2023

PULMONARY AND CRITICAL CARE LITERATURE UPDATES

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COPD – GOLD 2023 UPDATES

- Overall – 387 new references added to the GOLD 2023 report
- Etiotypes of COPD:

  Relatively little impact on current clinical practice but highlights the need to continually evaluate patients outside of Tobacco Use

Proposed Taxonomy (Etiotypes) for COPD — Table 1.1

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, HIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

USE OF CT IN COPD

- Learning more about the usefulness of CT due to more evals for Pes, Lung Cancer Screening (now 50 y/o) and for Endobronchial Valve Lung Volume Reduction
- Patients with persistent exacerbations, symptoms out of proportion to disease severity on lung function testing, FEV1 less than 45% predicted with significant hyperinflation and gas trapping, or for those who meet criteria for lung cancer screening, chest CT imaging should be considered

Use of CT in Stable COPD — Table 2.8

Differential Diagnosis	• Frequent exacerbations with excessive cough with sputum production, raising concern for bronchiectasis or atypical infection • Symptoms out of proportion to disease severity based on lung function testing
Lung Volume Reduction	• Endobronchial valve therapy may be a therapeutic option for patients if they demonstrate postbronchodilator FEV1 between 15-45% and evidence of hyperinflation • Lung volume reduction surgery may be a therapeutic option for patients with hyperinflation, severe upper lobe predominant emphysema and low exercise capacity after pulmonary rehabilitation
Lung Cancer Screening	• Annual low-dose CT scan is recommended for lung cancer screening in patients with COPD due to smoking according to recommendations for the general population

VACCINATIONS

- Pneumococcal Vaccination:

  Patients over 65 or 19-64 who have:

  Chronic Lung Disease (COPD, Emphysema, Asthma)

  Cigarette Smoking

  Solid Organ Transplant

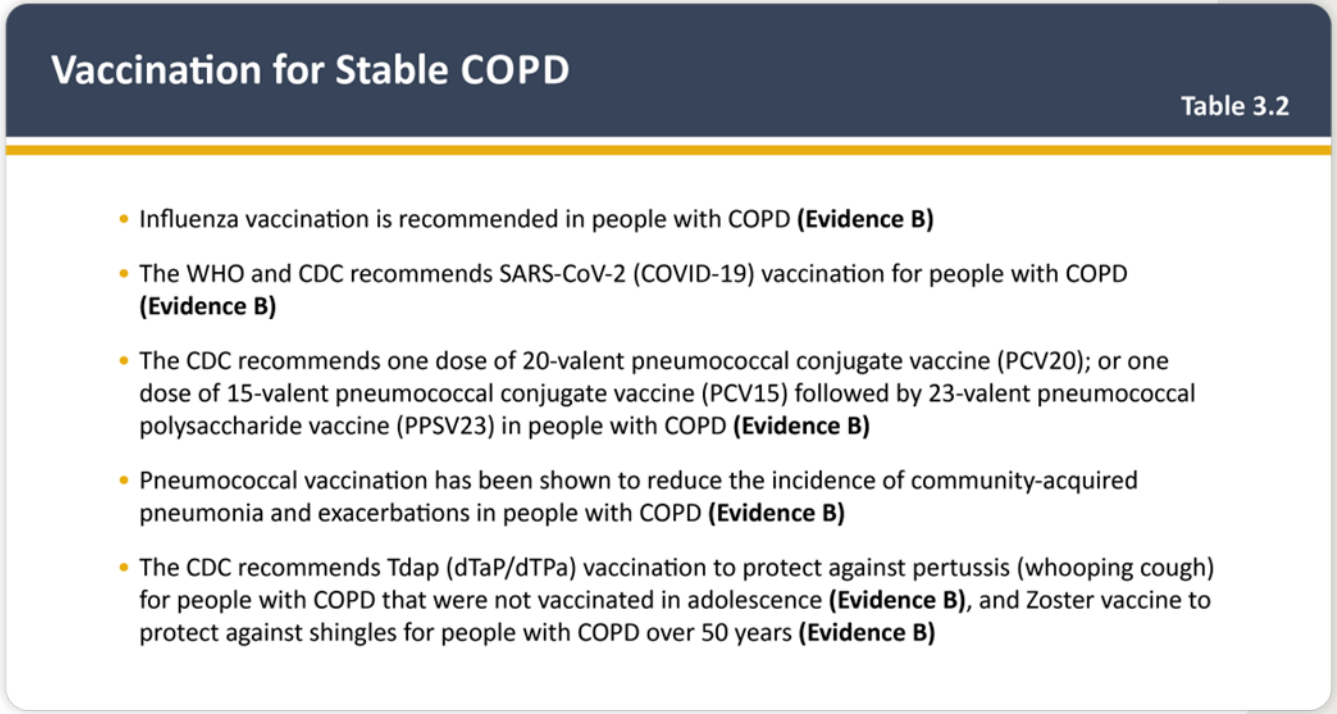
  No Hx of Immun. Or Unknown:

  PC15 then PPSV23 (one year later)

  or

  PCV20

  (If only PPSV23, then PCV 15 or PCV20 ≥ 1 year later)

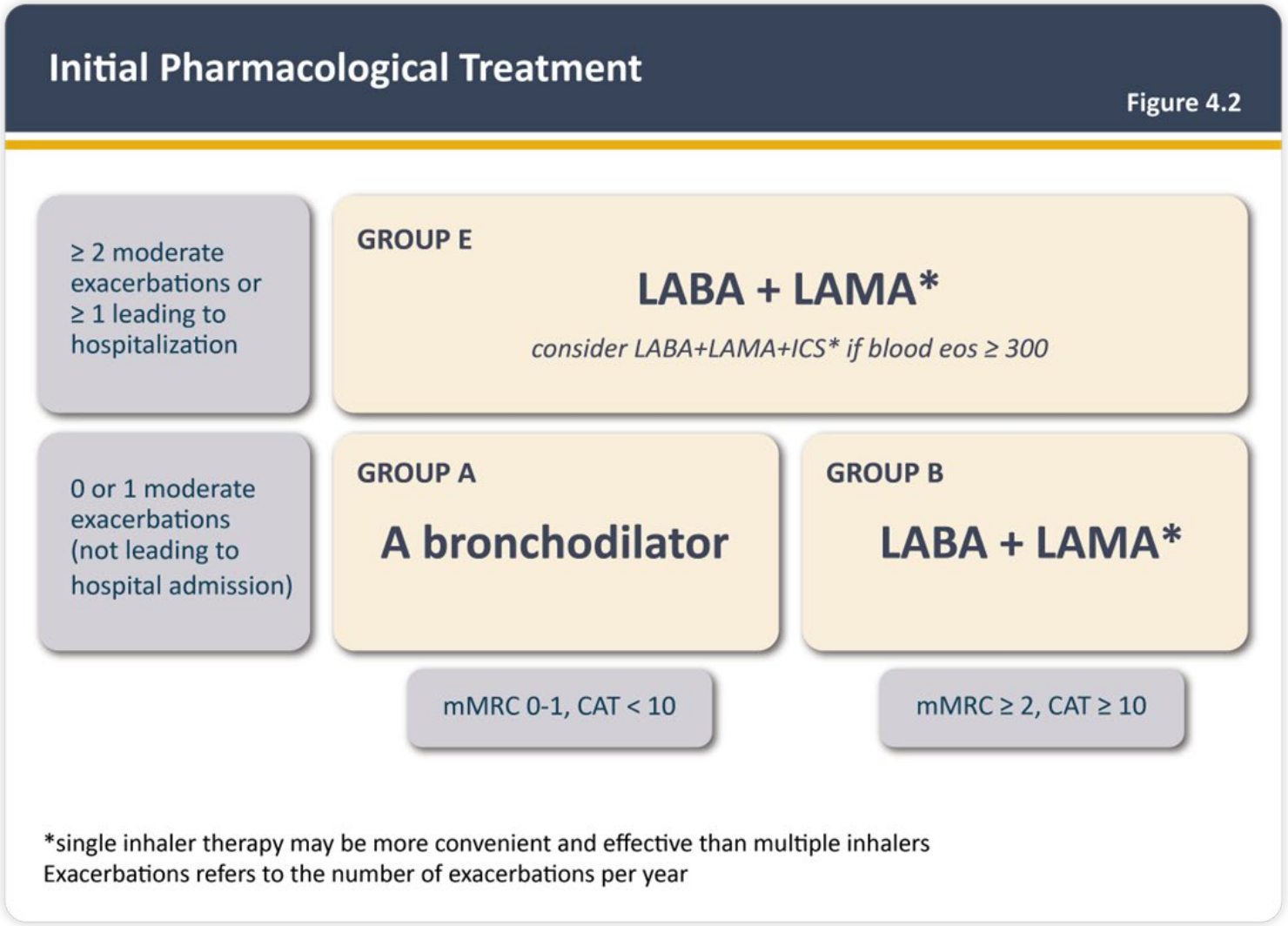


Vaccination for Stable COPD

Table 3.2

- Influenza vaccination is recommended in people with COPD **(Evidence B)**
- The WHO and CDC recommends SARS-CoV-2 (COVID-19) vaccination for people with COPD **(Evidence B)**
- The CDC recommends one dose of 20-valent pneumococcal conjugate vaccine (PCV20); or one dose of 15-valent pneumococcal conjugate vaccine (PCV15) followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) in people with COPD **(Evidence B)**
- Pneumococcal vaccination has been shown to reduce the incidence of community-acquired pneumonia and exacerbations in people with COPD **(Evidence B)**
- The CDC recommends Tdap (dTaP/dTPa) vaccination to protect against pertussis (whooping cough) for people with COPD that were not vaccinated in adolescence **(Evidence B)**, and Zoster vaccine to protect against shingles for people with COPD over 50 years **(Evidence B)**

ABCD IS NOW ABE



Factors to Consider when Initiating ICS Treatment

Figure 3.1

Factors to consider when adding ICS to long-acting bronchodilators:

(note the scenario is different when considering ICS withdrawal)

STRONGLY FAVORS USE	**History of hospitalization(s) for exacerbations of COPD[#]**
	≥ 2 moderate exacerbations of COPD per year[#]
	Blood eosinophils ≥ 300 cells/µL
	History of, or concomitant asthma
FAVORS USE	1 moderate exacerbation of COPD per year[#]
	Blood eosinophils 100 to < 300 cells/µL
AGAINST USE	**Repeated pneumonia events**
	Blood eosinophils < 100 cells/µL
	History of mycobacterial infection

[#]despite appropriate long-acting bronchodilator maintenance therapy (see Table 3.4 and Figure 4.3 for recommendations);
*note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

EXACERBATIONS

- Definition updated to an event characterized by dyspnea and/or cough and sputum that worsen over < 14 days.

