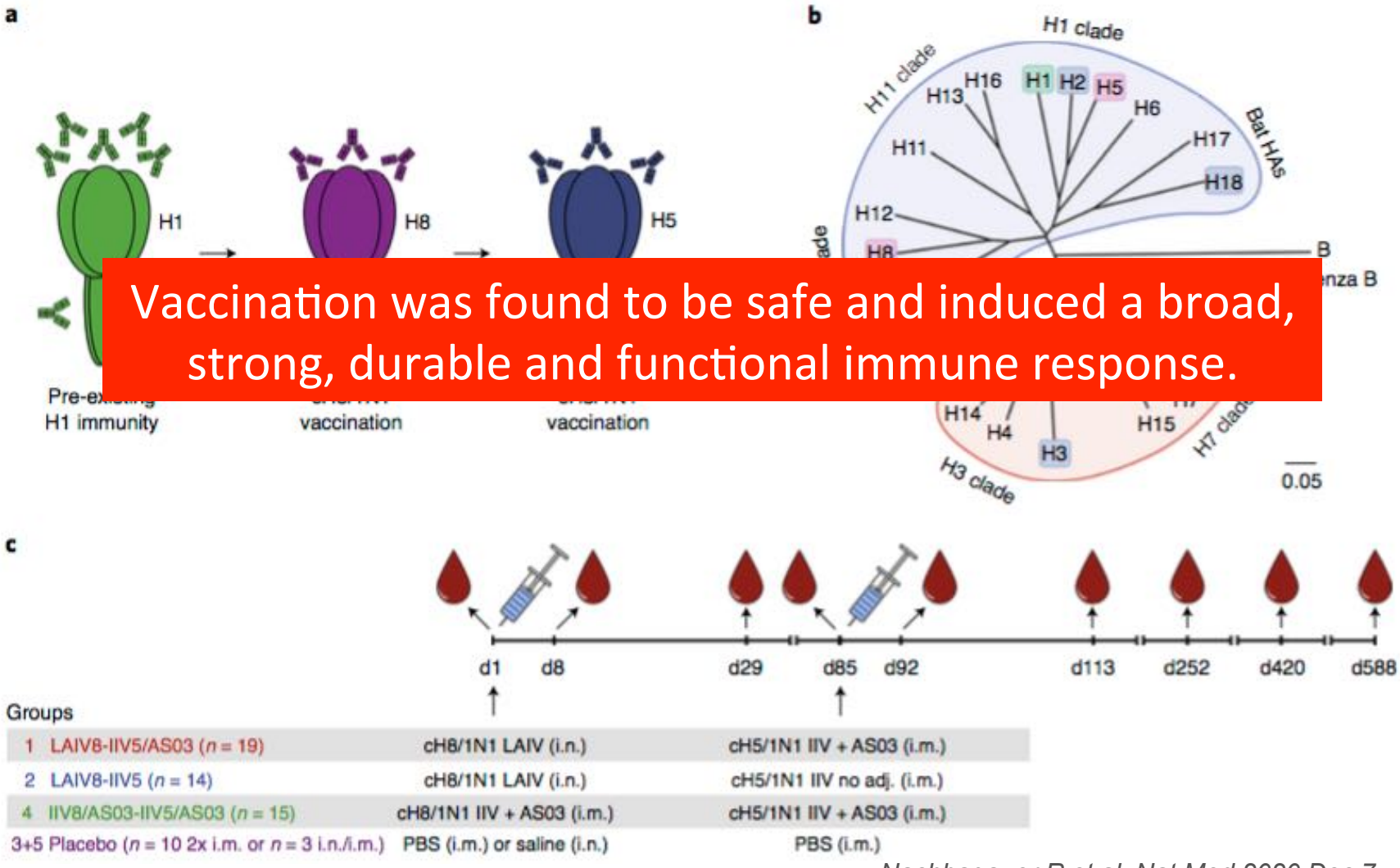


Vaccination was found to be safe and induced a broad, strong, durable and functional immune response.

Nachbagauer R et al. Nat Med 2020 Dec 7.

Rethinking Pneumococcal Vaccine Recommendations for Adults.

- A test-negative design study
  - To estimate PCV13 and PPSV23 effectiveness against pneumococcal CAP in adults aged ≥65 years.
  - Cases and test negative controls.
- 1525 cases with CAP hospitalization:
  - 167 (11.0%) pneumococcal CAP (case group).
  - 1358 (89%) nonpneumococcal CAP (control group).
- Vaccination rate within the previous year
  - Influenza : 55.5%,
  - PPSV23 (within the past 5 years): 39.1% .
  - PCV13 (within the past 5 years): 12.3%,
  - PCV13 and PPSV23: 9.3%.

Heo JY et al. *J Infect Dis* 2021.

Effectiveness of pneumococcal vaccination against hospitalized pneumococcal pneumonia in older adults.

Table 1. Comparison of Demographic Characteristics and Vaccination Status Between Pneumococcal and Nonpneumococcal Community-Acquired Pneumonia Cases

	All-Cause CAP	Case Group	Control Group	
Characteristic	Total (N = 1525)	Pneumococcal CAP (n = 167)	Nonpneumococcal CAP (n = 1358)	*P* Value[a]
Age, y, mean ± SD	76.7 ± 6.9	75.9 ± 6.7	76.8 ± 6.9	.476
Age group, y				
65–74	620 (40.7)	74 (44.3)	546 (40.2)	.308
≥75	905 (59.3)	93 (55.7)	812 (59.8)	
Male sex	893 (58.6)	106 (63.5)	787 (58.0)	.172
Underlying conditions (≥1)				
No underlying condition	304 (19.9)	31 (18.6)	273 (20.1)	.638
Diabetes mellitus	475 (31.1)	56 (33.5)	419 (30.9)	.481
Chronic lung disease	599 (39.3)	55 (32.9)	544 (40.1)	.075
Cardiovascular disease	418 (27.4)	52 (31.1)	366 (27.0)	.252
Cerebrovascular disease	276 (18.1)	32 (19.2)	244 (18.0)	.705
Chronic renal disease	152 (10.0)	18 (10.8)	134 (9.9)	.711
Chronic liver disease	55 (3.6)	6 (3.6)	49 (3.6)	.992
Malignancy, solid tumor	251 (16.5)	33 (19.8)	218 (16.1)	.223
Malignancy, hematologic	17 (1.1)	3 (1.8)	14 (1.0)	.421
Immunosuppressant use	64 (4.2)	7 (4.2)	57 (4.2)	.997
Underlying conditions (≥2)	687 (45.0)	75 (44.9)	612 (45.1)	.969
Risk group				
Healthy (low risk)	304 (19.9)	31 (18.6)	273 (20.1)	.416
At risk	923 (60.5)	97 (58.1)	826 (60.8)	
High risk	298 (19.5)	39 (23.4)	259 (19.1)	
CURB-65 score				
0–1	619 (40.6)	61 (36.5)	558 (41.1)	.100
2	583 (38.2)	60 (35.9)	523 (38.5)	
≥3	323 (21.2)	46 (27.5)	277 (20.4)	
Influenza vaccinated	847 (55.5)	83 (49.7)	763 (56.2)	.149
PPSV23 vaccinated	596 (39.1)	60 (35.9)	536 (39.5)	.376
PCV13 vaccinated	188 (12.3)	13 (7.8)	175 (12.9)	.058
PCV13/PPSV23 vaccinated[b]	142 (9.3)	10 (6.0)	132 (9.7)	.117

Heo JY et al. *J Infect Dis* 2021.

- Pneumococcal pneumonia was detected:
  - Urinary Ag test
    - BinaxNOW assay (116 patients [69.5%]).
    - ssUAD assay (67 patients [40.1%]).
  - Respiratory specimen/ blood culture (35 patients [21.0%])
  - In 48 patients (28.7%), was detected by ≥2 diagnostic methods.

Heo JY et al. *J Infect Dis* 2021.

Effectiveness of pneumococcal vaccination against hospitalized pneumococcal pneumonia in older adults.

Table 2. Vaccine Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Pneumococcal Community-Acquired Pneumonia Hospitalization

Type of CAP	Case		Control[a]		Unadjusted VE, % (95% CI)	Adjusted VE, % (95% CI)[b]
	No. of Vaccinees/No. of Cases	Vaccinated, %	No. of Vaccinees/No. of Controls	Vaccinated, %		
Pneumococcal CAP (167 cases)						
All ≥65 y	13/167	7.8	175/1358	12.9	42.9 (−2.7 to 68.3)	40.0 (−10.8 to 67.5)
65–74 y	4/78	5.4	77/546	14.1	65.2 (19–87.6)	66.4 (8–88.6)
≥75 y	9/93	9.7	98/812	12.1	21.9 (−60.2 to 62.3)	14.0 (−83.2 to 59.6
Nonbacteremic pneumococcal CAP (161 cases)						
All ≥65 y	13/161	8.1	175/1358	12.9	40.6 (−7.0 to 67.0)	38.8 (−13.0 to 66.9
65–74 y	4/70	5.7	77/546	14.1	63.1 (−4.2 to 86.9)	66.5 (7–88.7)
≥75 y	9/91	9.9	98/812	12.1	20.0 (−64.3 to 61.1)	12.5 (−86.5 to 59.0
PCV13-serotype CAP (36 cases)						
All ≥65 y	3/36	8.3	175/1358	12.9	36.5 (−102.5 to 81.4)	41.1 (−103.7 to 83.
65–74 y	1/16	6.3	77/546	14.1	59.4 (−211.8 to 94.7)	58.1 (−245.5 to 96.
≥75 y	2/20	10.0	98/812	12.1	19.0 (−294.2 to 81.5)	26.8 (−239.4 to 88.

