

COPD: Risk of infections in patients treated with Inhaled Corticosteroids

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**Community Acquired
Pneumonia**



COPD

Issues to address

- CAP cohort impact of COPD
- COPD cohort and CAP
- ICS use in COPD – risk CAP
- Type ICS – risk CAP
- Impact ICS – COPD – CAP outcome

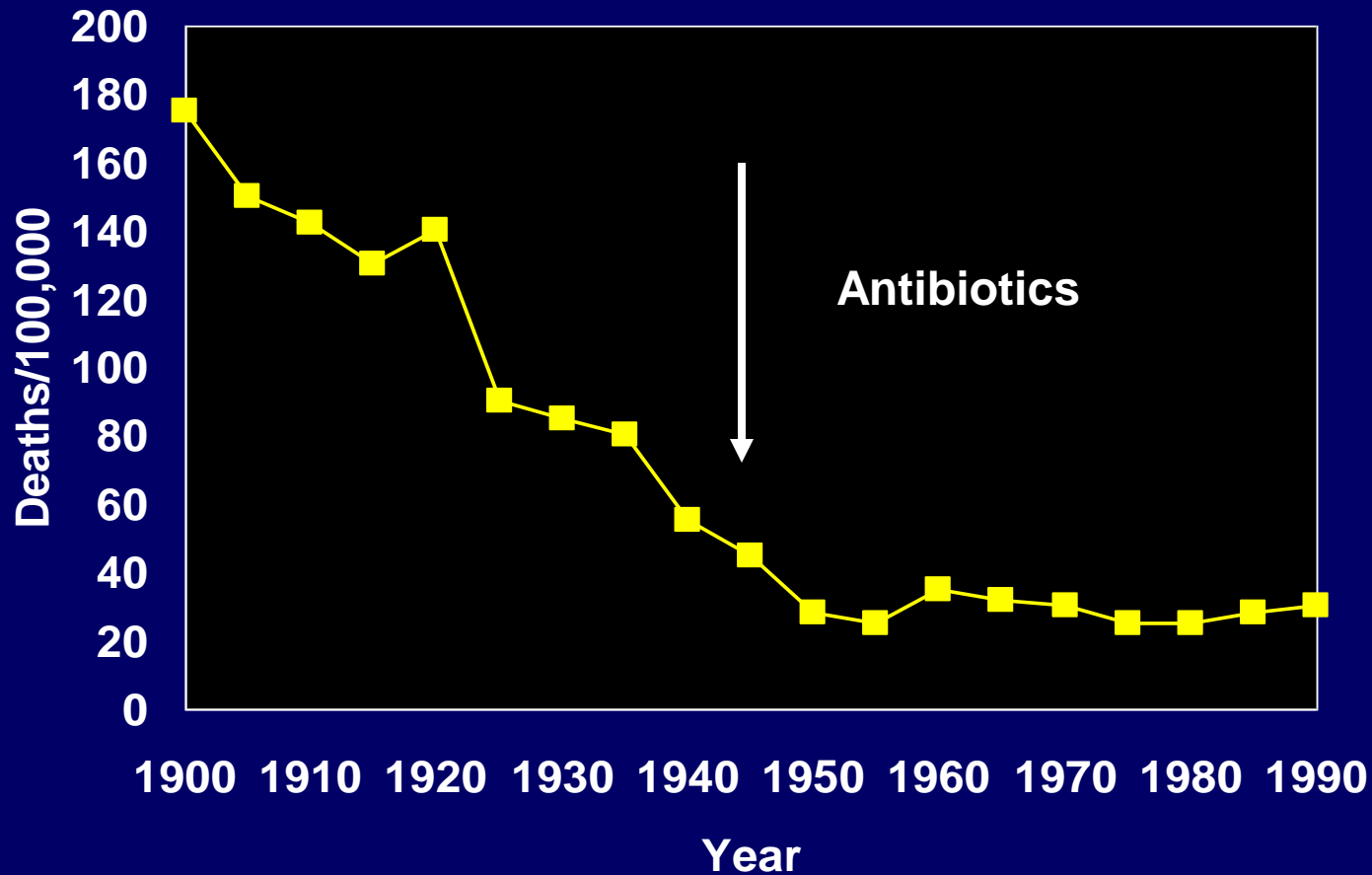
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Community Acquired Pneumonia