  Exacerbations of COPD are often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insults to the lungs

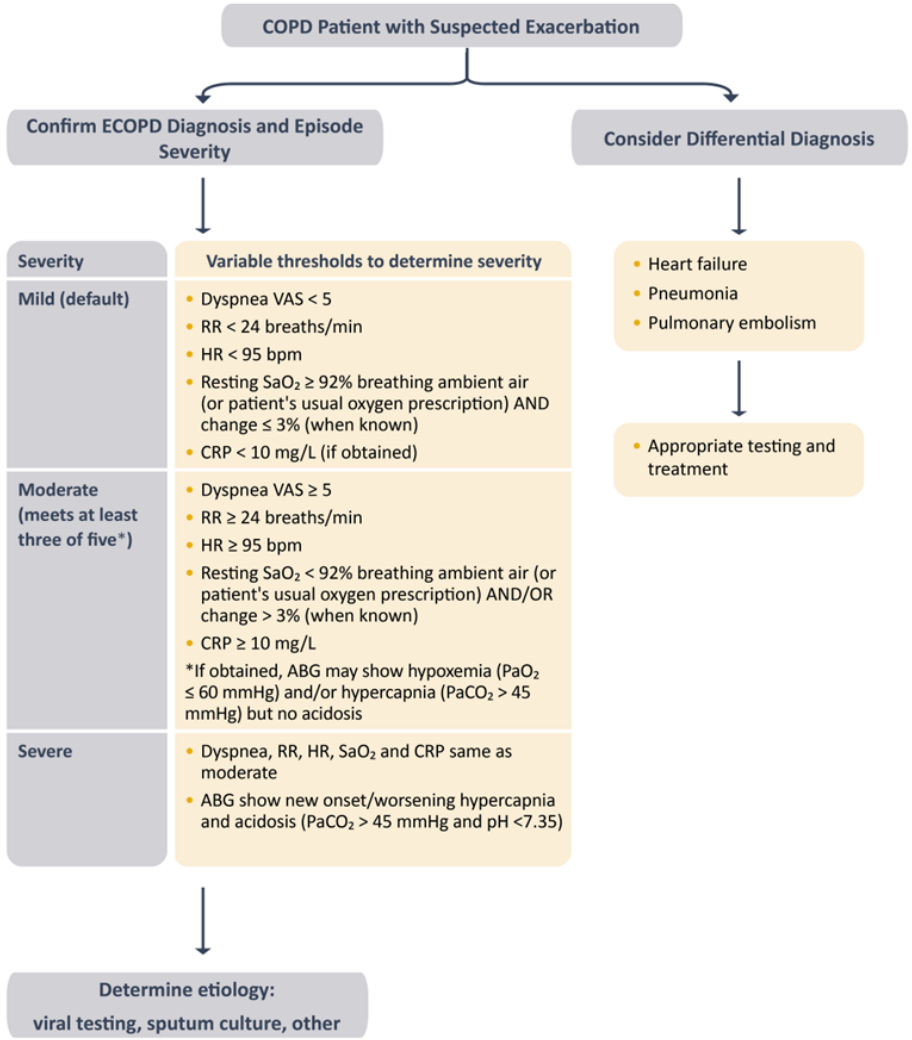
- Newer Push to Identify causes of Exacerbations

Confounders or Contributors to be Considered in Patients Presenting with Suspected COPD Exacerbation — Table 5.1

Most frequent	**Pneumonia**	• Chest radiograph
	Pulmonary embolism	• Clinical probability assessment (Hemoptysis, surgery, fracture, history of cancer, DVT) • D-dimer • CT angiography for pulmonary embolism
	Heart failure	• Chest radiograph • NT Pro-Brain Natriuretic Peptide (Pro-BNP) and BNP • Echocardiography
Less frequent	**Pneumothorax, pleural effusion**	• Chest radiograph • Thoracic ultrasound
	Myocardial infarction and/or cardic arrhythmias (atrial fibrillation/flutter)	• Electrocardiography • Troponin

Classification of the Severity of COPD Exacerbations

Figure 5.1



Adapted from: The ROME Proposal, Celli et al. (2021) Am J Respir Crit Care Med. 204(11): 1251-8. Abbreviations: VAS visual analog dyspnea scale; RR respiratory rate; HR heart rate; SaO_2 oxygen saturation; CRP C-reactive protein; ABG arterial blood gases; PaO_2 Arterial pressure of oxygen.

The NEW ENGLAND JOURNAL of MEDICINE

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Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

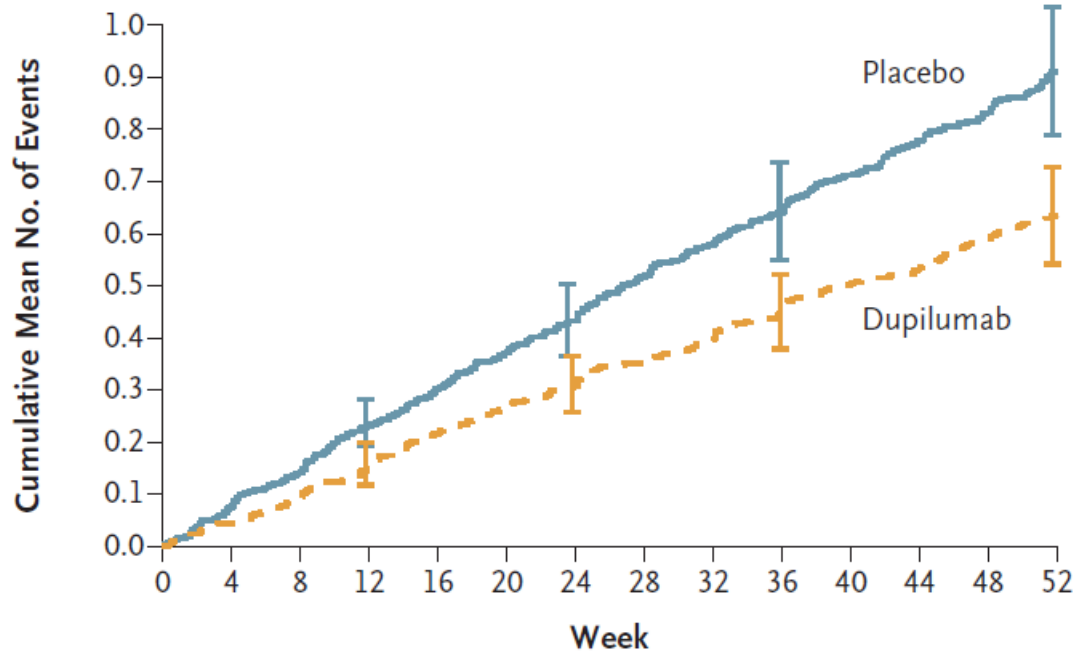
S.P. Bhatt, K.F. Rabe, N.A. Hanania, C.F. Vogelmeier, J. Cole, M. Bafadhel, S.A. Christenson, A. Papi, D. Singh, E. Laws, L.P. Mannent, N. Patel, H.W. Staudinger, G.D. Yancopoulos, E.R. Mortensen, B. Akinlade, J. Maloney, X. Lu, D. Bauer, A. Bansal, L.B. Robinson, and R.M. Abdulai, for the BOREAS Investigators*

- Could the use of biologics in the correct patient population in COPD patients show benefit?
- Phase 3 blinded trial
- 930 patient s with COPD, Chronic Bronchitis and Peripheral Eosinophilia
  - Recurrent moderate to severe exacerbations despite optimized treatment