Table 3. Vaccine Effectiveness of 23-Valent Pneumococcal Polysaccharide Vaccine Against Pneumococcal Community-Acquired Pneumonia Hospitalization

Type of CAP	Case		Control[a]		Unadjusted VE, % (95% CI)	Adjusted VE, % (95% CI)[b]
	No. of Vaccinees/No. of Cases	Vaccinated, %	No. of Vaccinees/No. of Controls	Vaccinated, %		
Pneumococcal CAP (167 cases)						
All ≥65 y	60/167	35.9	536/1358	39.5	14.0 (−20.1 to 38.4)	11.0 (−26.4 to 37.3)
65–74 y	26/78	35.1	216/546	39.6	17.2 (−37.4 to 50.3)	18.5 (−38.6 to 52.0)
≥75 y	34/93	36.6	320/812	39.4	11.4 (−38.2 to 43.3)	6.4 (−49.9 to 41.6)
Nonbacteremic pneumococcal CAP (161 cases)						
All ≥65 y	60/161	37.3	536/1358	39.5	8.9 (−27.7 to 35.9)	−0.1 (−43.7 to 30.2)
65–74 y	26/70	37.1	216/546	39.6	9.7 (−51.0 to 46.0)	1.4 (−59.4 to 39.0)
>75 y	34/91	37.4	320/812	39.4	8.3 (−43.5 to 41.4)	−3.8 (−60.0 to 40.1)
PPSV23-serotype CAP (52 cases)						
All ≥65 y	19/52	36.5	536/1358	39.5	11.7 (−96.8 to 50.3)	6.3 (−73.8 to 49.5)
65–74 y	8/23	34.8	216/546	39.6	18.5 (−95.5 to 34.3)	15.7 (−91.4 to 62.9)
>75 y	11/29	37.9	320/812	39.4	6.0 (−107.5 to 56.2)	−2.0 (−161.7 to 60.2)
PCV13-serotype CAP (36 cases)						

Table 4. Vaccine Effectiveness of Sequential Vaccination With 13-Valent Pneumococcal Conjugate and 23-Valent Pneumococcal Polysaccharide Vaccine Against Pneumococcal Community-Acquired Pneumonia Hospitalization

Type of CAP	Case		Control[a]		Unadjusted VE (95% CI)	Adjusted VE (95% CI)[b]
	No. of Vaccinees/No. of Cases	Vaccinated, %	No. of Vaccinees/No. of Controls	Vaccinated, %		
Pneumococcal CAP (167 cases)						
All ≥65 y	10/167	6.0	133/1358	9.7	40.8 (−14.9 to 69.5)	38.5 (−21.0 to 68.7)
65–74 y	2/78	2.7	64/546	11.7	79.1 (12.7–95.9)	80.3 (15.9–96.4)
≥75 y	8/93	8.6	69/812	8.4	−3.0 (−121.6 to 52.1)	−14.8 (−192.9 to 47.9
Nonbacteremic pneumococcal CAP (161 cases)						
All ≥65 y	10/161	6.2	133/1358	9.7	38.5 (−18.6 to 68.4)	36.5 (−26.0 to 67.0
65–74 y	2/70	2.9	64/546	11.7	77.9 (7.4–94.7)	80.0 (14.4–95.3
≥75 y	8/91	8.8	69/812	8.4	−5.5 (−127.1 to 51.0)	−18.1 (−192.4 to 46.4
PCV13- and PPSV23-serotype CAP (95 cases)						
All ≥65 y	3/55	5.5	133/1358	9.7	46.4 (−74.0 to 83.5)	44.6 (−84.0 to 83.3)
65–74 y	1/24	4.2	64/546	11.7	67.3 (−144.6 to 95.7)	63.6 (−186.0 to 95.4)
>75 y	2/31	6.5	69/812	8.4	24.5 (−223.0 to 82.4)	24.8 (−233.1 to 83.0)

Heo JY et al. *J Infect Dis* 2021.

Vaccine effectiveness (VE).

- Aged ≥65 years: adjusted VE of pneumococcal vaccines (statistically insignificant):
  - PCV13: 40.0% (95% confidence interval [CI], –10.8% to 67.5%)
  - PPSV23: 11.0% (95% CI, –26.4% to 37.3%).
- Subgroup (aged 65–74 years).
  - PPSV23 (adjusted VE, 18.5% [95% CI, –38.6% to 52.0%]).
  - Single-dose PCV13 (adjusted VE, 66.4% [95% CI, .8%–88.6%]).
  - Adjusted VE sequential PCV13/PPSV23: 80.3% (95% CI, 15.9%–95.4%).

- ***Conclusions.***
  - Sequential PCV13/PPSV23 vaccination is most effective for preventing pneumococcal CAP among the elderly aged 65–74 years.

PCV13 should be given first, followed by a dose of PPV23 after 6 to 12 months.

Heo JY et al. *J Infect Dis* 2021.

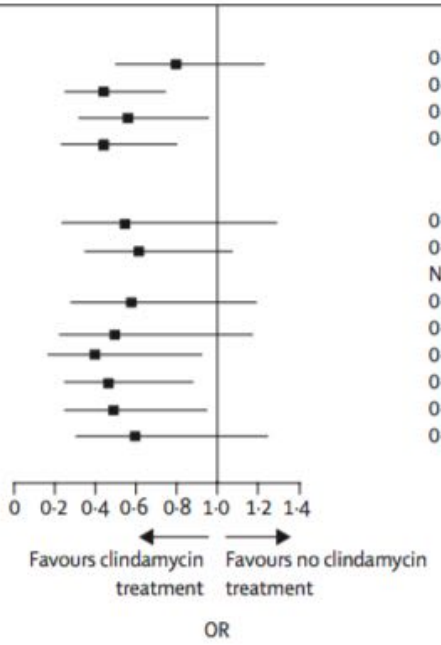
Adjunctive Clindamycin Improves Outcomes of Invasive Group A Streptococcal Infection: Best Evidence to Date.

- This protein synthesis inhibitor is recommended for management of iGAS infections, but data are limited.
- Retrospective multicentre cohort study.
  - Cerner Health Facts database (233 US hospitals).
  - Inpatients with clinical cultures positive for β-haemolytic streptococcal who had received β-lactam ± clindamycin.
  - Propensity-matched (1:2): with or without clindamycin.
- Primary outcome: aOR in-hospital mortality.
- 1956 patients (1079 with iGAS and 877 with iNABS infections).

Babiker A et al. *Lancet Infect Dis* 2020 Dec.

OR of in-hospital mortality in patients with invasive group A β-haemolytic streptococcal infection treated with versus without adjunctive clindamycin.

	Clindamycin treatment		No clindamycin treatment		p value	OR (95% CI)
	Patients	Mortality (%)	Patients	Mortality (%)		
Primary analysis						
Unmatched, unadjusted	343	28 (8·2%)	736	74 (10·1%)	0·32	0·80 (0·50–1·24)
Unmatched, adjusted*					0·0031	0·44 (0·25–0·75)
Propensity-matched (1:2), unadjusted	277	18 (6·5%)	500	55 (11·0%)	0·042	0·56 (0·32–0·96)
Propensity-matched (1:2), adjusted*					0·011	0·44 (0·23–0·81)
Subgroup analysis†						
Early clindamycin treatment	97	6 (6·2%)	500	55 (11·0%)	0·16	0·53 (0·22–1·28)
Proven invasive β-haemolytic streptococcal infection	153	18 (11·8%)	282	51 (18·1%)	0·087	0·60 (0·33–1·06)
Probable invasive β-haemolytic streptococcal infection	124	0	218	4 (1·8%)	1·00	NA‡
Intensive care unit patients	55	13 (23·6%)	90	32 (35·6%)	0·13	0·56 (0·26–1·18)
Vasopressor-dependent shock	37	12 (32·4%)	57	28 (49·1%)	0·11	0·48 (0·21–1·16)
Without vasopressor-dependent shock or necrotising fasciitis	239	6 (2·6%)	442	27 (6·1%)	0·043	0·40 (0·15–0·91)
Clindamycin treatment for >1 days	226	12 (5·3%)	500	55 (11·0%)	0·016	0·45 (0·23–0·87)
Clindamycin treatment for >2 days	183	10 (5·5%)	500	55 (11·0%)	0·032	0·47 (0·23–0·94)
Clindamycin treatment for >3 days	122	9 (6·9%)	500	55 (11·0%)	0·17	0·58 (0·29–1·24)

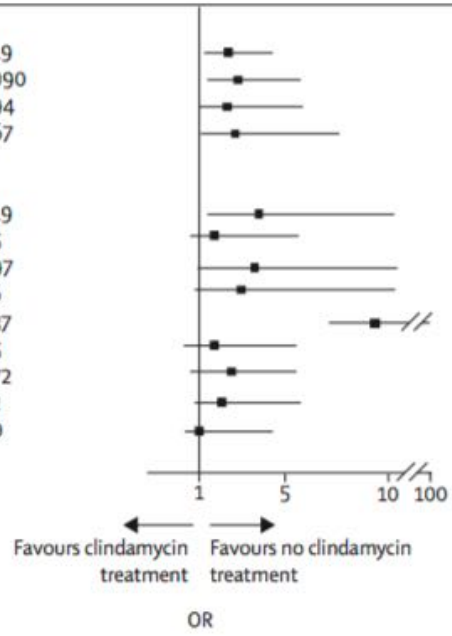


Babiker A et al. *Lancet Infect Dis* 2020 Dec.