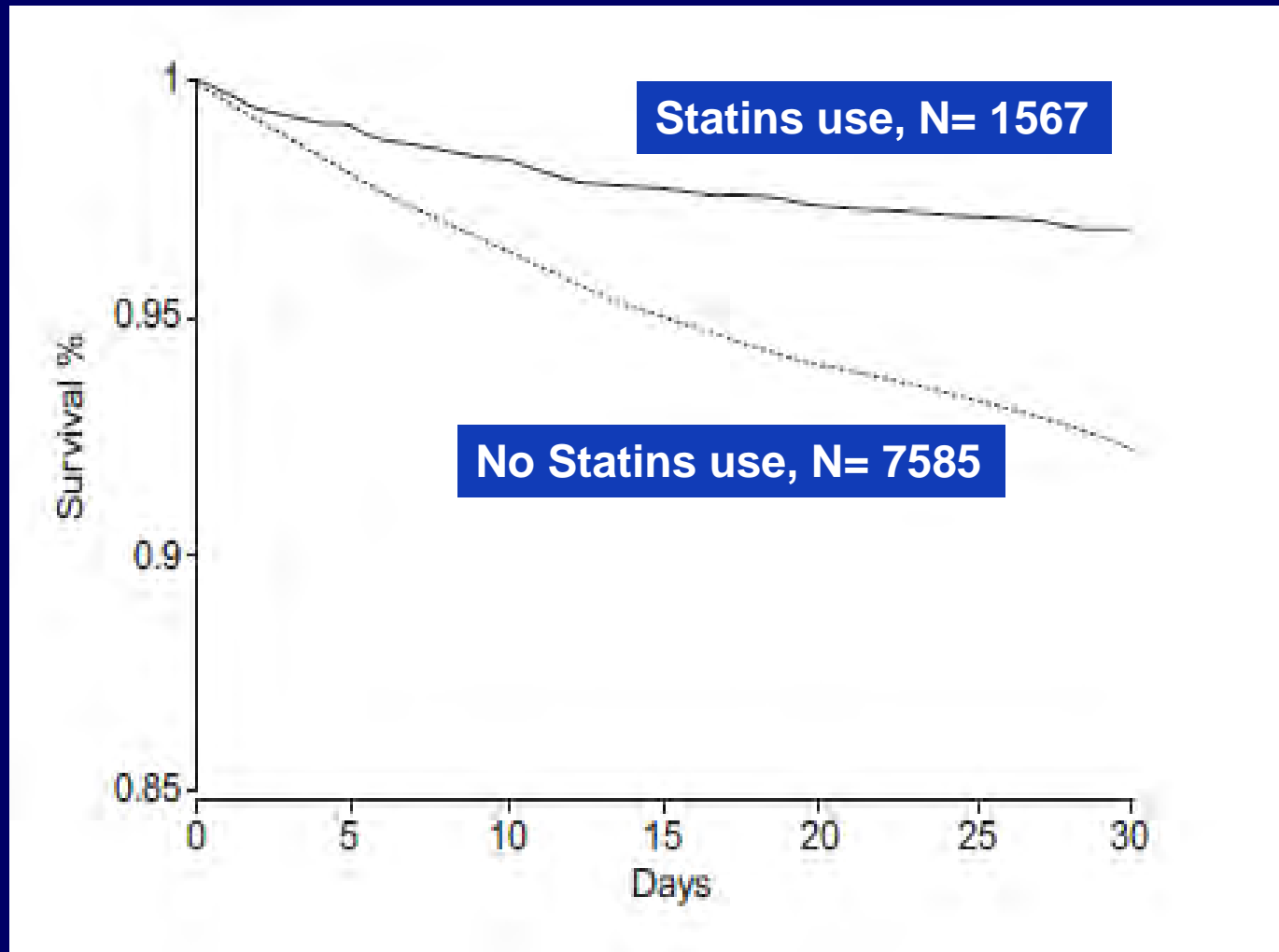
Pneumonia Mortality/100,000 Patients



CAP > 65 YRS OUTCOME

Variable	CAP	Controls	p value
Sample	158,960	794,333	
Hospital mortality	11 %	5.5 %	< 0.01
1 yr mortality hospital d/c	34 %	25 %	<0.01
1 yr mortality	41 %	29 %	< 0.001

Hospital Morality CAP: Use of Statins



CAP: What are we doing ?

Intervention	Benefit= OR mortality	1987	2005	% Mortality reduction
Early Abx	0.85	76	81	1.9
Blood Cx	0.90	57	86	7.3
Guidelines	0.72	54	86	22.2
Influenza Vx	0.61	28	66	27.1
Pneumovax	0.41	12.7	61	41.5

Ruhnke G CMS data



A Venn diagram consisting of two overlapping circles. The left circle is cyan and contains the text 'CAP'. The right circle is yellow and contains the text 'COPD'. The circles overlap in the center, representing the intersection of the two conditions.

CAP

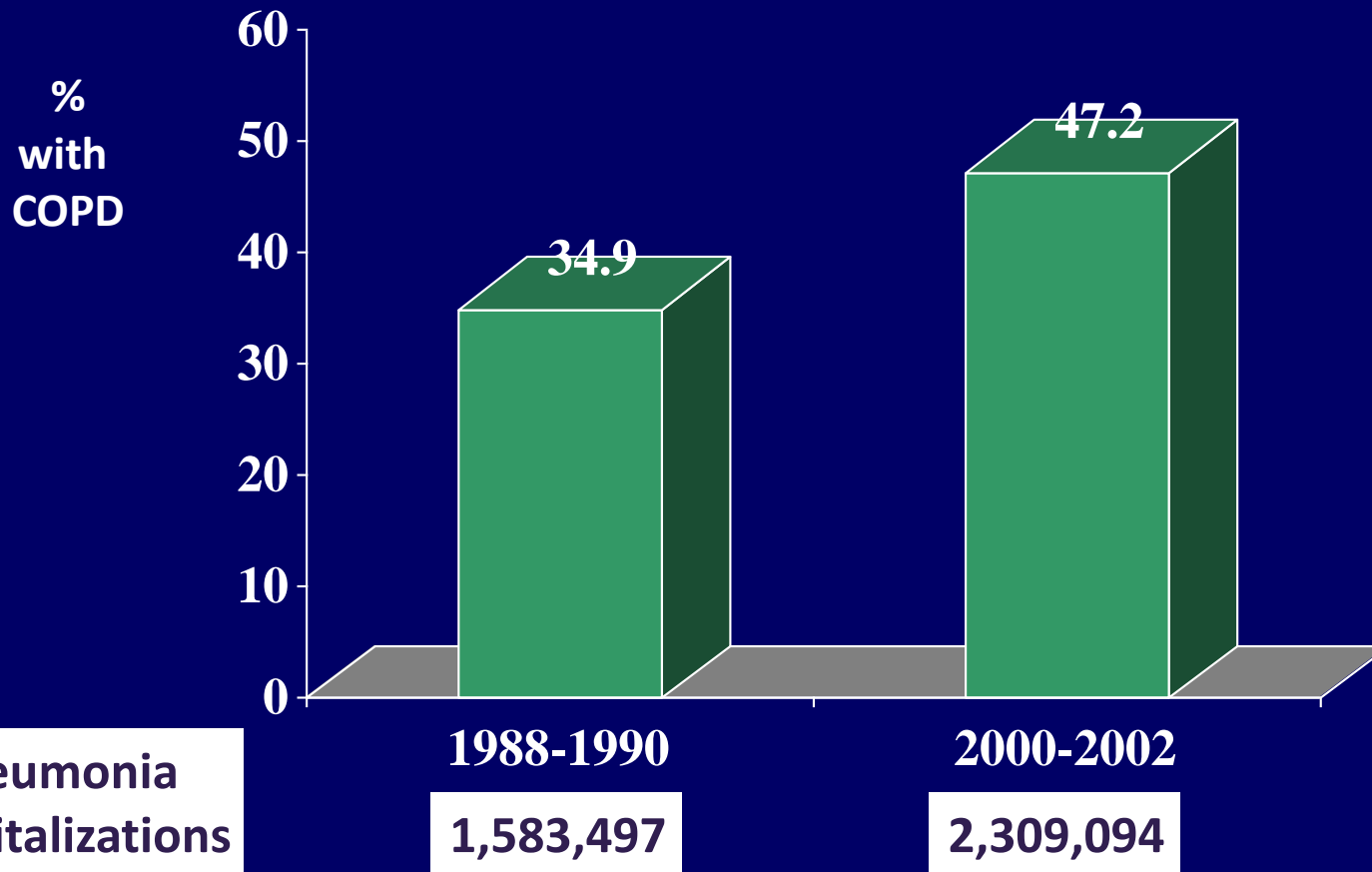
COPD

CAP and COPD

- COPD is one of the most frequent comorbidities found in CAP: 15 to 50%
 - NACE study (n: 468): 19% COPD and 16% chronic bronchitis
 - San Antonio cohort: 39 % COPD
 - S-CAP cohort: 41 % COPD
 - Eekety et al reported higher incidence of pneumococcal CAP

Chronic Pulmonary Disease in Pneumonia Admissions

173 million hospitalisations, 5.8% pneumonia
National Hospital Discharge Survey (> 65 yrs)



COPD in CAP: Clinical Characteristic

	Non-COPD	COPD	p value
Age	58 17	69 12	<0.001
Admitted ICU	18%	25%	0.04
Hx – CHF	13%	25%	<0.001
O ₂ sat <90%	20%	31%	0.001
Use steroid	15%	39%	<0.001
ICS	6%	33%	<0.001

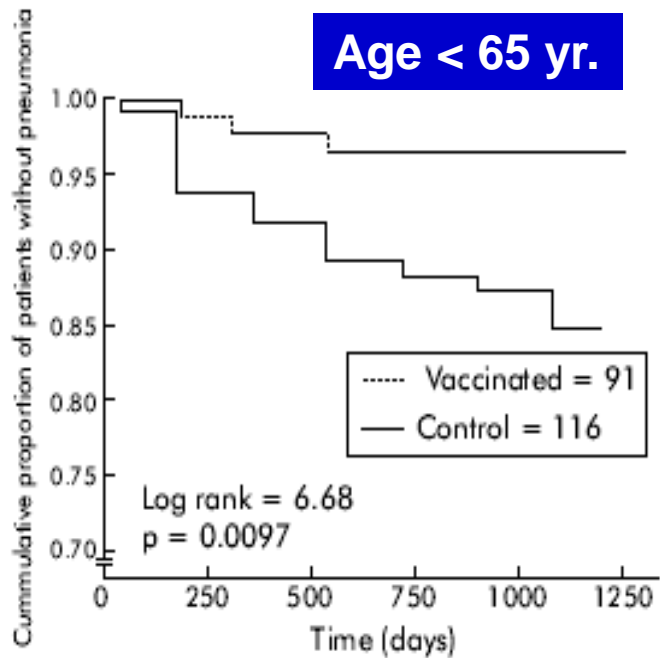


Figure 2 Kaplan-Meier survival curve showing the cumulative proportion of patients <65 years without pneumonia during the follow up period.