Table 1. Selected Demographic and Disease Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Placebo (N=471)	Dupilumab (N=468)	Total (N=939)
Age — yr	65.2±8.1	65.0±8.0	65.1±8.1
Male sex — no. (%)	322 (68.4)	298 (63.7)	620 (66.0)
Race or ethnic group — no. (%)†			
White	397 (84.3)	393 (84.0)	790 (84.1)
Black	2 (0.4)	3 (0.6)	5 (0.5)
Asian	67 (14.2)	67 (14.3)	134 (14.3)
American Indian or Alaska Native	4 (0.8)	3 (0.6)	7 (0.7)
Native Hawaiian or other Pacific Islander	1 (0.2)	0	1 (0.1)
Multiple	0	2 (0.4)	2 (0.2)
Hispanic or Latino ethnic group — no. (%)†			
Hispanic or Latino	129 (27.4)	132 (28.2)	261 (27.8)
Non-Hispanic or non-Latino	342 (72.6)	335 (71.6)	677 (72.1)
Unknown	0	1 (0.2)	1 (0.1)
Smoking status — no. (%)			
Former smoker	323 (68.6)	334 (71.4)	657 (70.0)
Current smoker	148 (31.4)	134 (28.6)	282 (30.0)
Smoking history — pack-yr‡	41.4±24.4	39.6±22.3	40.5±23.4
Body-mass index§	27.6±5.7	27.5±5.4	27.6±5.6
Background medication — no. (%)¶			
Triple therapy‖	461 (97.9)	455 (97.2)	916 (97.6)
Inhaled high-dose glucocorticoid	126 (26.8)	131 (28.0)	257 (27.4)
Biomarkers of type 2 inflammation			
Blood eosinophil count at randomization			
Mean — per μl	408±331	394±261	401±298
Median (interquartile range) — per μl	330 (230–460)	340 (250–460)	340 (240–460)
Postbronchodilator $F_{E}NO$ — ppb**	23.51±22.00	25.18±22.79	24.33±22.40
Distribution — no./total no. (%)			
≥20 ppb	188/442 (42.5)	195/433 (45.0)	383/875 (43.8)
<20 ppb	254/442 (57.5)	238/433 (55.0)	492/875 (56.2)
No. of moderate or severe COPD exacerbations in previous yr	2.3±1.0	2.2±1.1	2.3±1.0

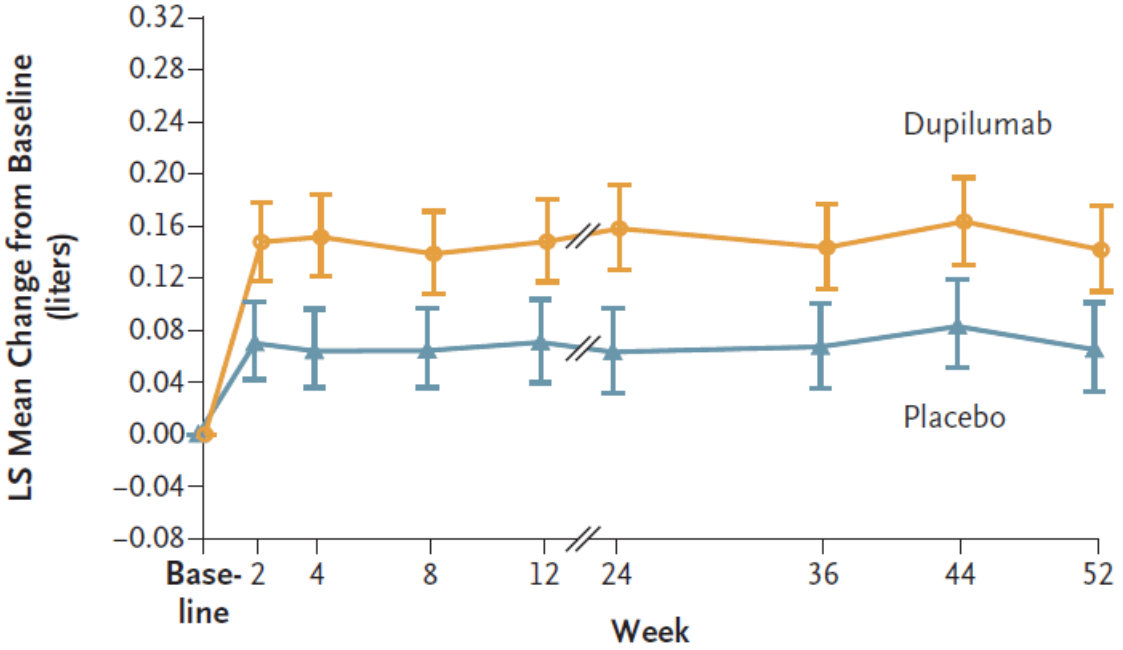
A Cumulative Moderate or Severe COPD Exacerbations



No. at Risk

Placebo	471	470	466	461	457	457	456	451	451	449	445	442	441	437
Dupilumab	468	467	465	464	462	460	458	457	456	454	451	450	448	437

B Prebronchodilator FEV_1



No. of Patients with Data

Placebo	471	455	459	439	439	435	415	404	420
Dupilumab	467	457	454	446	449	443	415	410	426

SUMMARY

- Study Focus: Treatment of symptomatic COPD with type 2 inflammation at high risk of exacerbation.
- Outcome with Dupilumab vs. Placebo:
  Lower annual rate of moderate/severe exacerbations.
  Greater improvements in lung function & quality of life.
- Observed improvements within 2-4 weeks; sustained over 52 weeks.
- Comparison to Other Biologics: Mixed results with interleukin-5 or its receptor-targeting agents
  Distinct beneficial role of IL-4/IL-13 pathway.
- Strengths: Adequately powered, international, low dropout, similar adverse events between groups.
- Limitations: Conducted during COVID-19, underrepresentation of Black patients, unstratified by smoking status.
  - Take Home Point: Dupilumab may be a beneficial option for COPD patients with Type 2 inflammation and recurrent exacerbations

JAMA | Original Investigation

Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease

- Are mucus plugs that occlude airways on CT associated with an increase in all-cause mortality in COPD patients?
  - Particularly interested in medium to large sized airways (2mm-10mm)
  - 4363 patients with COPD
  - Mucous Plugs effecting the medium to large sized airways

- Patients with higher mucous plug burden had higher association with all-cause mortality
- This opens up new avenues for risk assessment of COPD patients and potential targets for therapy
- Weakness of the study is this is an observational study – no conclusions drawn to causation

Table 1. Characteristics of Participants With COPD by Mucus Plug Score Category

Characteristic	Mucus plug score category (No. of lung segments with mucus plugs), No. (%)		
	0 (n = 2585)	1-2 (n = 953)	≥3 (n = 825)
Age, median (IQR), y	62.4 (55.9-68.7)	63.9 (57.6-70.6)	65.3 (57.9-71.1)
Sex			
Female	1072 (41.5)	448 (47.0)	400 (48.5)
Male	1513 (58.5)	505 (53.0)	425 (51.5)
Race and ethnicity[a]			
Non-Hispanic Black	636 (24.6)	199 (20.9)	142 (17.2)
Non-Hispanic White	1949 (75.4)	754 (79.1)	683 (82.8)
BMI, median (IQR)	27.6 (24.2-31.9)	26.8 (23.4-31.0)	25.5 (22.1-30.1)
Current smoker, No. (%) [No.]	1155 (44.7) [2584]	383 (40.2)	347 (42.1) [824]
Pack-years of smoking, median (IQR)	44.3 (33.2-64)	46.1 (35.0-65.7)	47.6 (35.0-67.6)
Medical history			
Chronic bronchitis	584 (22.6)	248 (26.0)	293 (35.5)
Coronary artery disease	417 (16.1)	154 (16.2)	113 (13.7)
Asthma[b]	406 (15.7)	168 (17.6)	187 (22.7)
COPD GOLD stage of severity[c]			
1 (Mild)	597 (23.1)	116 (12.2)	53 (6.4)
2 (Moderate)	1250 (48.4)	389 (40.8)	248 (30.1)
3 (Severe)	523 (20.2)	297 (31.2)	307 (37.2)
4 (Very severe)	215 (8.3)	151 (15.8)	217 (26.3)
BODE index, median (IQR) [No.][d]	2 (0-4) [2525]	3 (1-5) [924]	4 (2-6) [803]
FEV_1, L	1.8 (1.3-2.4)	1.4 (0.9-1.9)	1.1 (0.8-1.6)
FEV_1, % predicted	65.0 (47.1-78.4)	51.9 (36.4-69.7)	42.1 (29.1-59.4)
Emphysema on CT, median (IQR) [No.], %[e]	5.6 (1.8-14.9) [2466]	9.2 (2.8-22.1) [916]	12.4 (3.4-24.2) [787]
Airway wall thickness, median (IQR) [No.], mm[f]	2.5 (2.1-2.9) [2466]	2.7 (2.3-3.1) [916]	2.9 (2.5-3.3) [787]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BODE, body mass index, obstruction, dyspnea, and exercise mortality risk score; COPD, chronic obstructive pulmonary disease; CT, computed tomography; FEV_1, forced expiratory volume in the first second of expiration; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

[a] Race and ethnic group were reported by the participant. Only non-Hispanic Black and non-Hispanic White participants were included.

[b] Asthma was defined as current asthma.

[c] GOLD stages were defined with postbronchodilator FEV_1 percentage of predicted (pp) values as follows: 1 (mild), FEV_1 pp ≥80; 2 (moderate), FEV_1 pp ≥50 to <80; 3 (severe) FEV_1 pp ≥30 to <50; and 4 (very severe), FEV_1 pp <30.

[d] The multidimensional mortality BODE index is composed of 4 factors: BMI, FEV_1 percentage predicted, distance walked in 6 minutes, and the modified Medical Research Council dyspnea scale. The BODE index ranges from 0 (lowest risk of death) to 10 (highest risk of death).