Effectiveness of adjunctive clindamycin in β-lactam antibiotic-treated patients with invasive β-haemolytic streptococcal infections.

OR of in-hospital mortality in patients with invasive non-group A/B β-haemolytic streptococcal infection treated with versus without adjunctive clindamycin

	Clindamycin treatment		No clindamycin treatment		p value	OR (95% CI)
	Patients	Mortality (%)	Patients	Mortality (%)		
Primary analysis						
Unmatched, unadjusted	116	12 (10%)	761	37 (5%)	0·019	2·26 (1·10–4·35)
Unmatched, adjusted*					0·0090	2·73 (1·24–5·67)
Propensity-matched (1:2), unadjusted	102	10 (10%)	193	9 (5%)	0·094	2·22 (0·87–5·78)
Propensity-matched (1:2), adjusted*					0·067	2·60 (0·94–7·52)
Subgroup analysis†						
Early clindamycin treatment	39	6 (15%)	193	9 (5%)	0·019	3·72 (1·23–11·14)
Proven invasive β-haemolytic streptococcal infection	57	5 (9%)	106	6 (6%)	0·45	1·60 (0·44–5·56)
Probable invasive β-haemolytic streptococcal infection	45	5 (11%)	87	3 (4%)	0·097	3·50 (0·82–17·75)
Intensive care unit patients	19	5 (26%)	36	4 (11%)	0·16	2·86 (0·66–13·14)
Vasopressor-dependent shock	7	5 (71%)	14	3 (21%)	0·037	9·17 (1·29–93·76)
Without vasopressor-dependent shock or necrotising fasciitis	95	5 (5%)	177	6 (3%)	0·45	1·60 (0·15–5·46)
Clindamycin treatment for >1 days	85	9 (1%)	193	9 (5%)	0·072	2·42 (0·93–6·33)
Clindamycin treatment for >2 days	69	6 (9%)	193	9 (5%)	0·22	1·95 (0·67–5·69)
Clindamycin treatment for >3 days	47	2 (4%)	193	9 (5%)	0·90	0·91 (0·19–4·35)



Clindamicina + B lactam AB mejora el pronóstico de infecciones invasivas por GAS.

Babiker A et al. *Lancet Infect Dis* 2020 Dec.

Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial.

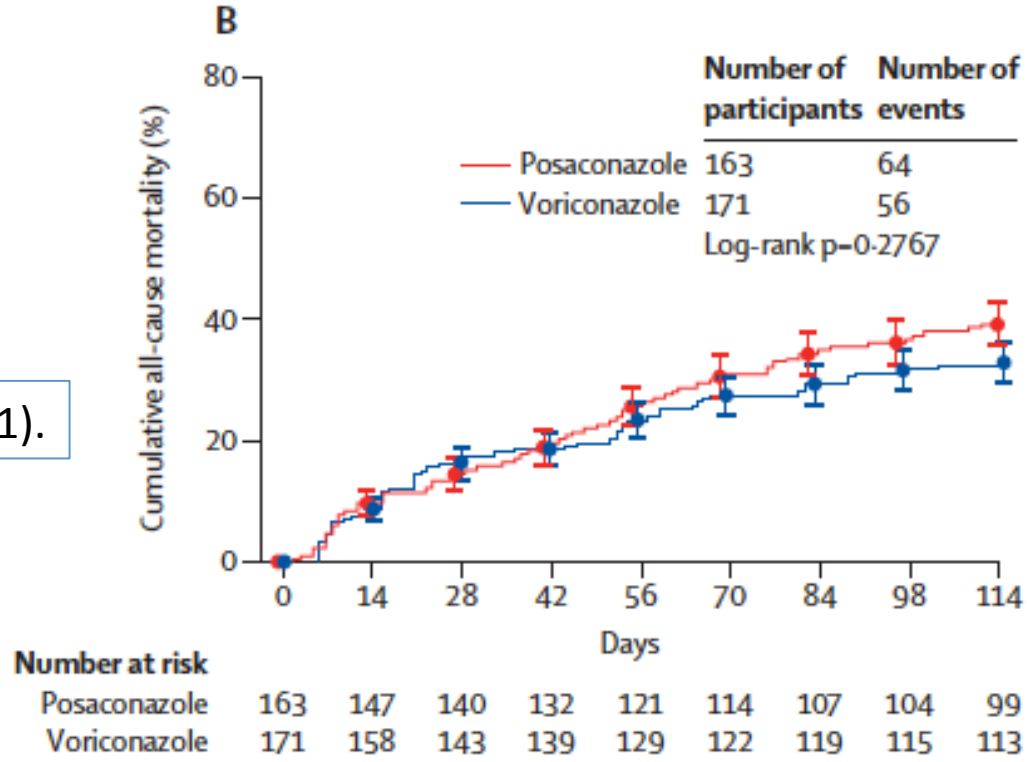
- Methods
  - Randomised, prospective, double-blind, double-dummy, controlled trial.
  - 91 study sites in 26 countries.
  - Participants met criteria for proven, probable, or possible fungal disease.
  - Randomly assigned (1:1) with stratification by risk status.
  - Primary endpoint:
    - Cumulative all-cause mortality up until day 42 (ITT).
    - 10% non-inferiority margin.

JA Maertens. Lancet 2021.

Posaconazole versus voriconazole for primary treatment of invasive aspergillosis.

- 575 patients.
- *Mortality at 42 days:*
  - *Posaconazol: 15%.*
  - *Voriconazole: 21%.*

-5·3% [95% CI -11·6 to 1·0]; p<0·0001).



JA Maertens. Lancet 2021.

Posaconazole versus voriconazole for primary treatment of invasive aspergillosis.

Table 2: **Analysis of all-cause mortality up until day 42 by subgroup in the intention-to-treat population**

	Posaconazole group	Voriconazole group	Treatment difference* (95% CI)
Age, years			
<18	1/3 (33%)	0/2	33·3% (−51·9 to 82·0)
18–57	14/151 (9%)	27/151 (18%)	−8·6% (−16·6 to −0·9)
>57	29/134 (22%)	32/134 (24%)	−2·2% (−12·3 to 7·9)
Sex			
Male	21/172 (12%)	38/172 (22%)	−9·9% (−17·9 to −1·9)
Female	23/116 (20%)	21/115 (18%)	1·6% (−8·7 to 11·8)
Region			
USA	3/21 (14%)	0/12	14·3% (−11·9 to 35·0)
Not USA	41/267 (15%)	59/275 (21%)	−6·1% (−12·6 to 0·4)
Ethnicity			
Hispanic or Latino	7/48 (15%)	14/57 (25%)	−10·0% (−25·0 to 5·8)
Not Hispanic or Latino	37/220 (17%)	43/218 (20%)	−2·8% (−10·1 to 4·5)
Unknown	0/20	2/11 (18%)	−18·2% (−48·2 to 0·3)
Race			
American Indian or Alaskan Native	0/4	4/6 (67%)	−66·7% (−90·9 to −1·5)
Asian	10/62 (16%)	4/60 (7%)	9·5% (−2·1 to 21·6)
Black	0/3	0/4	NA
Multiracial	5/25 (20%)	4/25 (16%)	4·0% (−18·5 to 26·4)
White	29/194 (15%)	47/192 (24%)	−9·5% (−17·5 to −1·6)
Risk status			
High risk	20/113 (18%)	23/113 (20%)	−2·7% (−13·0 to 7·7)
Not high risk	24/175 (14%)	36/174 (21%)	−7·0% (−15·0 to 1·0)
Type of invasive aspergillosis per adjudicator assessment			
Proven	7/26 (27%)	4/15 (27%)	0·3% (−29·6 to 26·5)
Probable	24/137 (18%)	28/156 (18%)	−0·4% (−9·2 to 8·5)
Possible	7/81 (9%)	18/79 (23%)	−14·1% (−25·7 to −3·0)
Cannot be determined	6/44 (14%)	9/37 (24%)	−10·7% (−28·7 to 6·5)
Site of invasive aspergillosis			
Lung	31/230 (13%)	39/230 (17%)	−3·5% (−10·1 to 3·1)
Multiple sites	12/48 (25%)	17/45 (38%)	−12·8% (−31·1 to 6·2)
Sinus	1/3 (33%)	2/7 (29%)	4·8% (−47·5 to 62·1)
Other	0/2	1/2 (50)	−50·0% (−92·4 to 46·8)
Missing	0/5	0/3	NA
Underlying disease			
Prolonged neutropenia temporally related to onset of fungal disease	30/179 (17%)	47/189 (25%)	−8·1% (−16·4 to 0·2)
Allogeneic HSCT	14/65 (22%)	9/59 (15%)	6·3% (−7·8 to 20·1)
Treatment with other recognised T-cell immunosuppressant drugs	20/126 (16%)	22/109 (20%)	−4·3% (−14·5 to 5·5)
Prolonged use of corticosteroid	23/93 (25%)	18/89 (20%)	4·5% (−7·8 to 16·7)
Inherited severe immunodeficiency	0/2	1/1 (100%)	−100·0% (−100·0 to 31·5)
None of the above	3/17 (18%)	1/18 (6%)	12·1% (−11·6 to 37·0)
Neutropenia status at baseline, cells per L			
$<0{\cdot}5\times10^9$	23/132 (17%)	34/137 (25%)	−7·4% (−17·1 to 2·4)
$\geq0{\cdot}5\times10^9$	20/142 (14%)	21/138 (15%)	−1·1% (−9·6 to 7·3)
Unknown	1/14 (7%)	4/12 (33%)	−26·2% (−56·2 to 5·4)

JA Maertens. Lancet 2021.