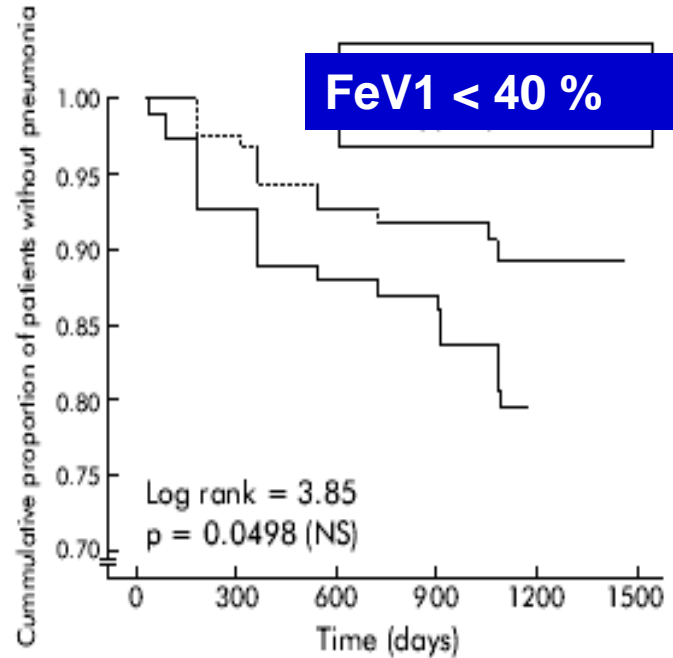


Figure 3 Kaplan-Meier survival curve showing cumulative proportion of patients with severe COPD ($FEV_1 < 40\%$) without pneumonia during the follow up period.

•23 valent Pneumococcal vaccination was effective in preventing pneumonia in COPD <65 yrs and severe obstruction

CAP in COPD

Spanish Multicenter Study

•8 Spanish Hospitals

•124 COPD patients:

- FEV1: $40 \pm 11\%$
- Age : 67 ± 11 yrs
- C Smokers: 43%
- Cardiovasc: 28%

- Home oxygen: 13%
- Oral steroids: 7%
- Prior admission: 54%
- Prior pneumonia: 54%

Neumofail Study-Main Protective and Risk Factors for Non-Response

PROTECTIVE

- Influenza Vac. (rr:0.4)
- COPD (rr:0.6)
- Quinolones (rr:0.5)

RISK

- PSI score (1.4)
- Multilobar (2.1)
- Liver disease (2)
- Pleural effusion (2.8)
- Leucopenia (3.8)

COPD is associated with increased mortality in patients with community-acquired pneumonia

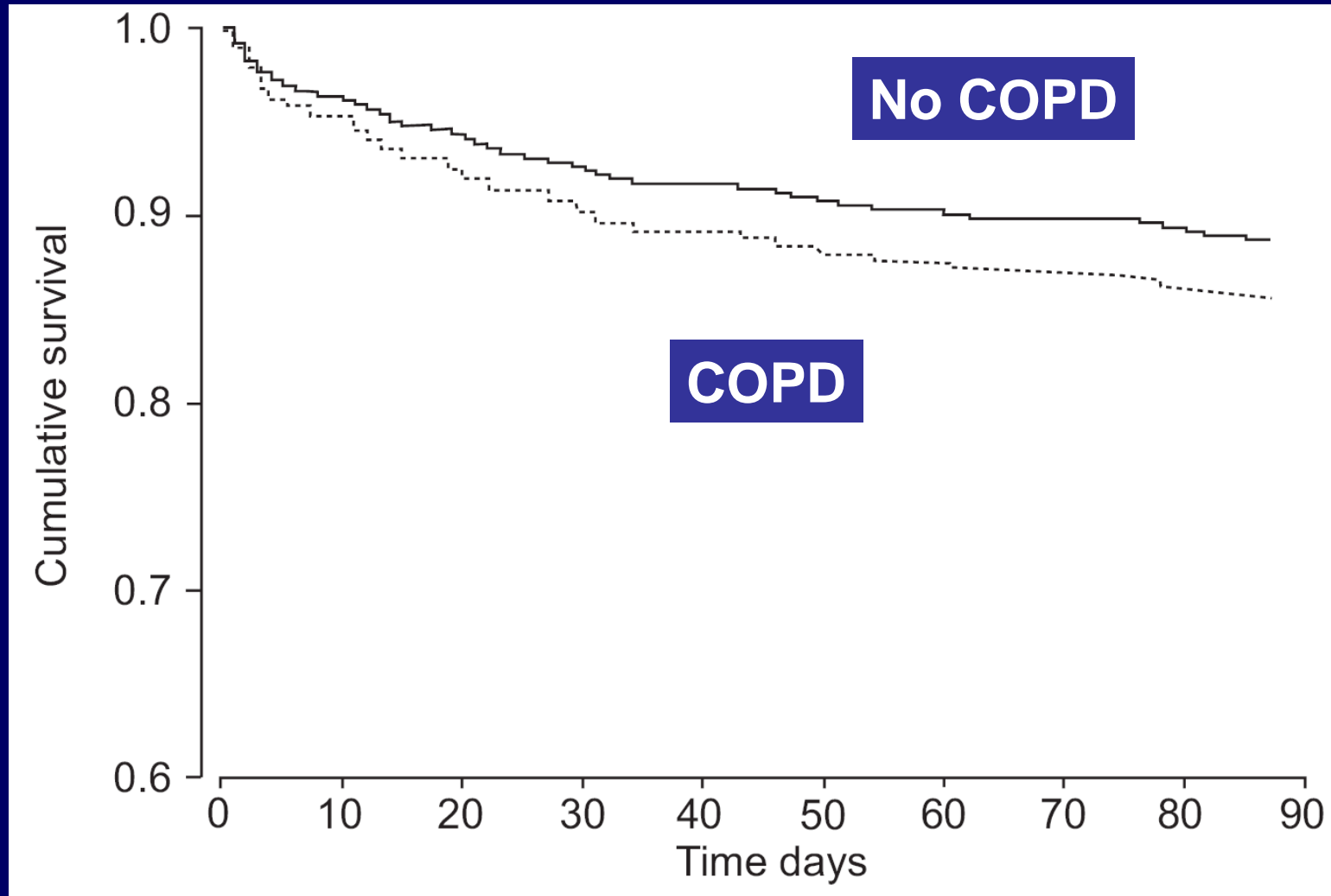
M.I. Restrepo^{*,†}, E.M. Mortensen^{*,#}, J.A. Pugh^{*,#} and A. Anzueto[†]

Implications of COPD in patients admitted to the intensive care unit by community-acquired pneumonia