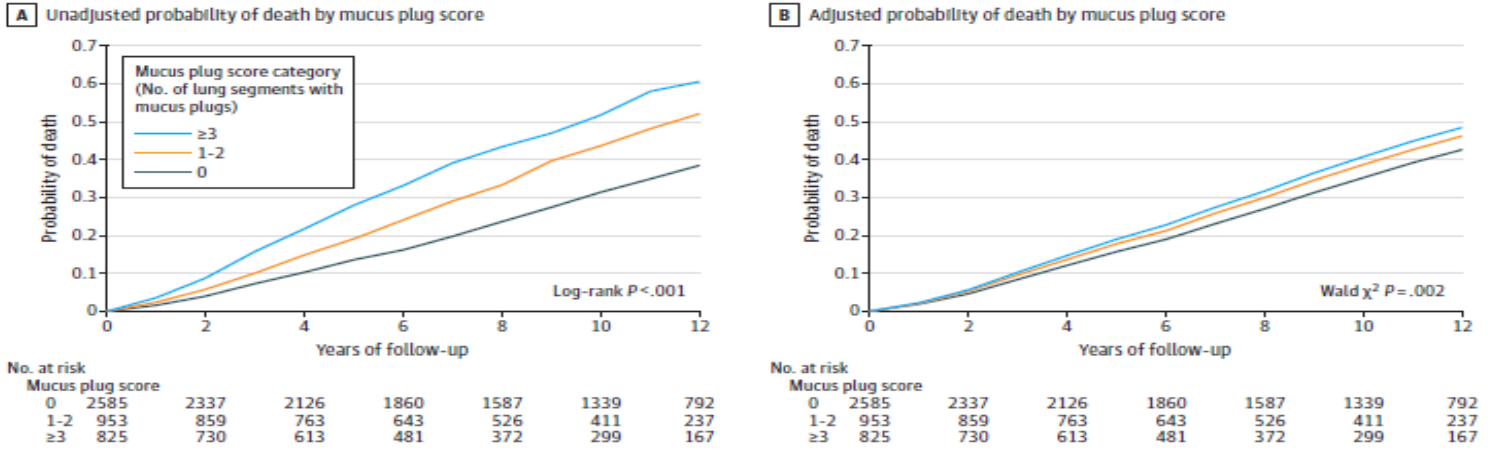
[e] Emphysema on CT was measured as percentage of voxels less than −950 Hounsfield units.

[f] Airway wall thickness was measured on CT as the square root of the wall area of an ideal 10-mm-inner-perimeter airway.

Table 2. Association Between Mucus Plug Score and All-Cause Mortality in Participants With COPD

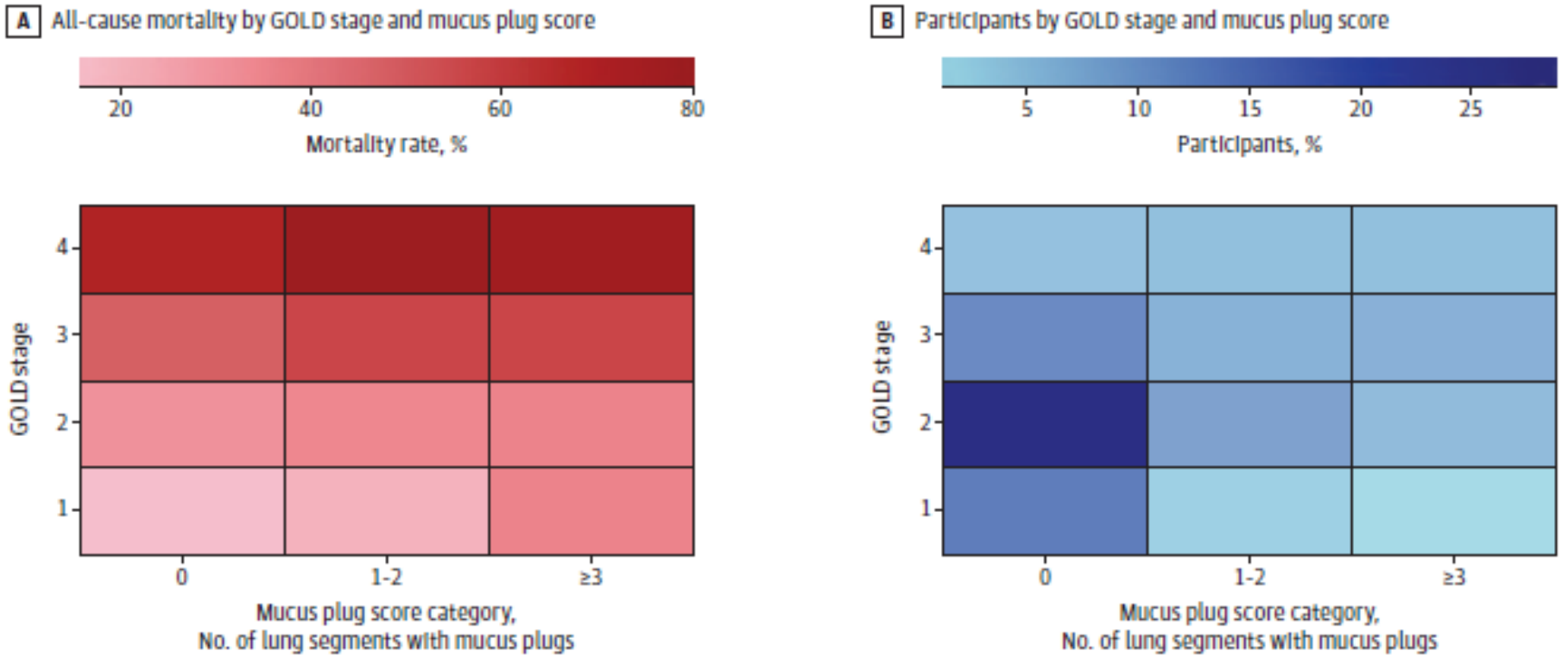
	No.	Mucus plug score (No. of lung segments with mucus plugs)				
		0 (n = 2585)	1-2 (n = 953)		≥3 (n = 825)	
Mortality rate, % (95% CI)		34.0 (32.2-35.8)	46.7 (43.5-49.9)		54.1 (50.7-57.4)	
Unadjusted mortality rate difference, % (95% CI)			1-2 vs 0: 12.7 (9.1-16.4)		≥3 vs 0: 20.1 (16.2-24.0)	
Model		**HR (95% CI)**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Unadjusted model	4363	1 [Reference]	1.51 (1.34-1.69)	<.001	1.98 (1.76-2.22)	<.001
Adjusted model[a]	4166	1 [Reference]	1.15 (1.02-1.29)	.02	1.24 (1.10-1.41)	<.001
Plus coronary artery disease[b]	4166	1 [Reference]	1.16 (1.03-1.30)	.02	1.26 (1.11-1.43)	<.001
Plus chronic bronchitis[c]	4166	1 [Reference]	1.15 (1.02-1.30)	.02	1.25 (1.10-1.42)	<.001
Plus current asthma[d]	4166	1 [Reference]	1.15 (1.02-1.30)	.02	1.25 (1.10-1.41)	<.001
Plus exacerbations per year[e]	3759	1 [Reference]	1.10 (0.96-1.25)	.17	1.20 (1.05-1.38)	.008
Plus BODE index[f]	4060	1 [Reference]	1.14 (1.01-1.29)	.03	1.21 (1.06-1.37)	.004

Figure 2. Mortality Plots by Mucus Plug Score Category



Of the 4363 participants with chronic obstructive pulmonary disease (COPD) included in the analysis, 1769 died from any cause. A, Unadjusted plot included all the 4363 participants with COPD. B, Plot adjusted for age, sex, race and ethnicity, body mass index, smoking status, pack-years of smoking, postbronchodilator forced expiratory volume in 1 second, and computed tomography measures of emphysema and airway wall thickness and included 4166 participants with COPD. The median years of follow-up were 10.3 (IQR, 5.4-12.3), 8.7 (IQR, 5.0-12.0), and 7.1 (IQR, 3.9-11.6) for participants in mucus plug score categories of 0, 1 to 2, and 3 or more, respectively.

Figure 3. All-Cause Mortality by Mucus Plug Score Category and Chronic Obstructive Pulmonary Disease (COPD) Severity (N = 4363)



Values represent proportion of all-cause mortality (A) and the percentage of participants (B) by Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity stage of COPD and mucus plug score category. Mortality rate was calculated as the number of participants who died divided by the number of participants (GOLD and mucus plug score category) × 100. GOLD stages were defined with postbronchodilator forced expiratory volume in the first second of expiration (FEV_1) percentage of predicted (pp) values as follows: 1 (mild, n = 766), FEV_1 pp ≥80; 2 (moderate, n = 1887), FEV_1 pp ≥50 to <80; 3 (severe, n = 1127) FEV_1 pp ≥30 to <50; and 4 (very severe, n = 583), FEV_1 pp <30.

- Obstructive lung disease is diagnosed with a reduced FEV1/FVC

  What about patients who have Tobacco Exposure (smoked or continue to smoke) and have a preserved ratio? What about their clinical status, their longitudinal follow up, and potential risks?