- Incidence of treatment-related adverse event:
  - 30% for posaconazole and 40% for voriconazole (−10·2% [95% CI −17·9 to −2·4]).

	Posaconazole group (n=288)	Voriconazole group (n=287)	Treatment difference (95% CI)*
Participants with treatment-related adverse events	86 (30%)	115 (40%)	−10·2% (−17·9 to −2·4)
Serious	16 (6%)	20 (7%)	−1·4% (−5·6 to 2·7)
Deaths	0	3 (1%)	−1·0% (−3·0 to 0·3)
Leading to discontinuation of study drug	18 (6%)	28 (10%)	−3·5% (−8·1 to 1·0)

*Based on Miettinen and Nurminen's method.[11]

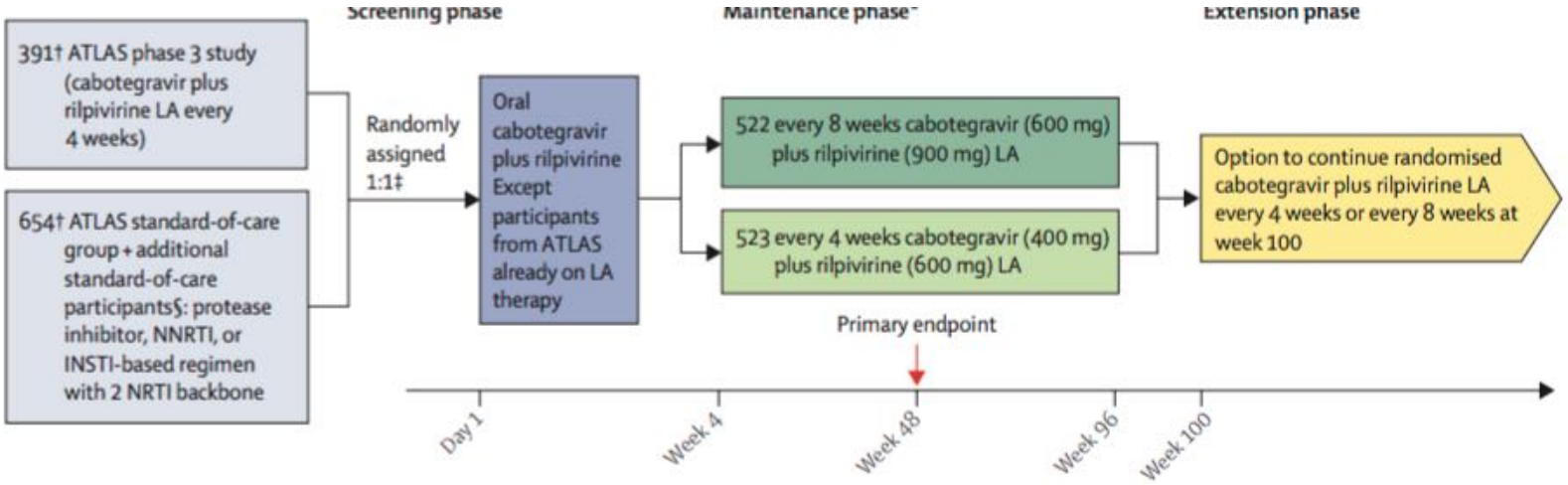
Table 3: **Adverse events in the intention-to-treat population**

Posaconazol es no inferior y menos tóxico.

JA Maertens. Lancet 2021.

Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M).

Long-Acting Cabotegravir plus Rilpivirine: A Viable Option for Management of HIV Infection?

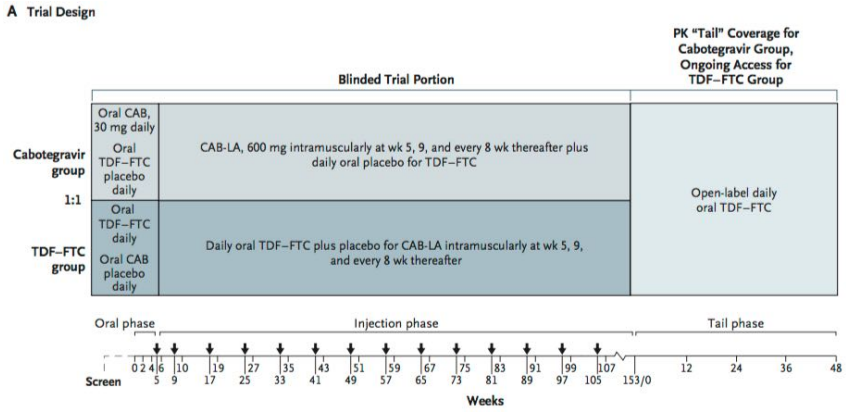


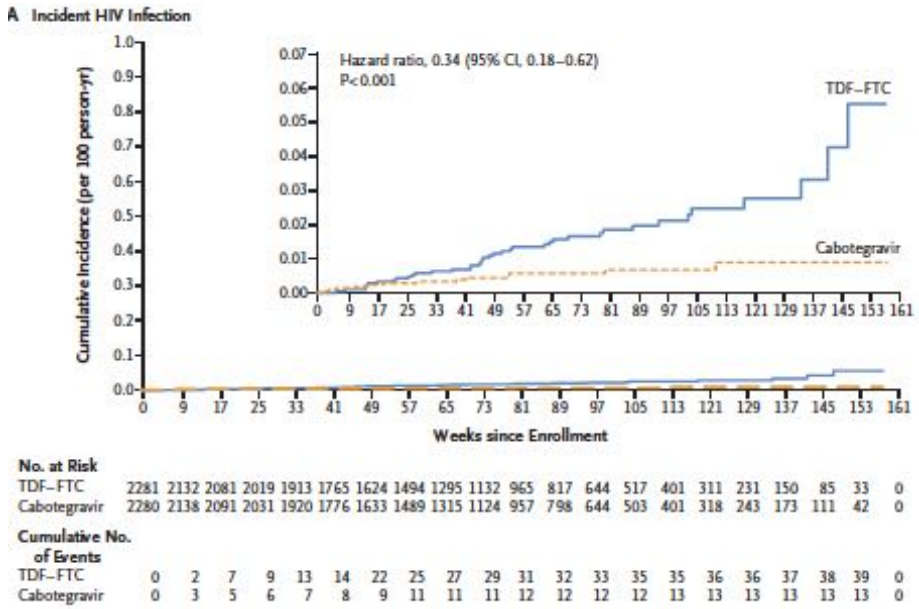
- The efficacy and safety profiles of dosing every 8 weeks and dosing every 4 weeks were similar.

McMahon J. Lancet 2020 Dec 19

Long-Acting PrEP Is Here to Stay

- 4570 Underwent randomization





- Incident HIV infection occurred in 52 participants:
  - 13 in the cabotegravir group (incidence, 0.41 per 100 person-years).
  - 39 in the TDF–FTC group (incidence, 1.22 per 100 person-years).

Landovitz RJ et al. *N Engl J Med* 2021.

Management of Lyme Disease: An Update.
Key Recommendations

- Doxycycline is recommended for antibiotic prophylaxis after high-risk tick bites.
- Erythema migrans: oral antibiotic therapy: doxycycline, amoxicillin.
- Neuroborreliosis treatment
  - Acute neurologic manifestations without parenchymal involvement (MRI or objective focal neurologic examination findings).
    - (IV) ceftriaxone, cefotaxime, or penicillin or oral doxycycline.
  - Acute neurologic manifestations with parenchymal involvement:
    - IV antibiotic therapy
- For patients with symptoms suggesting Lyme arthritis:
  - Serologic studies, followed by polymerase chain reaction (PCR) studies of synovial fluid or tissue.
- Do not use additional antibiotic therapy:
  - Patients who have persistent nonspecific symptoms without objective findings after they have received appropriate antibiotic therapy for Lyme disease.

Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the prevention, diagnosis and treatment of Lyme Disease. *Clin Infect Dis* 2020 Nov 30.

Management of Lyme Disease: An Update.

What's Changed.

- Lyme neuroborreliosis:
  - Specific neurologic symptoms that should prompt testing:
    - Meningitis, painful radiculoneuritis, mononeuropathy multiplex, acute cranial neuropathies, and spinal cord or brain inflammation in the setting of likely exposure to *Borrelia burgdorferi*.
  - CSF /serum antibody index (no PCR or culture of either CSF or serum).
- More detailed discussion of all aspects of the management of Lyme carditis.
- Oral antibiotic therapy is still recommended for initial management of Lyme arthritis.
  - IV antibiotic therapy for individuals who have no or minimal response to initial treatment.