J. Rello^{*}, A. Rodriguez^{*}, A. Torres[#], J. Roig[†], J. Sole-Violan[†], J. Garnacho-Montero[§], M.V. de la Torre[‡], J.M. Sirvent^{**} and M. Bodi^{*} for the CAPUCI study investigators

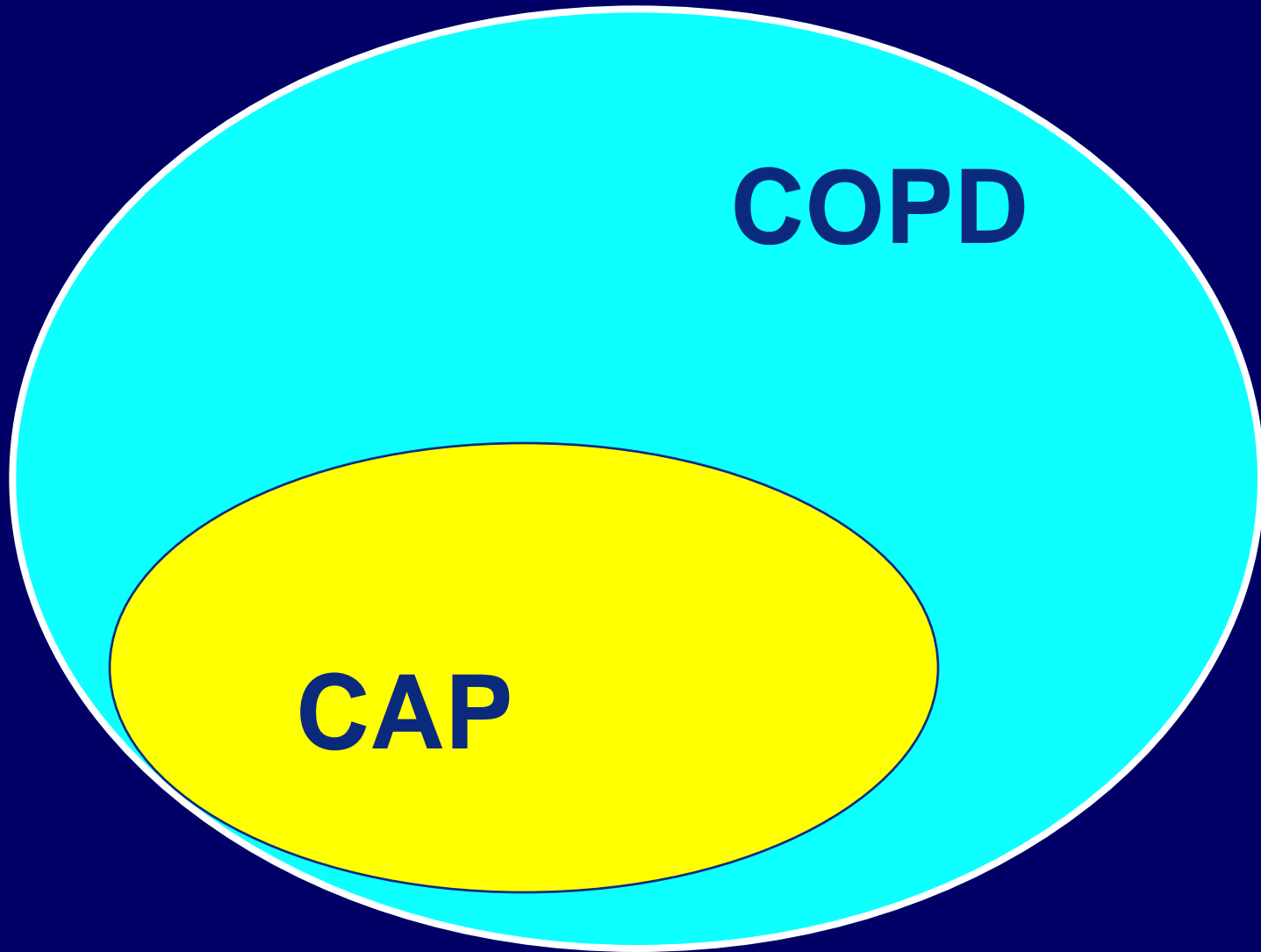
COPD vs non COPD exhibited higher 30 and 90 day mortality, in ICU and non-ICU patients

CAP: Survival based on history of COPD



Issues to address

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This is what we need to understand



COPD and Co-Morbidities

COPD patients are at increased risk for:

- **Myocardial infarction, angina**
- **Osteoporosis**
- **Respiratory infection**
- **Depression**
- **Diabetes**
- **Lung cancer**

Pneumonia incidence among patients with COPD

	Pneumonia rate /100 person / year	
Kardos et al <i>AmJRCCM</i> 2007;175:144-149	1.44 (95% CIs 0.58-2.94) salmeterol	Randomised, double blind, parallel-group multicenter study in 95 centres of Salmeterol vs Salmeterol/Fluticasone n=994
Calverley et al <i>NEJM</i> 2007;356:775-789	4.03 (95% CIs 3.5-4.6) placebo 4.43 (95% CIs 3.8-4.9) salmeterol	Randomised, double blind, multicenter study in 444 centres of Placebo vs Salmeterol vs Salmeterol/Fluticasone n=3769
Ferguson et al <i>Respir Med</i> 2007;356:775-789	3.87 (95% CIs 2.18-6.13) salmeterol	Randomised, double blind, parallel-group multicenter study in 94 centres of Salmeterol vs Salmeterol/Fluticasone n=782
Wedzicha et al <i>AmJRCCM</i> 2008;177:19-26	3.61 (95% CIs 2.33 – 5.32) tiotrop	Randomised, double blind, double dummy multicenter study in 94 centres of tiotropium bromide vs Salmeterol/Fluticasone n=1323
Ernst et al <i>AmJRCCM</i> 2007;176:162-6	1.9	Population based cohort study Health Insurance database. Age 65 and older 175,906 'COPD' patients. Follow up 7.1 (4.04 years). 23,942 hospital admissions for pneumonia

CAP Incidence

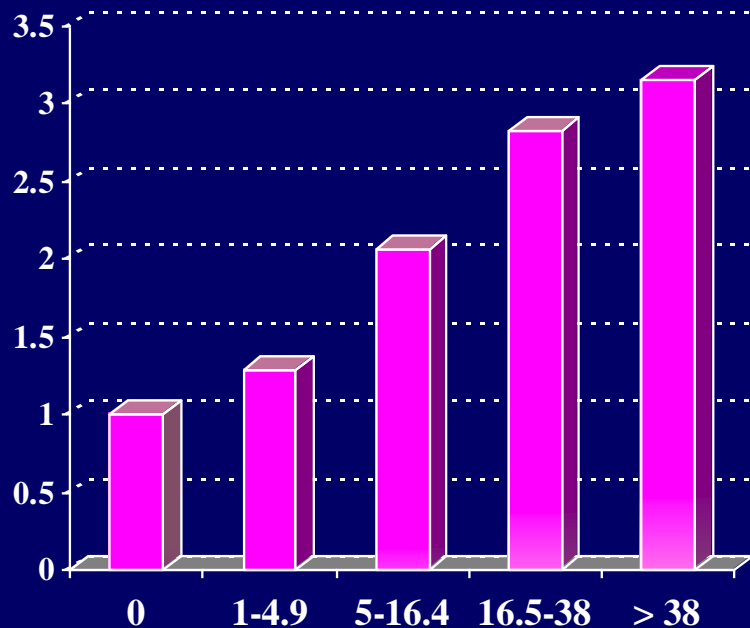
	CAP Incidence
General population	1.54 – 9.05 / 1000 / year
Patients with COPD	1.9 – 4.43 / 100 / year