  1397 patients with Tobacco Exposure with Preserved Spirometry (TEPS)

  Asymptomatic TEPS and Symptomatic TEPS

  Comparable rates of lung function decline as those diagnosed with COPD

  SYMPTOMATIC TEPS patients had significantly higher rates of exacerbations

Table 2. Estimated Rates of Decline for Forced Expiratory Volume in the First Second (FEV_1)[a]

	Tobacco exposure and preserved spirometry		Mild to moderate COPD		
	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	Never smoked
No. of participants at baseline	226	269	459	279	164
No. of participants at visit 5	169	190	297	186	103
Observation time, median (IQR), y	5.76 (3.86 to 6.81)	5.76 (3.24 to 6.89)	5.35 (3.07 to 6.82)	5.83 (3.10 to 6.97)	5.72 (3.10 to 7.20)
FEV_1, mean (SD), mL					
At baseline	2.60 (0.59)	2.85 (0.70)	2.03 (0.60)	2.32 (0.69)	2.95 (0.71)
At visit 5	2.45 (0.61)	2.63 (0.73)	1.81 (0.58)	2.11 (0.71)	2.86 (0.72)
Unadjusted FEV_1 rate of decline (95% CI), mL/y (n = 1397)[b]	−32.2 (−38.8 to −25.6)	−35.1 (−41.2 to −29.0)	−39.0 (−43.7 to −34.2)	−41.7 (−47.7 to −35.8)	−21.6 (−29.5 to −13.8)
Model 1 (n = 1395)[c]	−31.3 (−37.9 to −24.7)	−38.8 (−45.0 to −32.6)	−42.3 (−47.2 to −37.4)	−46.7 (−52.9 to −40.4)	−27.8 (−36.3 to −19.3)
Model 2 (n = 1381)[d]	−31.0 (−37.6 to −24.3)	−39.3 (−45.5 to −33.0)	−42.1 (−47.1 to −37.2)	−46.4 (−52.7 to −40.1)	−27.8 (−36.3 to −19.2)
FEV_1 rate of decline among those currently smoking (95% CI), mL/y[b]					
Model 1 (n = 1395)[c]	−38.6 (−45.9 to −31.4)	−46.1 (−53.7 to −38.6)	−49.7 (−56.0 to −43.4)	−54.0 (−61.7 to −46.3)	
Model 2 (n = 1381)[d]	−38.6 (−45.9 to −31.4)	−46.9 (−54.5 to −39.3)	−49.8 (−56.1 to −43.4)	−54.1 (−61.8 to −46.3)	
FEV_1 rate of decline among those not currently smoking (95% CI), mL/y[b]					
Model 1 (n = 1395)[c]	−23.9 (−31.3 to −16.6)	−31.5 (−37.7 to −25.2)	−35.0 (−40.2 to −29.8)	−39.3 (−45.5 to −33.2)	−20.5 (−28.4 to −12.6)
Model 2 (n = 1381)[d]	−23.3 (−30.7 to −16.0)	−31.6 (−37.9 to −25.3)	−34.5 (−39.8 to −29.3)	−38.8 (−45.0 to −32.6)	−20.1 (−28.1 to −12.2)
Acute COPD exacerbations[e,f]					
Per person-year	0.23	0.08	0.39	0.15	0.03
Total No.	397	170	1337	320	43
Severe acute COPD exacerbations[e,g]					
Per person-year	0.10	0.02	0.15	0.05	0.01
Total No.	167	39	504	105	10

Abbreviation: COPD, chronic obstructive pulmonary disease.

[a] The between-group difference-in-difference calculations appear in eTable 3 in Supplement 3. The details on observation time for each group appear in eTable 9 in Supplement 3.

[b] All models included symptom and obstruction group, time (in years since visit 1), and the symptom and obstruction group × time interaction.

[c] Includes covariates for mean centered age, body mass index, height (cm), and pack-years of smoking at the baseline visit (visit 1), sex (reference group = male), race (reference group = White), and time-varying current smoking status (reference group = not currently smoking).

[d] Includes all model 1 covariates and mean centered airway to lung ratio at visit 1.

[e] Recorded using a structured questionnaire.

[f] Answered "yes" to having experienced an "episode of breathing problems" for which they were treated with oral corticosteroids, antibiotics, or both.

[g] Visited an emergency department or were admitted to a hospital during the episode.

TAKE HOME POINT FOR TEPS PATIENTS

- People with tobacco exposure and preserved spirometry (TEPS) who present with respiratory symptoms do not experience an accelerated rate of decline in lung function or an increased incidence of COPD compared to those with asymptomatic TEPS. However, symptomatic TEPS is associated with significantly more respiratory exacerbations. Therefore, physicians should be vigilant in monitoring and managing respiratory symptoms in patients with TEPS, recognizing that this population may have unmet clinical needs, even in the absence of traditional COPD diagnosis.

- Clear data for the use of IV in septic shock
- What about the use of hydrocortisone in severe community acquired pneumonia and its effect on 28-day mortality?
- ATS/IDSA recommend against steroids in sCAP while the ESICM/SCCM guidelines favor their use.
  - Recent study showed no benefit with 60-day mortality in sCAP and steroid usage (called for larger RCT)
  - Double blind, placebo controlled, multi-center RCT
  - Age>18, severe CAP diagnosis by criteria
  - 800 patients randomized (401 vs 399)
  - 200mg/day hydrocortisone x 4 days
  - Then met criteria for taper, 8 days, 14 days

OUTCOMES

- Primary outcomes:
  - Death by day 28: Hydrocortisone 6.2% vs Placebo 11.9%
  - Difference -5.6% (-9.6 to -1.7%), p = 0.006

- Secondary outcomes:
  - No significant difference in:
    - Hospital acquired infection (9.8 vs 11.1%)
    - GI bleeding by day 28 (2.2 vs 3.3%)
  - Significantly more insulin in steroid group by day 7 (35.5 vs 20 U/day)
  - Significantly Less:
    - Death by day 90 (9.3% vs 14.7%)
    - Incidence of endotracheal intubation by day 28 (18.0 vs 29.5%)
    - Vasopressor initiation by day 28 in those not receiving at baseline (15.3 vs 25.0%)

Authors conclude that Early treatment with hydrocortisone reduced 28-day mortality in patients admitted to the ICU with severe CAP

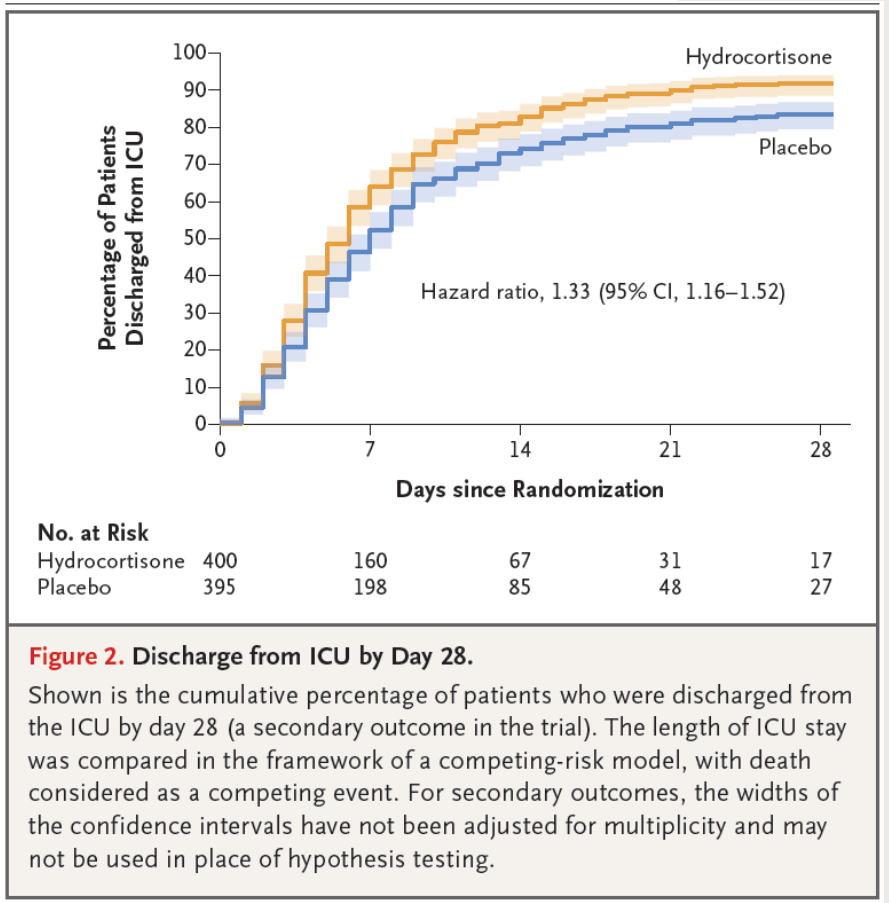
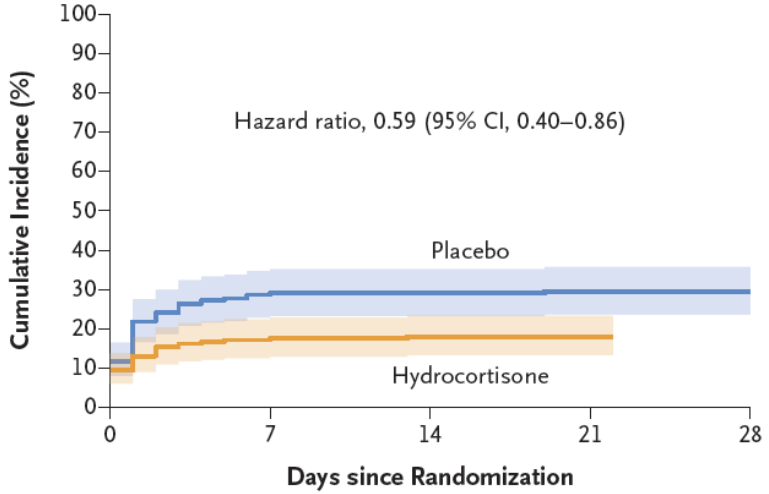


Figure 2. Discharge from ICU by Day 28.