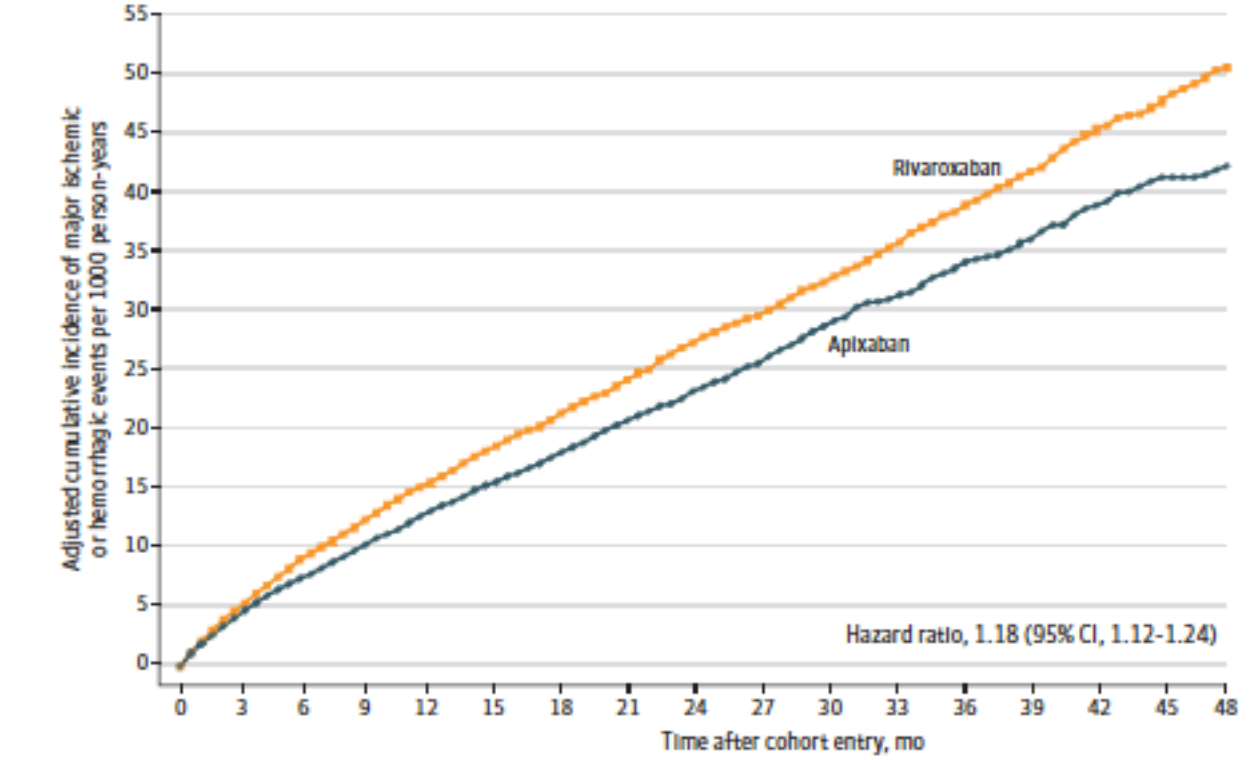
A Comparison of DOACs Using Real-World Data.

- DESIGN, SETTING, AND PARTICIPANTS
  - Retrospective cohort study using computerized enrollment and claims files for US Medicare beneficiaries 65 years or older.
  - 581.451 patients with atrial fibrillation began rivaroxaban or apixaban
  - Treatment and were followed up for 4 years.
- EXPOSURES
  - Rivaroxaban (n = 227 572) and apixaban (n = 353 879), either standard or reduced dose.
- MAIN OUTCOMES AND MEASURES
  - The primary outcome
    - Composite of major ischemic (stroke/systemic embolism) and hemorrhagic (intracerebral hemorrhage/other intracranial bleeding/fatal extracranial bleeding) events.
  - Secondary outcomes:
    - Nonfatal extracranial bleeding and total mortality (fatal ischemic/hemorrhagic event or other death during follow-up).
  - Rates, hazard ratios (HRs), and rate differences (RDs) were adjusted for baseline differences in comorbidity with inverse probability of treatment weighting.

Wayne A. Ray, et al. JAMA. 2021. Dec.

A Comparison of DOACs Using Real-World Data

Primary Outcome in a Study of the Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Atrial Fibrillation



Wayne A. Ray, et al. JAMA. 2021. Dec.

Outcomes in a Study of the Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Atrial Fibrillation[a]

Outcome	Rivaroxaban (191 153 person-years)		Apixaban (283 452 person-years)		Adjusted Rate per 1000 person-years		Rate difference (95% CI)	Hazard ratio (95% CI)
	Patients with event, No.	Rate/1000 person-years	Patients with event, No.	Rate/1000 person-years	Rivaroxaban	Apixaban		
Primary outcome and its components								
Major ischemic or hemorrhagic event	2838	14.8	4108	14.5	16.1	13.4	2.7 (1.9 to 3.5)	1.18 (1.12 to 1.24)
Ischemic event	1514	7.9	2293	8.1	8.6	7.6	1.1 (0.5 to 1.7)	1.12 (1.04 to 1.20)
Ischemic stroke	1447	7.6	2196	7.7	8.3	7.2	1.1 (0.5 to 1.6)	1.12 (1.05 to 1.21)
Systemic embolism	67	0.4	97	0.3	0.4	0.3	0.0 (−0.1 to 0.1)	1.05 (0.75 to 1.46)
Hemorrhagic event	1324	6.9	1815	6.4	7.5	5.9	1.6 (1.1 to 2.1)	1.26 (1.16 to 1.36)
Hemorrhagic stroke	459	2.4	515	1.8	2.5	1.7	0.8 (0.5 to 1.1)	1.48 (1.30 to 1.70)
Other intracranial hemorrhage	624	3.3	994	3.5	3.5	3.2	0.3 (−0.1 to 0.7)	1.09 (0.98 to 1.22)
Fatal extracranial bleeding	241	1.3	306	1.1	1.4	1.0	0.4 (0.2 to 0.7)	1.41 (1.18 to 1.70)
Secondary outcomes								
Nonfatal extracranial bleeding	6919	36.2	5672	20.0	39.7	18.5	21.1 (20.0 to 22.3)	2.07 (1.99 to 2.15)
Gastrointestinal	6132	32.1	4974	17.5	35.2	16.3	19.0 (17.9 to 20.1)	2.09 (2.01 to 2.18)
Other or unspecified	787	4.1	698	2.5	4.4	2.3	2.2 (1.8 to 2.5)	1.89 (1.69 to 2.11)
Total mortality	7497	39.2	12 839	45.3	44.2	41.0	3.1 (1.8 to 4.5)	1.06 (1.02 to 1.09)
Fatal ischemic or hemorrhagic event	767	4.0	1039	3.7	4.5	3.3	1.2 (0.8 to 1.6)	1.34 (1.21 to 1.48)
Other death during follow-up	6730	35.2	11 800	41.6	39.7	37.7	1.9 (0.6 to 3.2)	1.03 (0.995 to 1.07)

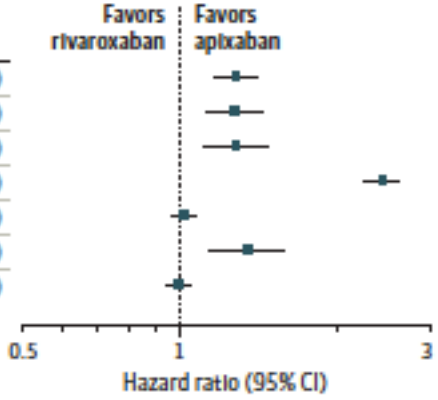
[a] Adjusted rates, rate differences, and hazard ratios are adjusted with inverse probability of treatment weighting. The variables used in the adjustment are shown in eTable 5 in the Supplement.

Wayne A. Ray, et al. JAMA. 2021. Dec.

2,5 mg/ 15 mg

A Reduced dose

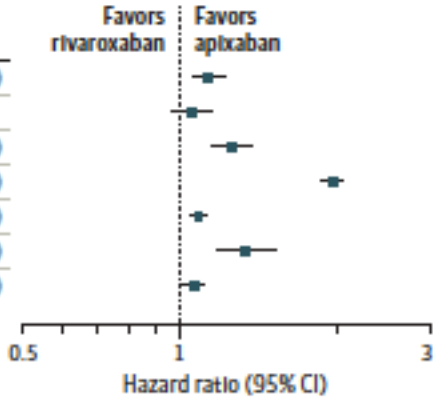
Outcome	Rate per 1000 person-years: Rivaroxaban	Rate per 1000 person-years: Apixaban	Rate difference (95% CI)	Hazard ratio (95% CI)
Major ischemic/hemorrhagic event	27.4	21.0	6.4 (4.1 to 8.7)	1.28 (1.16 to 1.40)
Ischemic	15.5	11.9	3.6 (1.9 to 5.3)	1.27 (1.13 to 1.44)
Hemorrhagic	11.9	9.1	2.8 (1.3 to 4.3)	1.28 (1.11 to 30.0)
Nonfatal extracranial bleeding	57.5	22.5	35.0 (31.9 to 38.1)	2.44 (2.26 to 34.0)
Total mortality	87.0	82.7	4.2 (-0.1 to 8.6)	1.02 (0.97 to 1.08)
Fatal ischemic/hemorrhagic event	8.5	6.2	2.3 (1.1 to 3.6)	1.35 (1.14 to 1.59)
Other death during follow-up	78.4	76.5	1.9 (-2.3 to 6.0)	1.00 (0.95 to 1.05)



5 mg/ 20 mg

B Standard dose

Outcome	Rate per 1000 person-years: Rivaroxaban	Rate per 1000 person-years: Apixaban	Rate difference (95% CI)	Hazard ratio (95% I)
Major ischemic/hemorrhagic event	13.2	11.4	1.8 (1.0 to 2.6)	1.13 (1.06 to 1.21)
Ischemic	6.8	6.4	0.5 (-0.1 to 1.0)	1.05 (.96 to 1.14)
Hemorrhagic	6.3	5.0	1.3 (0.8 to 1.8)	1.25 (1.14 to 1.37)
Nonfatal extracranial bleeding	35.0	17.5	17.5 (16.3 to 18.7)	1.94 (1.85 to 2.03)
Total mortality	32.9	29.7	3.1 (1.9 to 4.4)	1.08 (1.04 to 1.12)
Fatal ischemic/hemorrhagic event	3.4	2.5	0.9 (0.5 to 1.3)	1.33 (1.17 to 1.51)
Other death during follow-up	29.4	27.2	2.2 (1.0 to 3.4)	1.06 (1.01 to 1.10)



Wayne A. Ray, et al. JAMA. 2021. Dec.