x 10 - 20

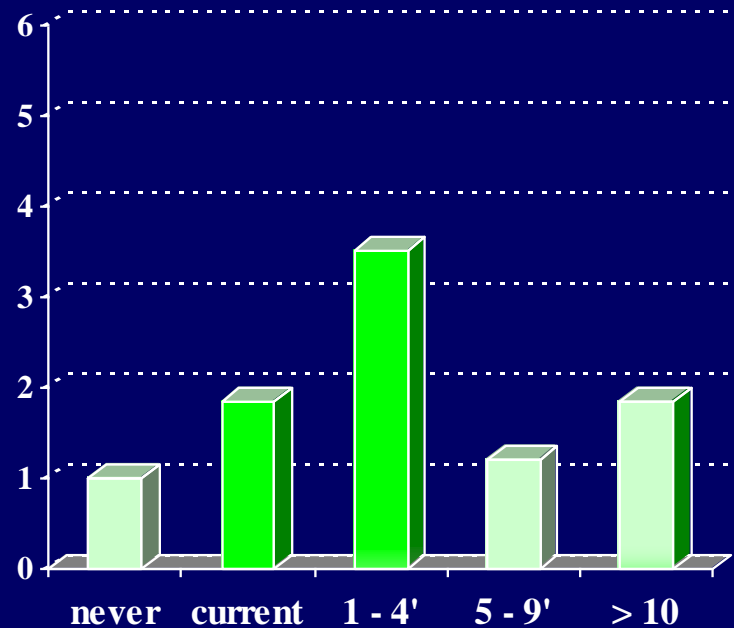
Smoking & Pneumonia incidence

205 CAP (15-74 yrs) in 74,610 population and 475 matched controls in Barcelona (1993-1995): A population based case control study

OR



Lifetime smoking pack-years



Years of ex smoking

COPD – CAP: Risk Factors

- Disease Severity: GOLD III and IV
- Frequency of Exacerbations
- Co-morbid conditions: CHF
- Pharmacotherapy

Conclusion

- COPD is frequent co-morbidity in patients with CAP
- Presence of CAP may contribute the :
 - longer hospital stay
 - increase intensive care admission
 - mortality of patients with COPD
- There is no evidence that CAP has an impact on the management of COPD

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COPD: Inhaled Corticosteroids

- ✓ Improvement in patients quality of life
- ✓ Decrease exacerbation rates
- ✓ Improve symptoms
- ✓ May decreased mortality

■ May increase the risk of pneumonia ?.

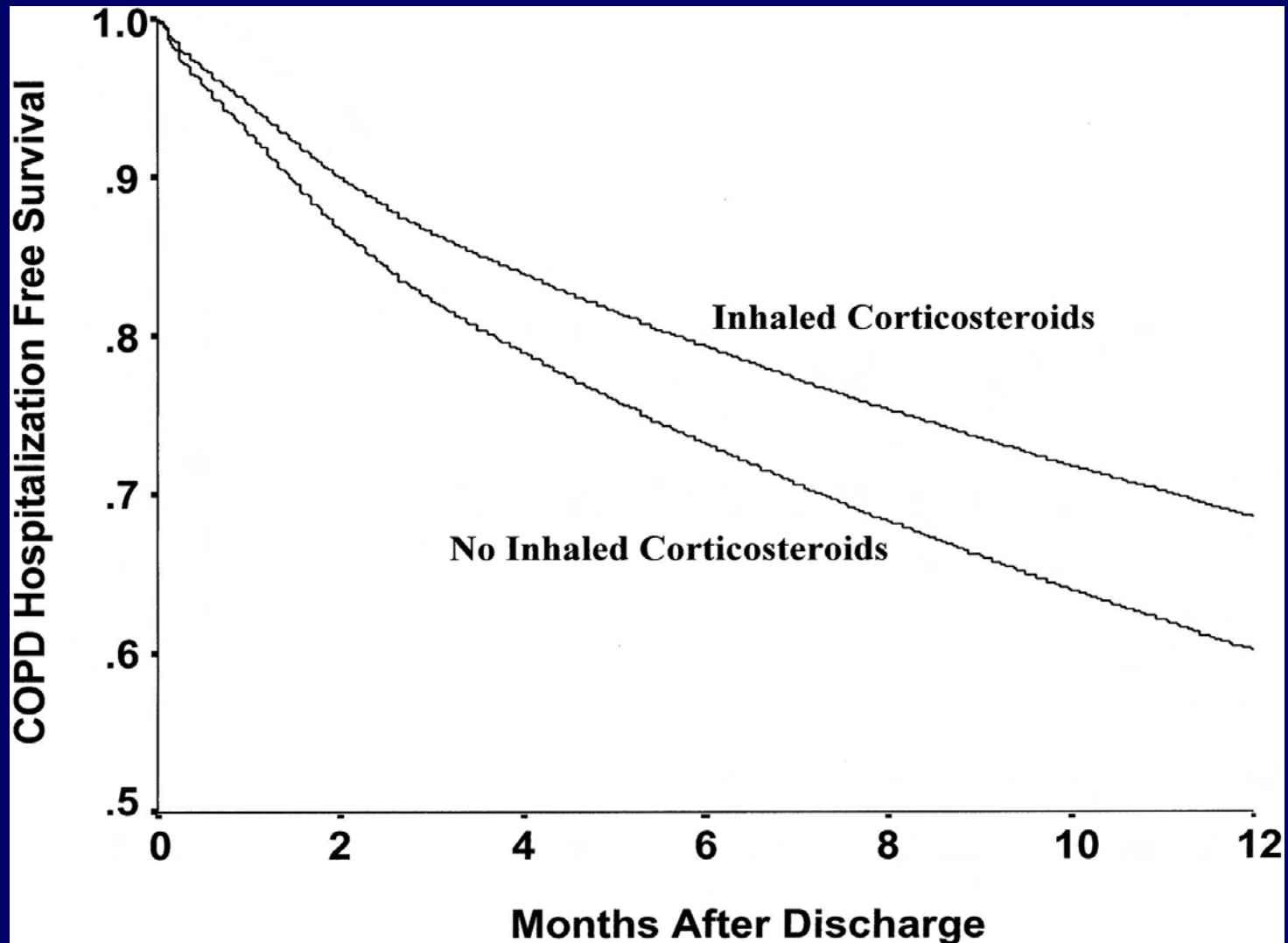
Inhaled Corticosteroids and the Risk of Mortality and Readmission In Elderly Patients with Chronic Obstructive Pulmonary Disease