Shown is the cumulative percentage of patients who were discharged from the ICU by day 28 (a secondary outcome in the trial). The length of ICU stay was compared in the framework of a competing-risk model, with death considered as a competing event. For secondary outcomes, the widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

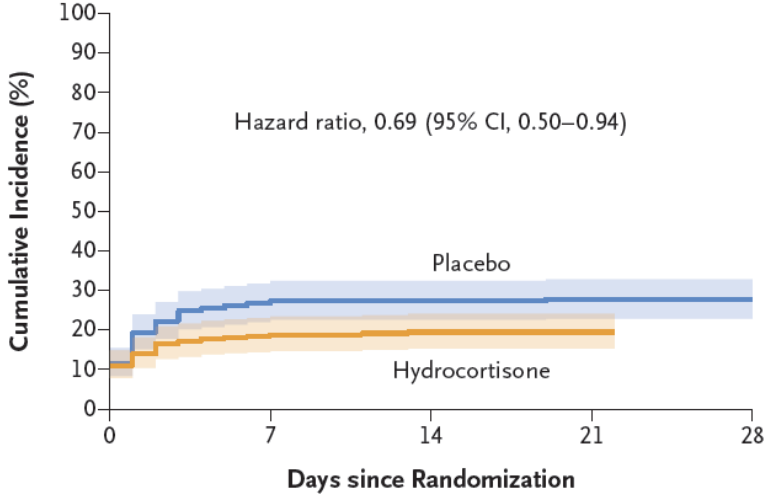
A Intubation in Patients Who Did Not Receive Any Mechanical Ventilation at Baseline



No. at Risk

Placebo	220	45	8	2	1
Hydrocortisone	222	49	6	1	0

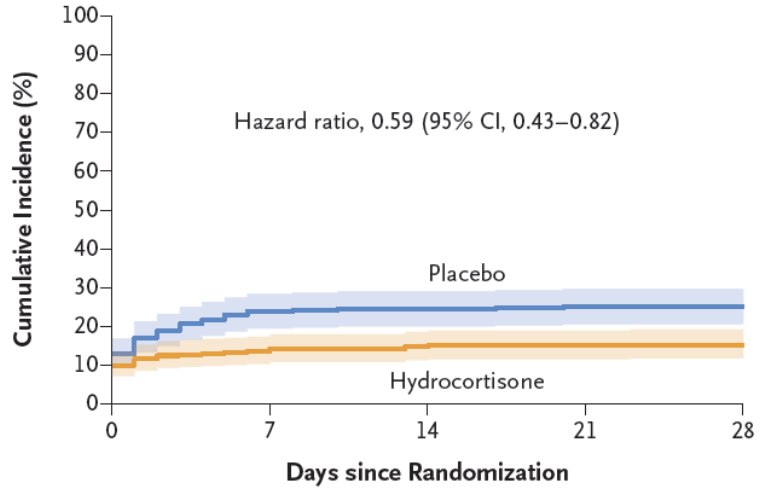
B Intubation in Patients Who Were Not Intubated at Baseline



No. at Risk

Placebo	310	66	11	3	1
Hydrocortisone	308	60	9	1	0

C Secondary Use of Vasopressors



No. at Risk

Placebo	344	102	30	13	6
Hydrocortisone	359	95	26	8	3

- What is the difference in the success rate of first-attempt intubations, complications, and other related outcomes between using a video-laryngoscope (VL) and a direct-laryngoscope (DL) in patients requiring tracheal intubation?
- 1417 patients intubated – mainly in ER or in the ICU

    Indications for tracheal intubation were mainly altered mental status (45.3%) and acute respiratory failure (30.4%)

    - Outcomes:
    - Successful intubation on the first attempt without severe complications
    - Failure due to inadequate view of the vocal chords
    - Median time interval for intubation

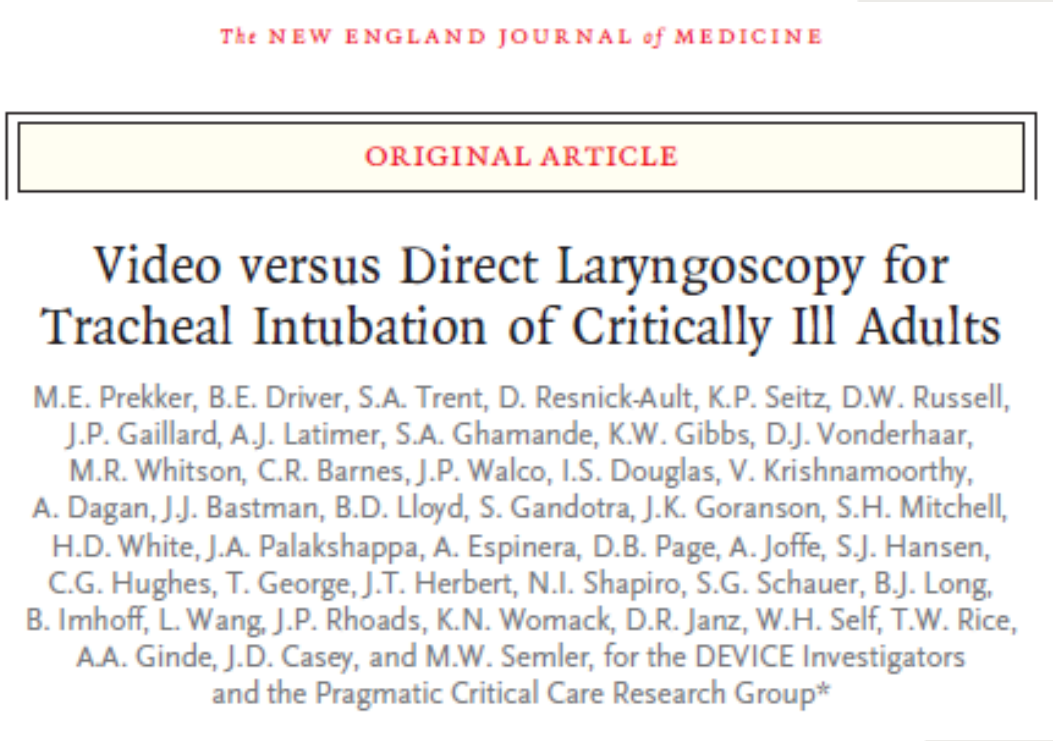


Table 2. Characteristics of the Operator and Intubation Procedure.

Characteristic	Video Laryngoscope (N=705)	Direct Laryngoscope (N=712)
Operator*		
Clinical specialty — no. (%)		
Emergency medicine	496 (70.4)	497 (69.8)
Critical care medicine	177 (25.1)	182 (25.6)
Anesthesiology	18 (2.6)	25 (3.5)
Other†	14 (2.0)	8 (1.1)
Level of training — no. (%)		
Resident physician	513 (72.8)	502 (70.5)
Fellow physician	164 (23.3)	173 (24.3)
Attending physician	9 (1.3)	18 (2.5)
Other clinician‡	19 (2.7)	19 (2.7)
Median no. of previous intubations performed (IQR)	50 (25–90)	50 (26–99)
Proportion of previous intubations performed with a video laryngoscope — no./total no. (%)§		
<0.25	44/704 (6.2)	34/711 (4.8)
0.25 to 0.75	398/704 (56.5)	429/711 (60.3)
>0.75	262/704 (37.2)	248/711 (34.9)
Intubation Procedure		
Preoxygenation received — no. (%)	702 (99.6)	711 (99.9)
Median oxygen saturation at induction (IQR)¶	100 (97–100)	100 (98–100)
Median systolic blood pressure at induction (IQR) — mm Hg‖	130 (111–150)	129 (110–148)
Sedative medication administered for induction — no./total no. (%)	668/695 (96.1)	676/705 (95.9)
Neuromuscular blocking medication administered — no./total no. (%)	668/696 (96.0)	677/706 (95.9)
Laryngoscope — no. (%)		
Direct**	0	704 (98.9)
Video††	705 (100)	8 (1.1)
Standard geometry blade	607	5
Hyperangulated blade	98	3
Cormack–Lehane grade of view — no. (%)‡‡		
1	538 (76.3)	318 (44.7)
2	141 (20.0)	244 (34.3)
3	19 (2.7)	97 (13.6)
4	7 (1.0)	53 (7.4)

OUTCOMES

- First Attempt Success Rate

  VL Group: 600 of 705 patients (85.1%) successfully intubated on the first attempt

  DL Group: 504 of 712 patients (70.8%) successfully intubated on the first attempt

  Absolute risk difference: 14.3 percentage points (95% CI, 9.9 to 18.7; P<0.001)

  Vocal Chord Visualization

  76.3% of patients in the VL group had grade 1 (clear view) on the Cormack-Lehane grading scale, compared to 44.7% in the DL group