Accuracy of Ultrasound Jugular Venous Pressure Height in Predicting Central Venous Congestion

- Background:
  - Assessment of volume status through the estimation of central venous pressure (CVP) is integral in the care of heart failure (HF).
  - Bedside assessment is limited by obesity, variation in physical examination skills, and expertise in ultrasonography.
- Objective:
  - To validate the accuracy of quantitative and qualitative point-of-care ultrasonography assessment of jugular venous pressure (JVP) in predicting elevated CVP.
- Design:
  - Prospective observational study using convenience sampling.
- Setting: 2 U.S. academic hospitals.
- Patients:
  - Adult patients undergoing right heart catheterization between 5 February 2019 and 1 March 2021.

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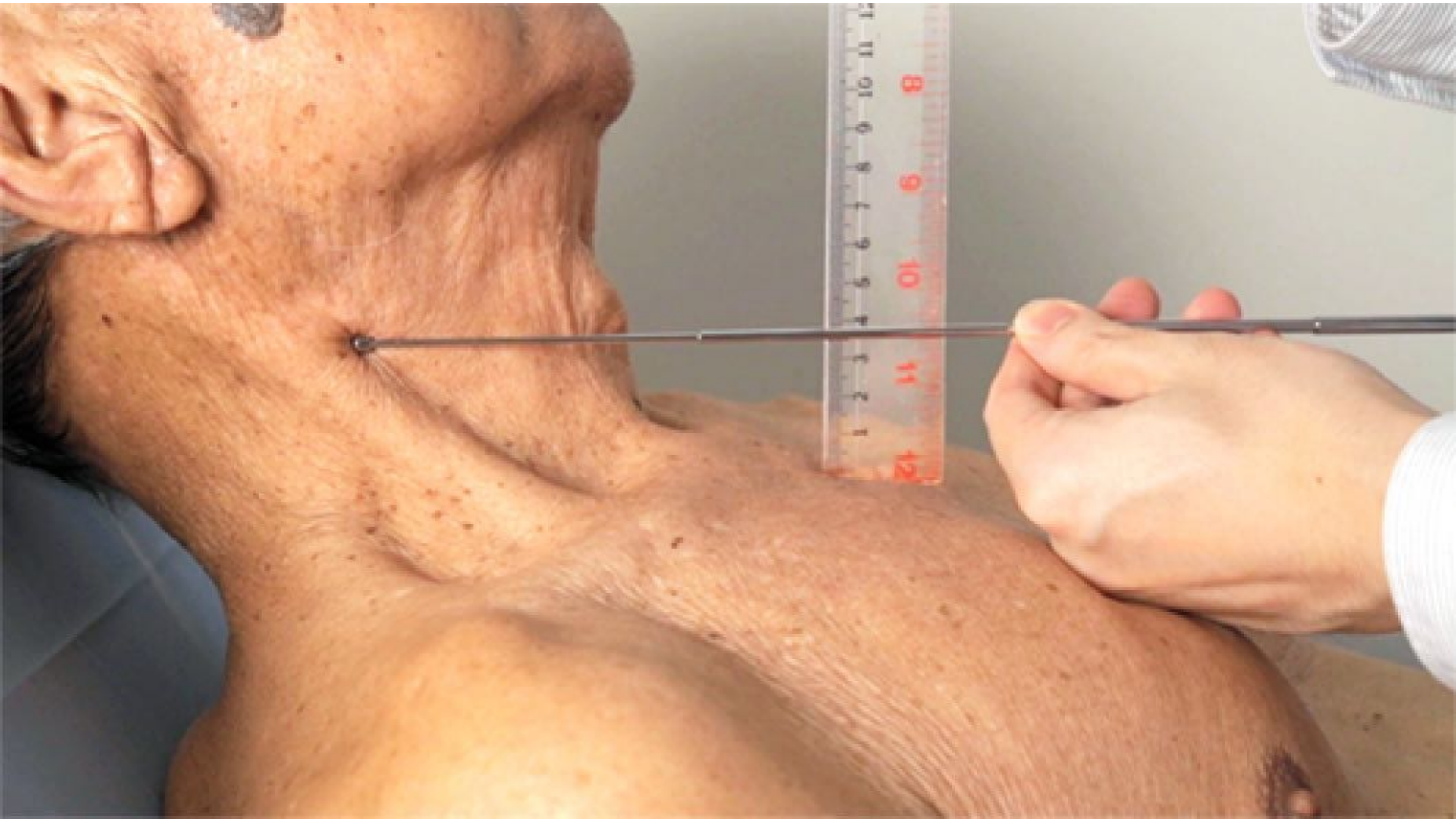
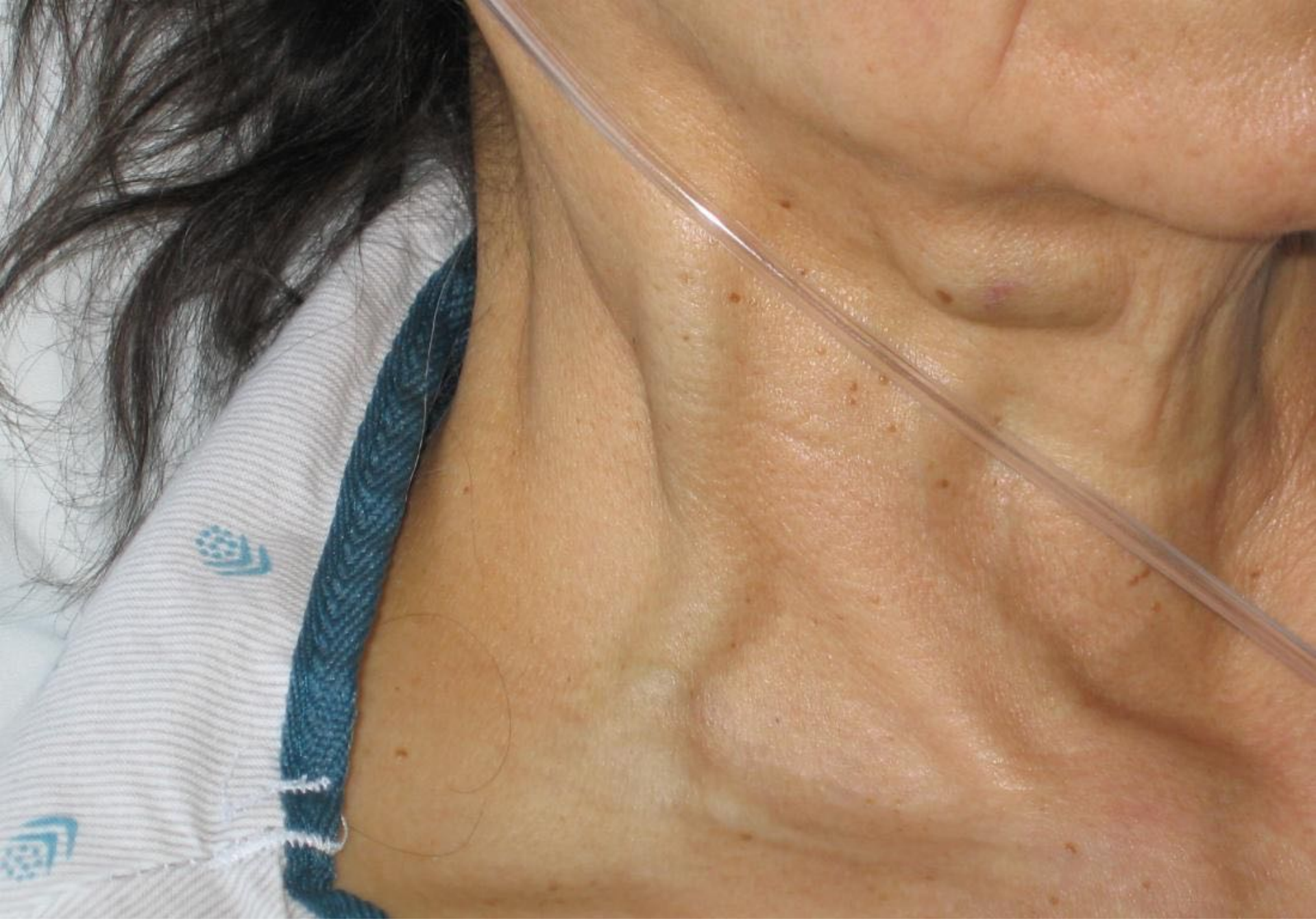
Accuracy of Ultrasound Jugular Venous Pressure Height in Predicting Central Venous Congestion