DON D. SIN and JACK V. TU

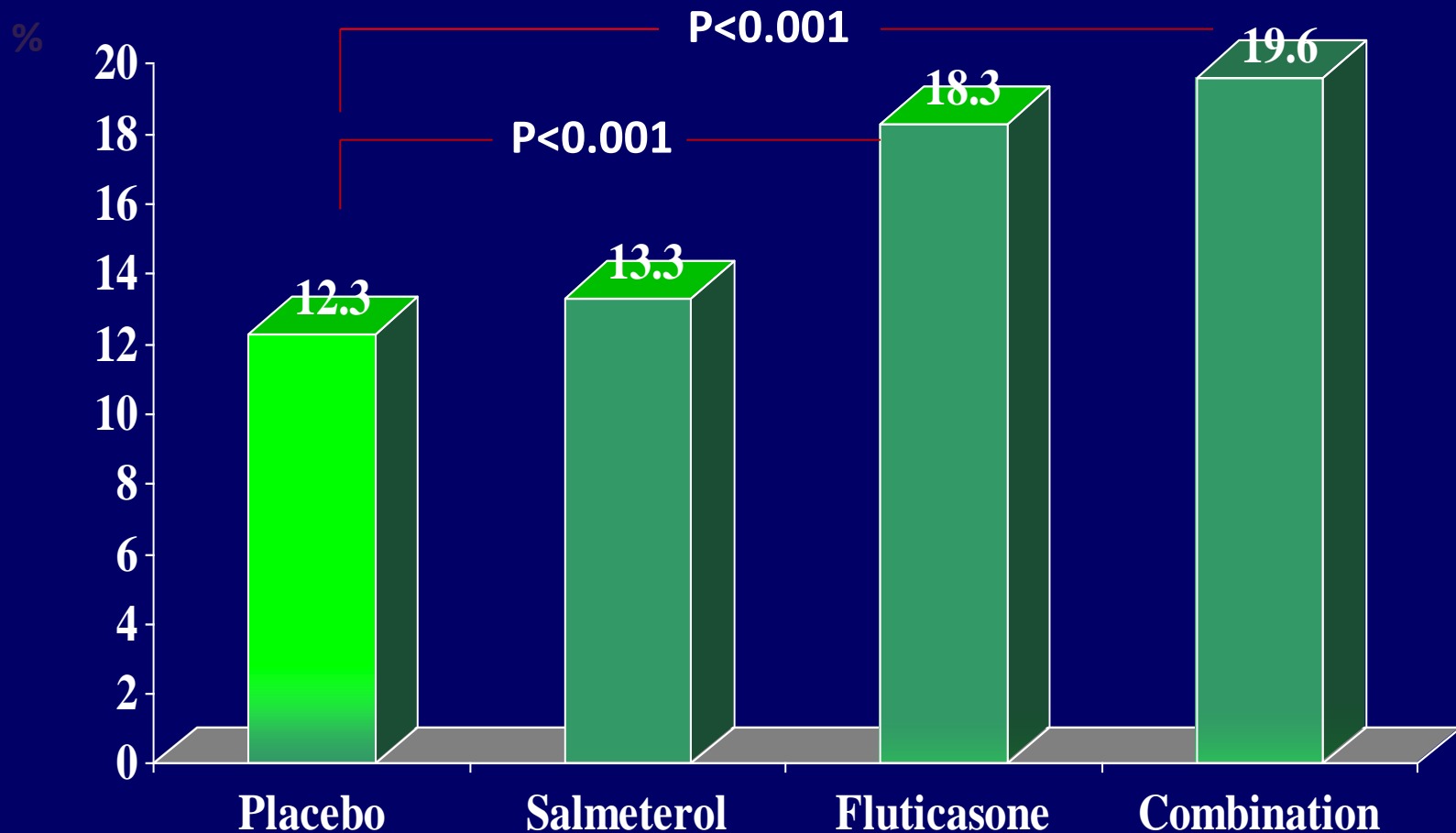
The Institute for Clinical Evaluative Sciences (ICES) and The Department of Medicine, Sunnybrook and Women's College Health Science Center, University of Toronto, Toronto, Ontario; and Department of Medicine, University of Alberta, Alberta, Canada

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 164 2001

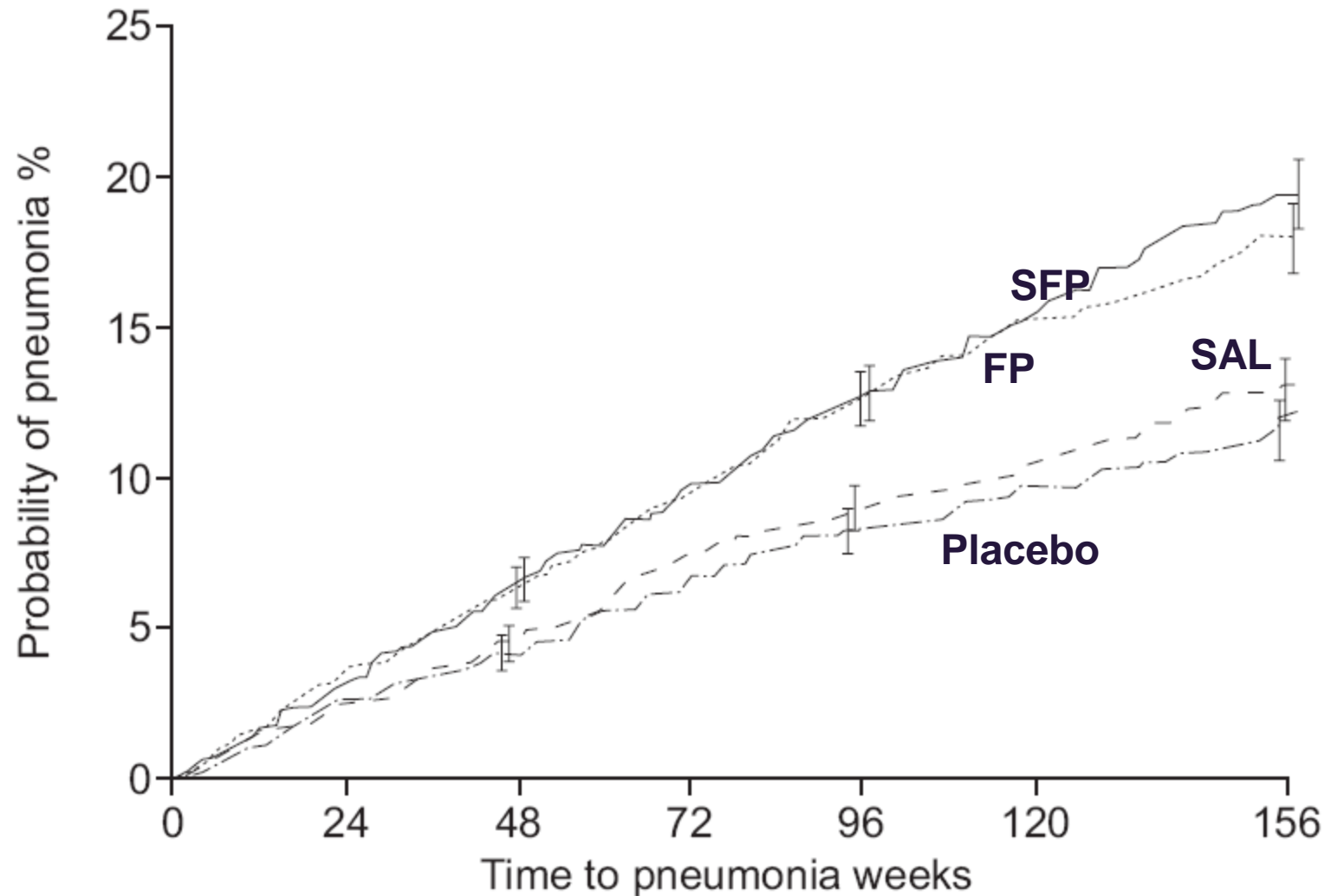
Ontario Study



The effect of ICS on the prevalence of pneumonia in patients with COPD



Kaplan-Meier Estimate to first Pneumonia



Pneumonia Rate During Treatment

Combined Results From the Two 12-Month Studies

	PBO	SAL	FP	SFC
Rate (per 1000 treatment years)	30	30	52	55
Probability CAP – 3 yrs	12.3	13.3	18.3	19.6
HR	--	1.09	1.53	1.64
p value		0.465	<0.001	<0.001