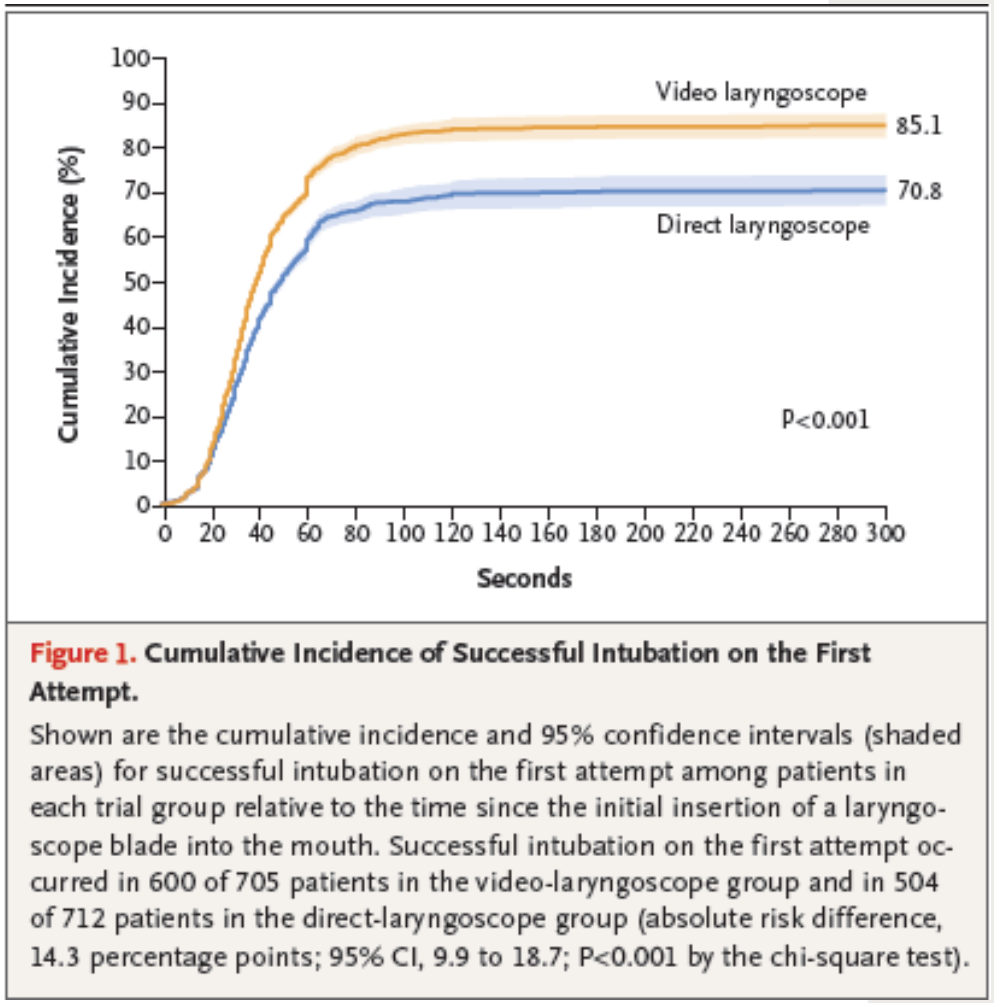


Figure 1. Cumulative Incidence of Successful Intubation on the First Attempt.

Shown are the cumulative incidence and 95% confidence intervals (shaded areas) for successful intubation on the first attempt among patients in each trial group relative to the time since the initial insertion of a laryngoscope blade into the mouth. Successful intubation on the first attempt occurred in 600 of 705 patients in the video-laryngoscope group and in 504 of 712 patients in the direct-laryngoscope group (absolute risk difference, 14.3 percentage points; 95% CI, 9.9 to 18.7; P<0.001 by the chi-square test).

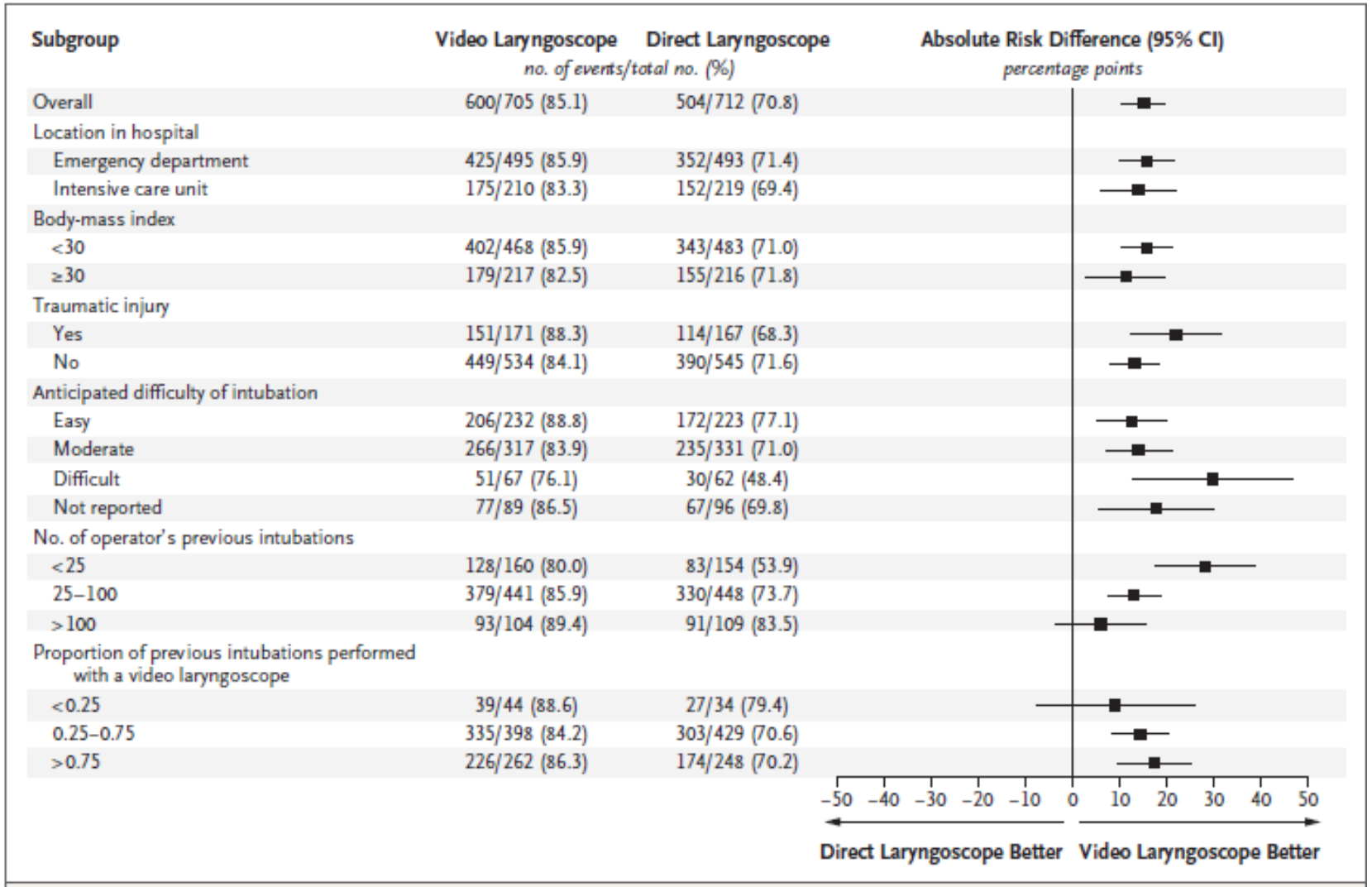
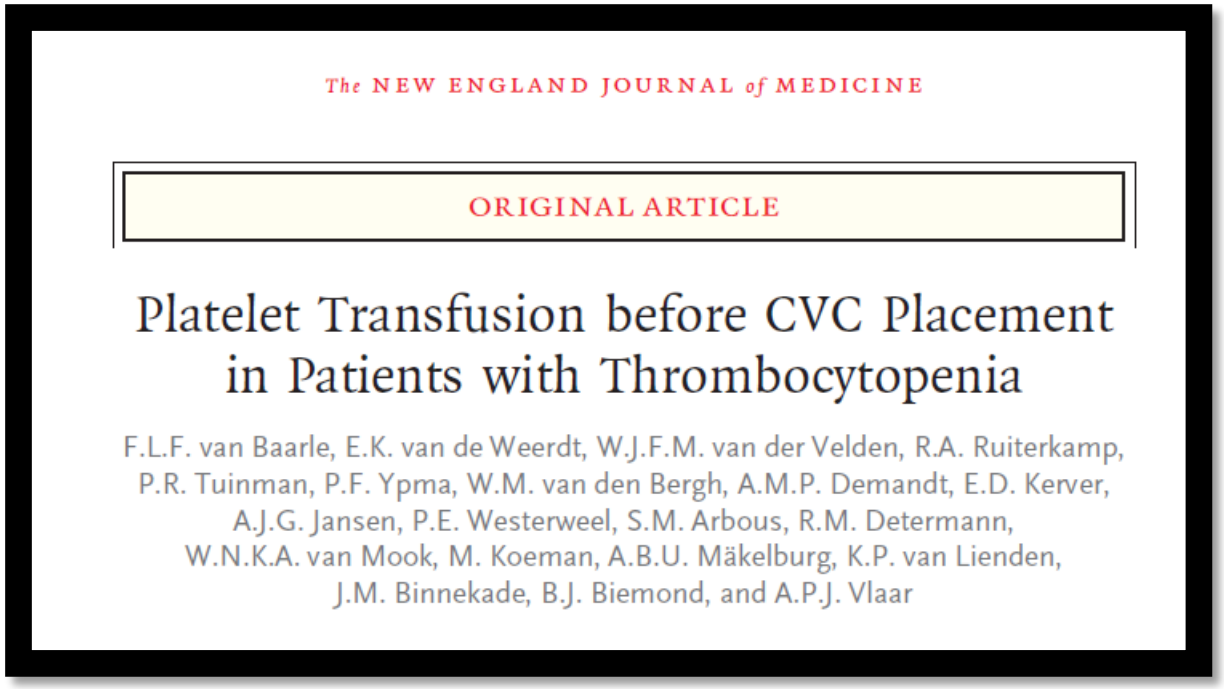


Figure 2. Subgroup Analyses of the Primary Outcome.