https://www.nejm.org/doi/full/10.1056/NEJMvcm1806474



https://www.medicalnewstoday.com/articles/320320

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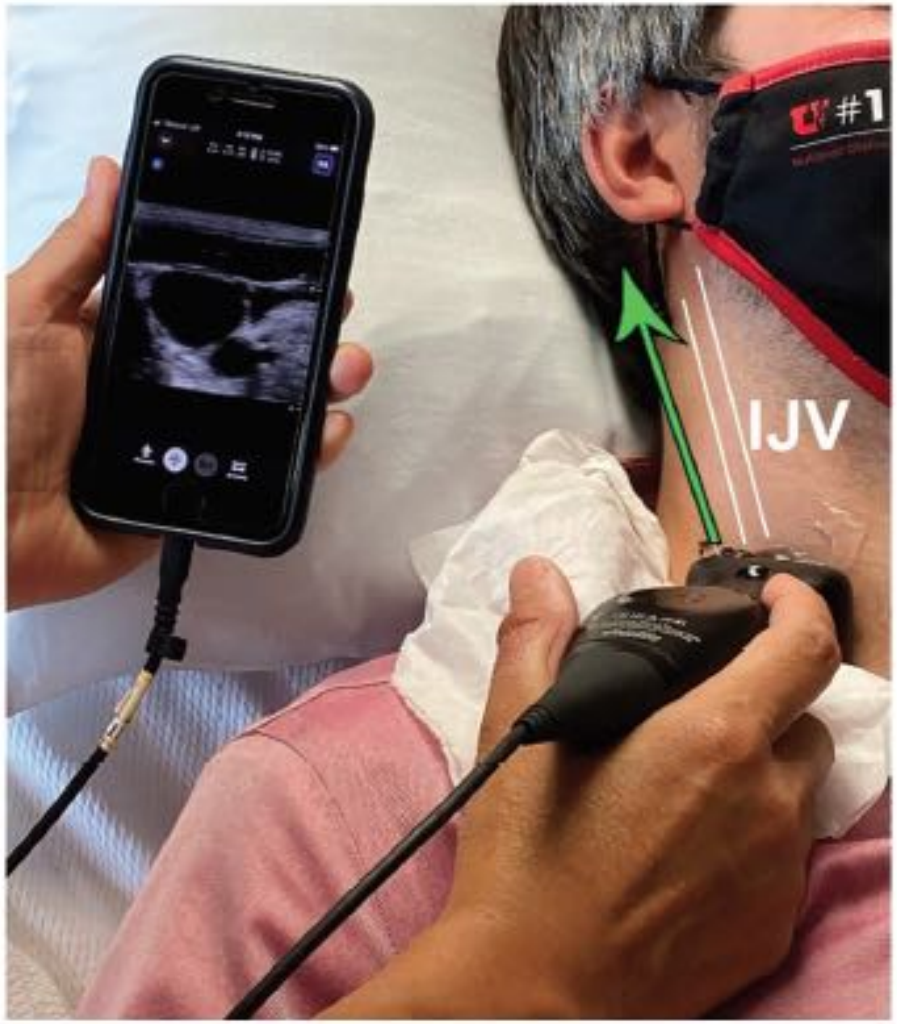
A.

B.



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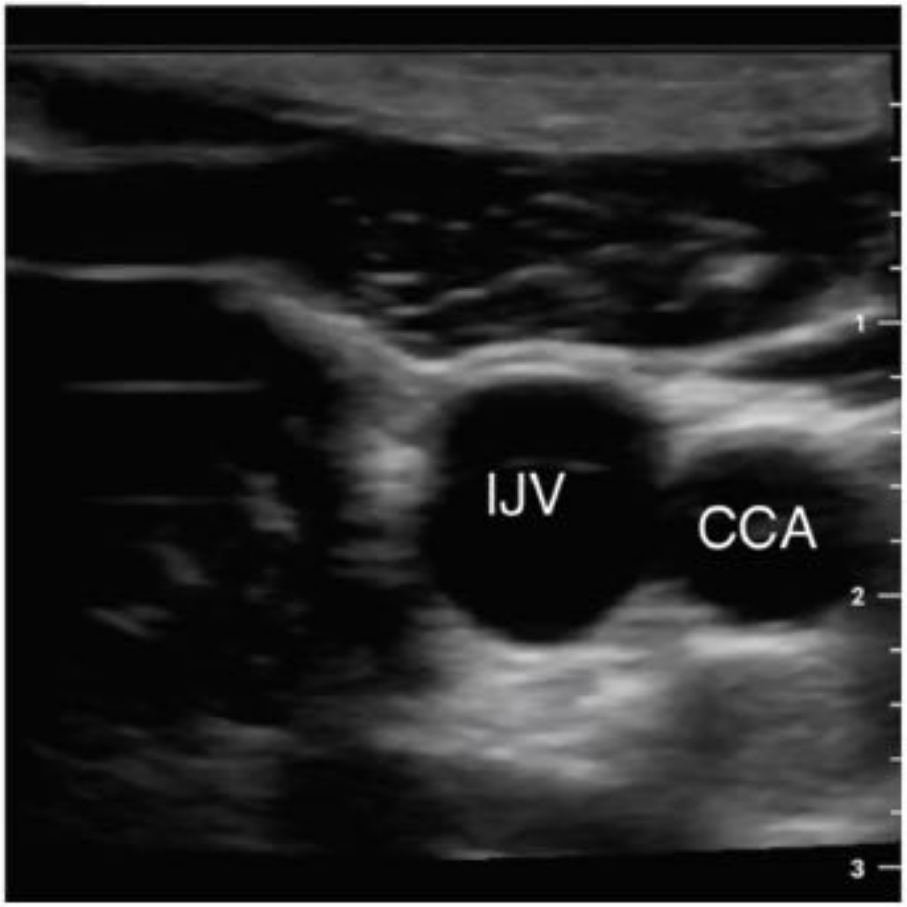
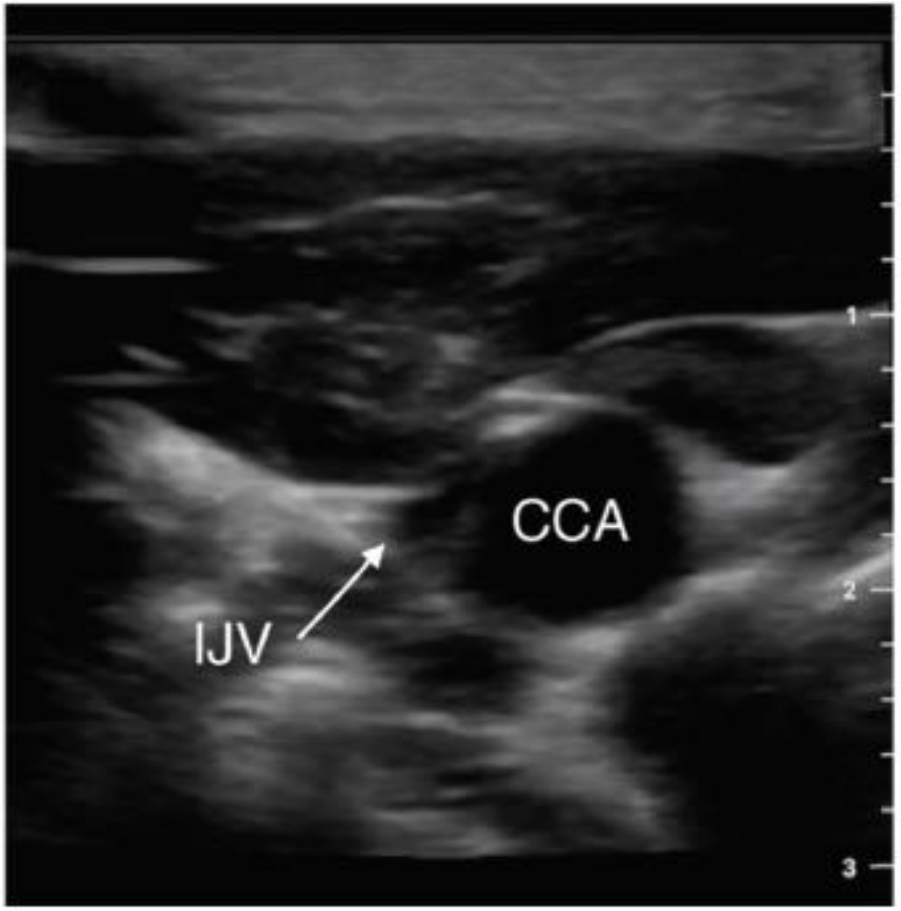
Internal jugular vein collapse point (ultrasound).





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Measurements

- JVP by traditional physical examination.
- Estimation of the JVP height by ultrasound device (uJVP).
- Qualitative presence of a distended uJVP in the upright position (upright-uJVP) was done.
- Invasive hemodynamics.
- Receiver-operating characteristic analysis of the uJVP was compared with invasive hemodynamics.

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Results

- 100 participants with right heart catheterization for HF.
  - Mean age: 59.6 years; 44% with pEF.
- Visualization of the JVP was possible:
  - uJVP: 100% of patients.
  - Traditional JVP: 42 of the 69 patients examined.
- The uJVP in a reclined position accurately predicted elevated right atrial pressure (RAP) (>10 mm Hg).
  - ROC AUC: 0.84.
  - Sensitivity: 72.7%. Specificity: 78.6%. Likelihood ratio: 3.40.
- A positive uJVP in the upright position:
  - Specific for predicting elevated RAP: 94.6%.
  - Sensitivity: 54.5%.
- Limitation:
  - Limited examiners, only 2 centers, and convenience sampling.