Crim et al ERJ 2009; 34:641

ICS and Pneumonia

- General Practice Research Database
- Case-control design

ICS/LABA	1.11 (0.7-1.7)
ICS	0.78 (0.5-1.1)
LABA	0.93 (0.5-1.9)
FP/SAL	1.15 (0.7-1.9)
SAL	0.88 (0.4-2)

Miller et al ATS 2008

CAP Frequency: COPD patients on ICS

Study	Year (n)	Study	ICS (%)	No ICS(%)	P value
TORCH ¹	2007 (n=6,112)	RCT	587(19)	190(12)	<0.001
Kardos ²	2007 (n=994)	RCT	23(5)	7(2)	NS
INSPIRE ³	2008 (n=1,323)	RCT	50(8)	24(4)	0.008
Ernst ⁴	2007	Case- Contro 	Case Subjects (Pneumonia)	Control Subjects (No Pneumonia)	RR (95%CI)
	All COPD patients		48%	30%	1.70 (1.63-1.77)

1. Carverley P. New Engl Jour Med.2007

3. Jadwiga A. Am J Respir Crit Care Med.2008

2. Kardos P. Am J Respir Crit Care Med.2006

4. Ernst P. Am J Respi Cr Care Med.2007

Pneumonia Rate: Lower dose FP (250/50)

Combined Results From the Two 12-Month Studies

	Salmeterol n=791	Fluticasone 250/50 n=788
Number of patients with events (%)	13%	55 (7%)
Number of events	27	56
Total Exposure (treatment years)	590	652
Rate (per 100 treatment years)	46	86

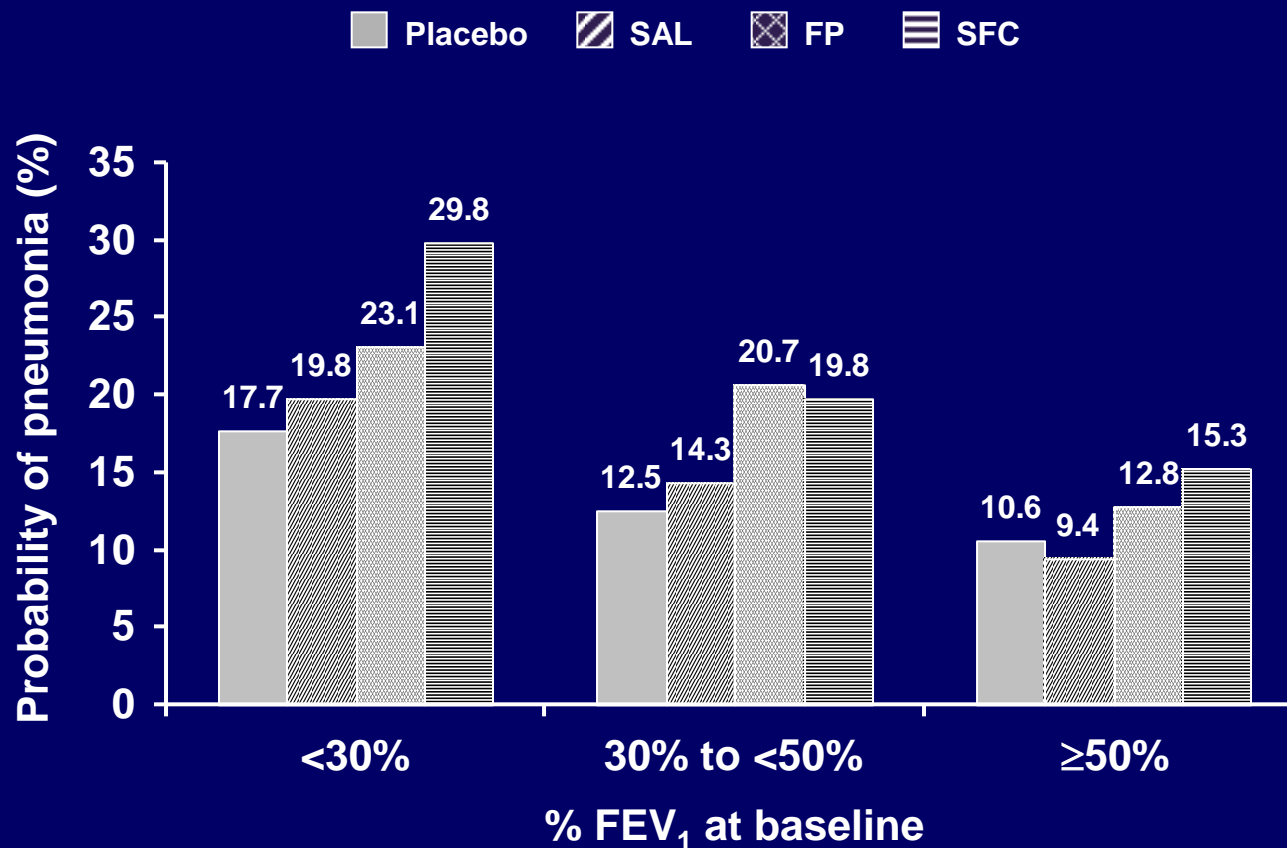
All Pneumonia patients had radiological confirmation