Shown are the absolute risk differences and 95% confidence intervals for the primary outcome (successful intubation on the first attempt) in the video-laryngoscope group as compared with the direct-laryngoscope group in each prespecified subgroup. Absolute risk differences were calculated with the use of a generalized linear mixed-effects model with a random effect for trial site and fixed effects for trial group, the proposed effect modifier, and the interaction between the trial group and the proposed effect modifier. Absolute risk differences of greater than 0 indicate a higher likelihood of successful intubation on the first attempt with use of a video laryngoscope. The body-mass index is the weight in kilograms divided by the square of the height in meters.

TAKE HOME POINT

Maybe you should think about using the Video Laryngoscope… (unless you're a very experienced airway expert)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Platelet Transfusion before CVC Placement in Patients with Thrombocytopenia

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- Is placing a central line with platelet counts of 10-50,000 non-inferior to giving 1U platelets before CVC with the intention to reduce procedure-related bleeding?
- Current guidance suggests that CVC insertion is safe with a plt count even below 20,000/mm3
- Conflicting guidelines for transfusion before CVC
  - <20,000: British Society of Hematology
  - <40-50,000: American Society of Oncology
  - <50,000: Assoc Anesthesiologist of GB (for "other major surgeries or invasive procedures
- 10 Hospitals in Netherlands

  8 Hematology wards, 7 ICUs

  393 CVC placements on patients with plt 10,000-50,000 24 hours before CVC

Table 1. CVC-Related Bleeding.*

Bleeding Grade	Definition
Grade 0	No bleeding
Grade 1	Oozing; hematoma; bleeding that results in <20 min of manual compression to stop
Grade 2	Bleeding that results in minor interventions to stop, such as prolonged manual compression (>20 min)
Grade 3	Bleeding that results in radiologic or elective operative intervention or red-cell transfusion without hemodynamic instability
Grade 4	Bleeding associated with severe hemodynamic instability (hypotension, defined as a decrease of >50 mm Hg or >50% in either systolic or diastolic blood pressure), with associated tachycardia (heart rate increase, >20% for 20 min) and resulting in increased red-cell transfusion or fatal bleeding

* CVC denotes central venous catheter.

Table 2. Characteristics of the Patients at Baseline.*

Characteristic	Transfusion (N=188)	No Transfusion (N=185)
Median age (IQR) — yr	58 (47–65)	59 (50–65)
Female sex — no. (%)	63 (33.5)	70 (37.8)
Median body-mass index (IQR)†	25.3 (22.6–28.4)	25.4 (23.0–29.0)
Median platelet count (IQR) — per mm^3	30,000 (20,000–38,000)	30,000 (20,000–37,000)
Median international normalized ratio (IQR)	1.1 (1.0–1.3)	1.1 (1.0–1.2)
Median activated partial thromboplastin time (IQR) — sec	29 (25–34)	31 (26–35)
Median hemoglobin (IQR) — g/dl	8.2 (7.4–9.2)	8.5 (7.7–9.5)
Hospital department — no. (%)		
Hematology ward	108 (57.4)	104 (56.2)
ICU	80 (42.6)	81 (43.8)
Catheter type — no. (%)		
Regular	155 (82.4)	155 (83.8)
Dialysis	33 (17.6)	30 (16.2)
Tunneled catheter — no. (%)	20 (10.6)	18 (9.7)
Catheter site — no. (%)		
Internal jugular vein	93 (49.5)	93 (50.3)
Subclavian vein	71 (37.8)	70 (37.8)
Femoral vein	24 (12.8)	22 (11.9)
Platelet transfusion <6 hr before randomization — no. (%)	16 (8.5)	19 (10.3)

* Characteristics are described per catheter placement in the multiply imputed per-protocol population. ICU denotes intensive care unit, and IQR interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.

OUTCOMES

- Primary outcome:
- Grade 2-4 catheter-related bleeding:
    - Transfusion 4.8% (transfusion) vs 11.9% (no transfusion)
    - Absolute risk reduction of 7.1% (90% CI: 1.3 to 17.8%), RR 2.45 (90% CI 1.27 – 4.70)

Selected secondary outcomes:

Comparing transfusion vs no transfusion

- Significant difference in transfusion group in:
    - Platelet count at 1h and 24h after CVC placement 54,000 vs 26,000 after 1h; 36,000 vs 26,000 after 24h
    - Median ICU LOS: 9 vs 7 days

No significant difference in:

- The risk of grade 3-4 catheter-related bleeding (2.1% vs 4.9%)
- Hematoma occurrence (12.2 % vs 18.9%)
- Rate of red-cell transfusion in ≤24 hr (0.48 vs 0.49)
- Allergic transfusion reaction (1 vs 0.5%)
- ICU mortality (57 vs 52%)
- Hospital mortality (28 vs 32%)

Subgroup of Bleeding Risk	Transfusion	No Transfusion	Relative Risk (90% or 95% CI)
	no. of events/total no. (%)		
Primary analysis	9/188 (4.9)	22/185 (11.9)	2.45 (1.27–4.70)
Type of catheter			
Tunneled	3/20 (15.0)	3/18 (16.7)	1.26 (0.25–6.34)
Nontunneled	6/168 (3.6)	18/167 (10.8)	3.01 (1.20–7.55)
Insertion site			
Internal jugular vein	7/93 (7.5)	6/93 (6.5)	0.93 (0.31–2.79)
Subclavian vein	2/71 (2.8)	13/70 (18.6)	6.19 (1.39–27.64)
Femoral vein	0/24	2/22 (9.1)	3.72 (0.38–36.52)
Department			
Hematology ward	6/108 (5.6)	18/104 (17.3)	2.99 (1.19–7.54)
Intensive care unit	3/80 (3.8)	4/81 (4.9)	1.36 (0.30–6.11)
Platelet count per mm^3			
10,000–19,000	7/45 (15.6)	9/41 (22.0)	1.30 (0.48–3.55)
20,000–29,000	0/46	8/51 (15.7)	7.53 (0.91–62.50)
30,000–39,000	1/59 (1.7)	3/51 (5.9)	3.90 (0.41–37.05)
40,000–50,000	1/38 (2.6)	2/42 (4.8)	1.68 (0.15–18.68)

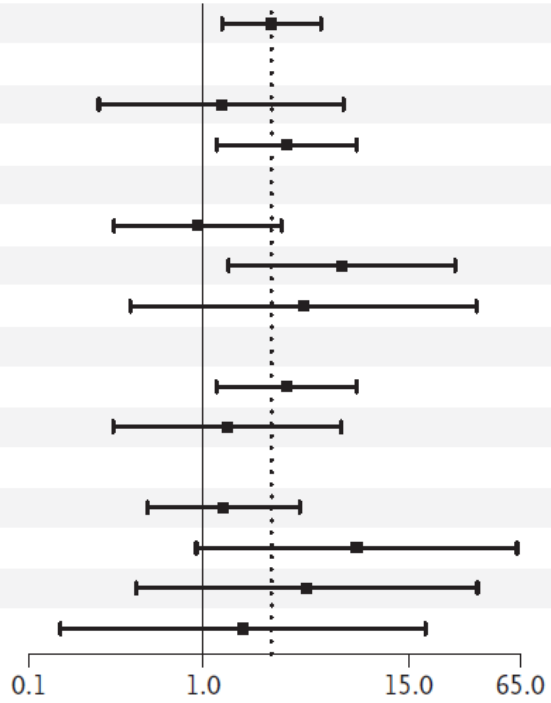

Figure 2. Bleeding Risk in Primary and Subgroup Analyses.

Shown is a forest plot of the risk of bleeding of grade 2 to 4 among patients with severe thrombocytopenia who had received prophylactic platelet transfusion and among those who had not received a platelet transfusion, according to overall numbers of central venous catheter (CVC) placements in the primary analysis and in prespecified exploratory subgroup analyses. The vertical dotted line represents the relative risk in the primary analysis (per-protocol population). A two-sided 90% confidence interval was calculated for the primary analysis and two-sided 95% confidence intervals for the subgroup analyses. The confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Relative risks in two subcategories — femoral vein placement and a platelet count of 20,000 to 29,000 per cubic millimeter — were calculated with 1 event added to each cell in the two-by-two table (used to evaluate the association between a possible risk factor and an outcome) to circumvent the analytic problem of no events in the control group.

TAKE HOME POINT

Given the lower incidence of post CVC bleeding (regardless of the type (tunneled or not) and location), it may be better to transfuse patients before CVC insertion if their platelet count is <50,000

THANK YOU

ENJOY THE CONFERENCE