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Figure 4. The RAP and height of uJVP by neck zones.

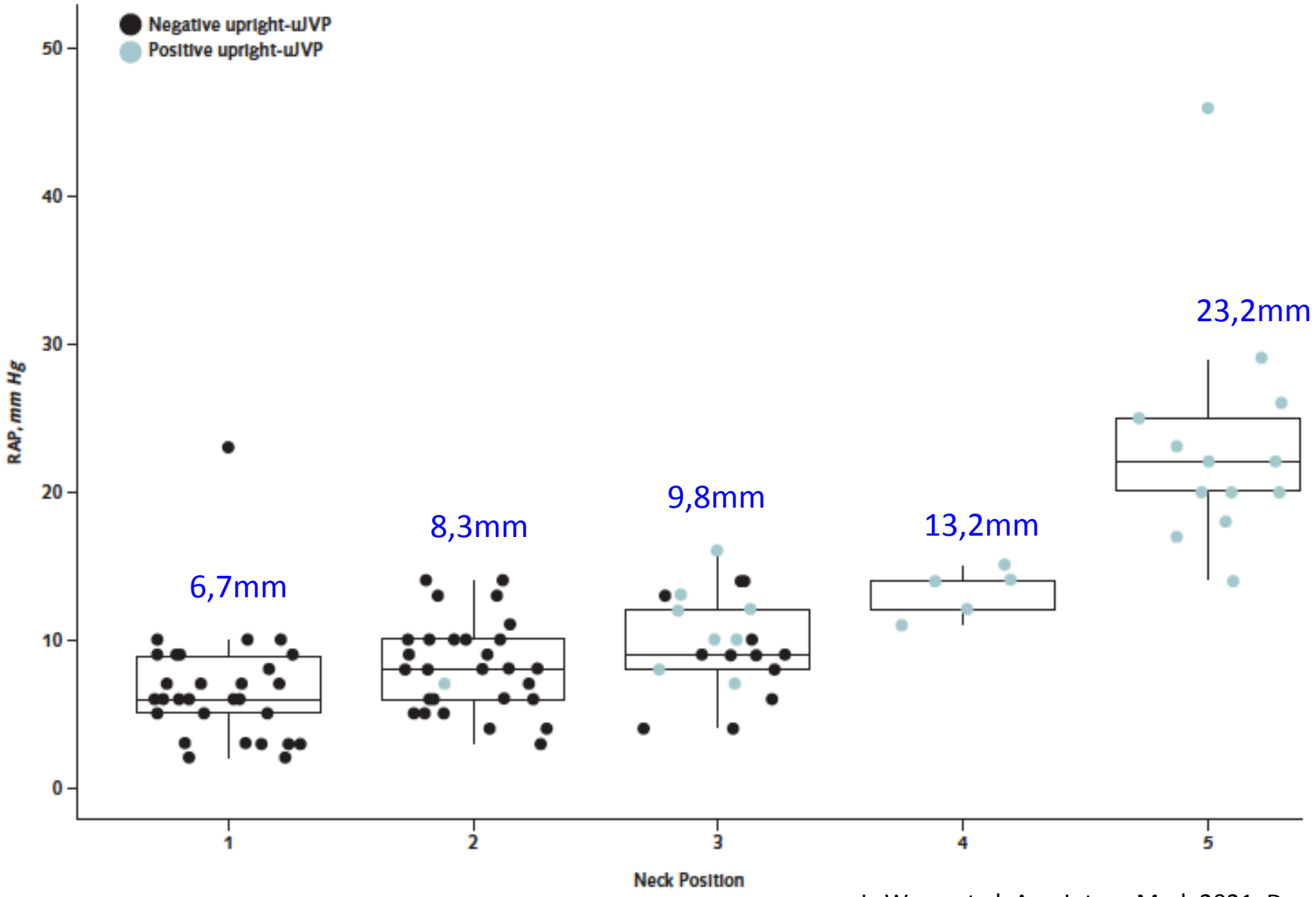

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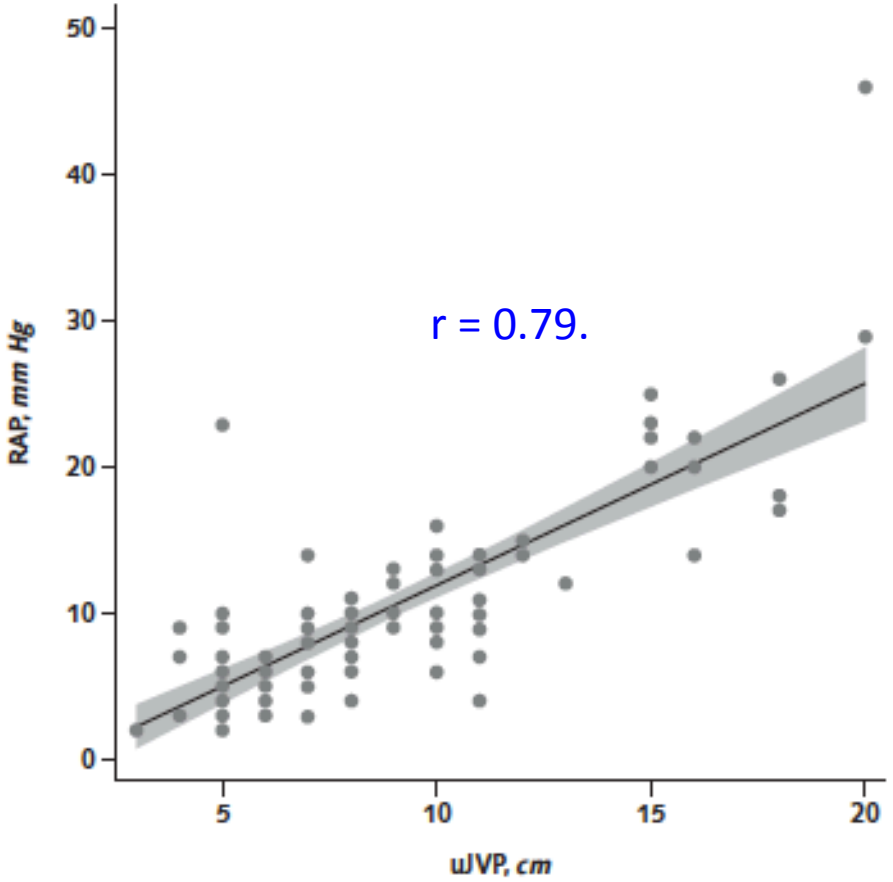
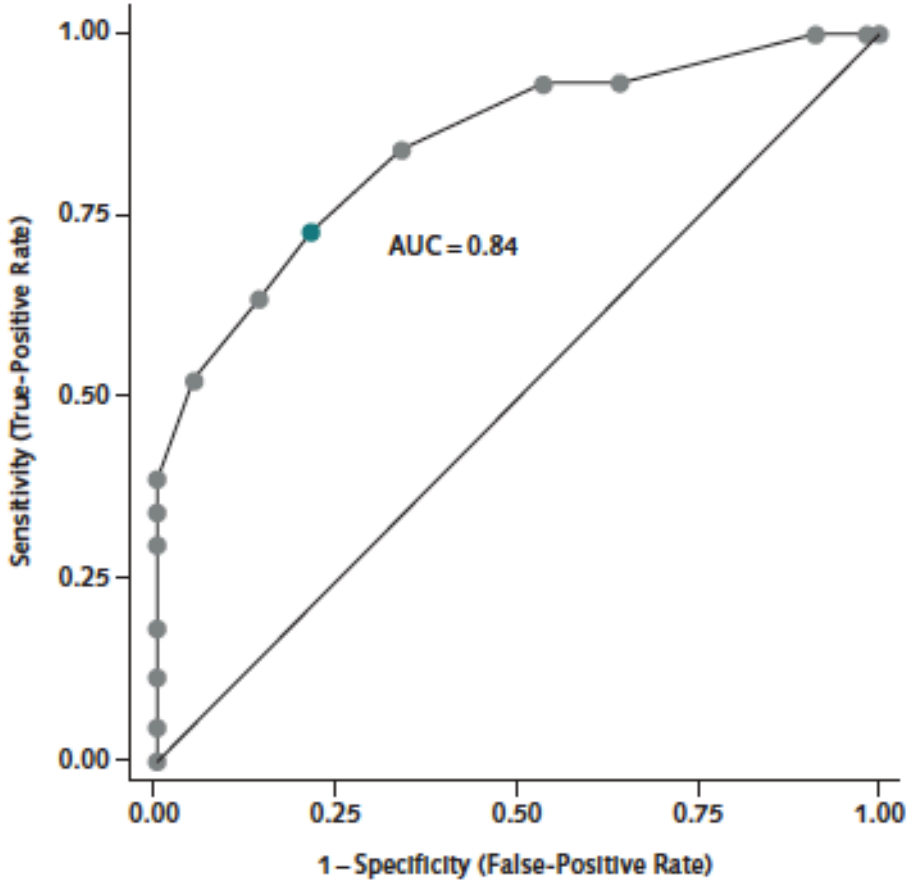
Figure 2. Correlation of uJVP with invasive RAP and receiver-operating characteristics curve of uJVP.





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- Conclusion:
  - Point-of-care ultrasonography assessment of the uJVP is feasible, reproducible, and accurately predictive of elevated CVPs in patients undergoing right heart catheterization.

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