Inhaled corticosteroids and pneumonia

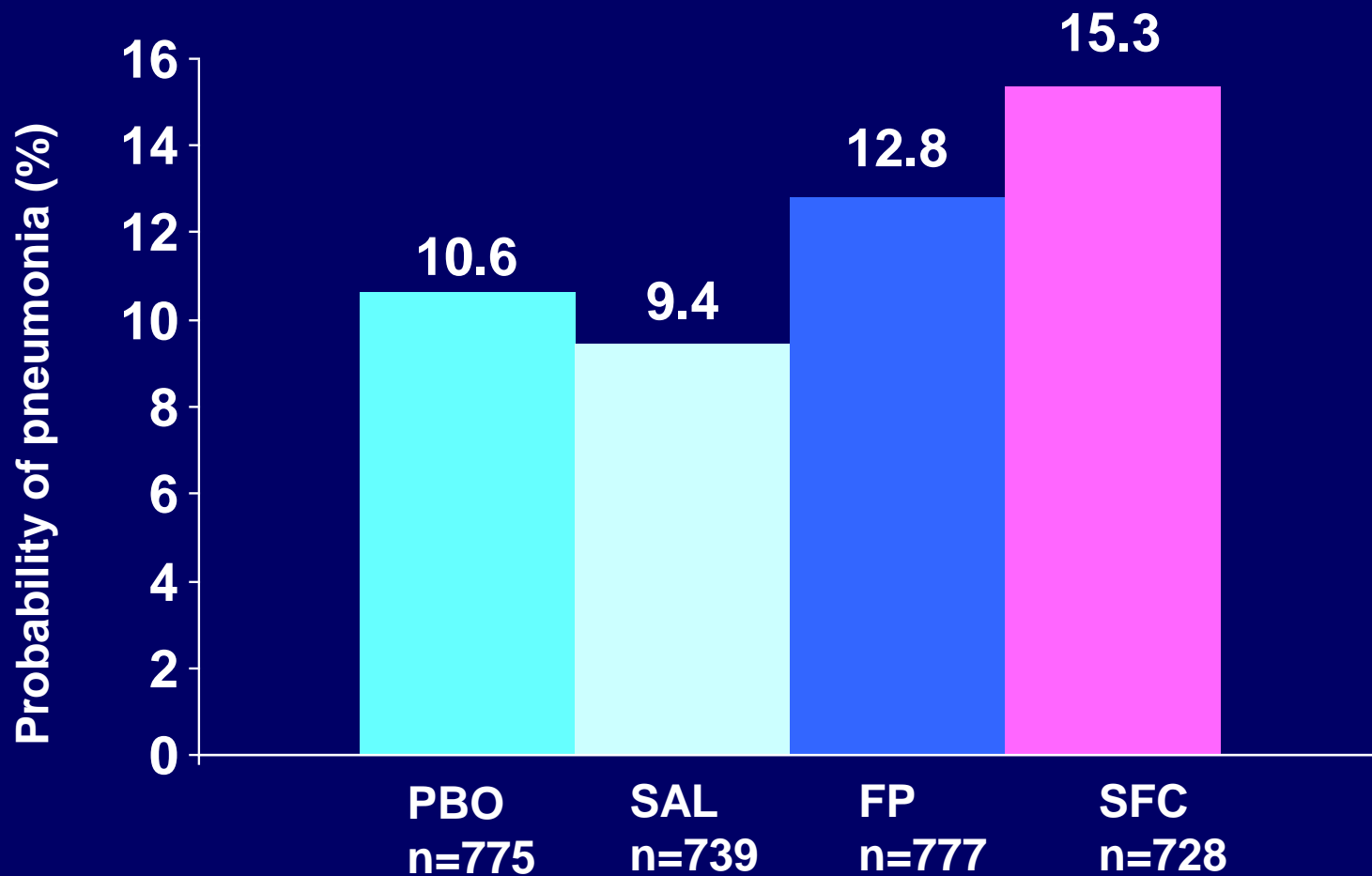
	Adjusted Rate Ratio	95% CI
Current use of ICS	1.70	1.63 - 1.77
Low dose	1.50	1.38 – 1.62
Medium dose	1.63	1.55 – 1.71
High dose	2.25	2.07 – 2.44

Ernst et al. AJRCCM 2007; 176: 162-166

TORCH: Probability of Pneumonia by Baseline Postbronchodilator FEV₁



TORCH: Probability of Pneumonia in GOLD Stage II Patients



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Adverse Event Profile for Formoterol/Budesonide (Symbicort) Registration Trials

Adverse Events Reported by ≥3% of Subjects in Any Treatment Group

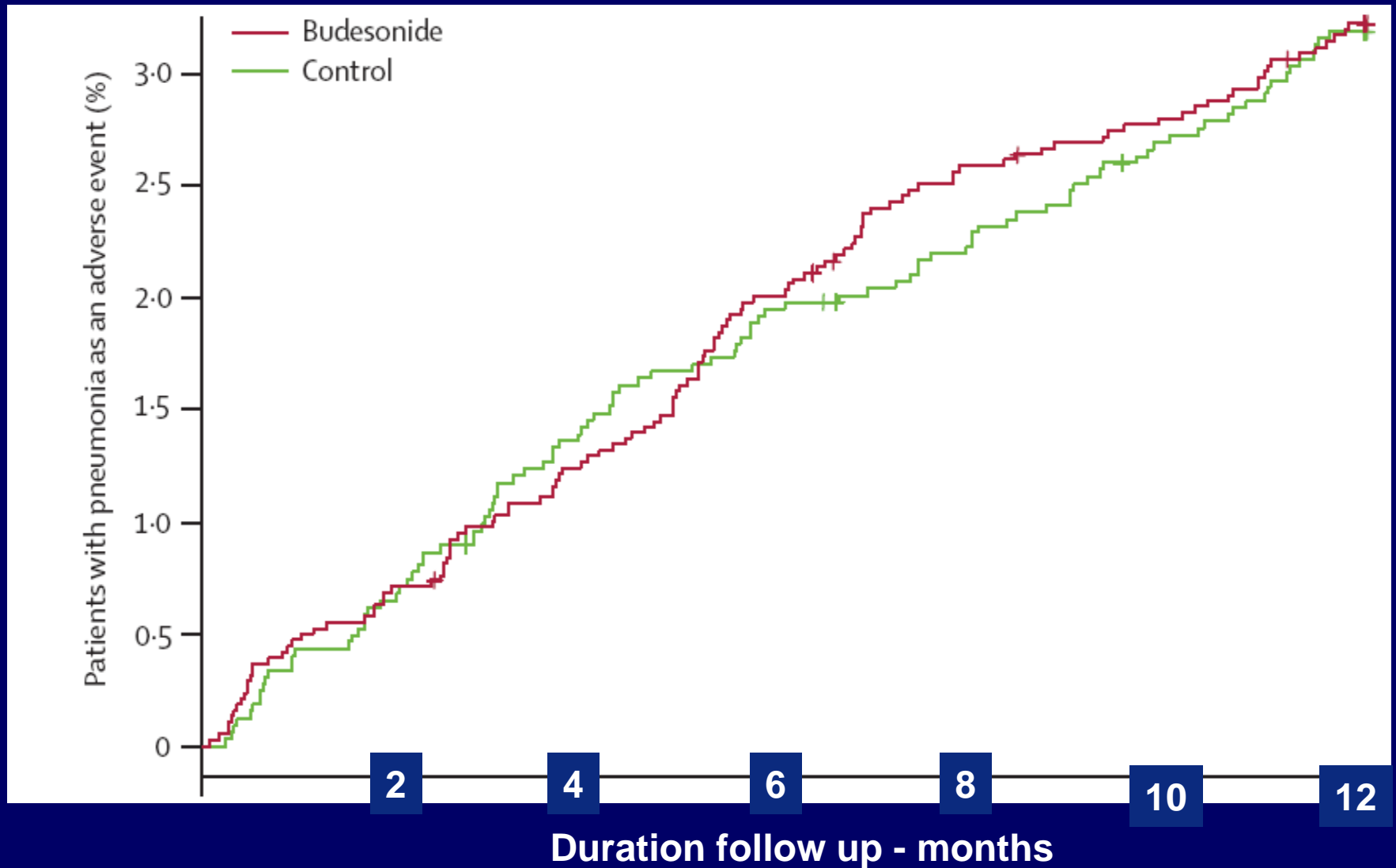
	SYMBICORT 160/4.5 µg (n=771) %	Budesonide 160 µg (n=275) %	Formoterol 4.5 µg (n=779) %	Placebo (n=781) %
COPD-related respiratory events	13.4	12.4	17.1	14.3
Nasopharyngitis	7.3	3.3	5.8	4.9
Oral candidiasis	6.0	4.4	1.2	1.8
Bronchitis	5.4	4.7	4.5	3.5
Sinusitis	3.5	1.5	3.1	1.8
Viral upper respiratory tract infection	3.5	1.8	3.6	2.7
Pneumonia	2.3	1.8	2.6	3.3

Represents pooled data from both SUN and SHINE studies, at a dose of 2 inhalations BID.
Data on File, 273073, AZPLP.

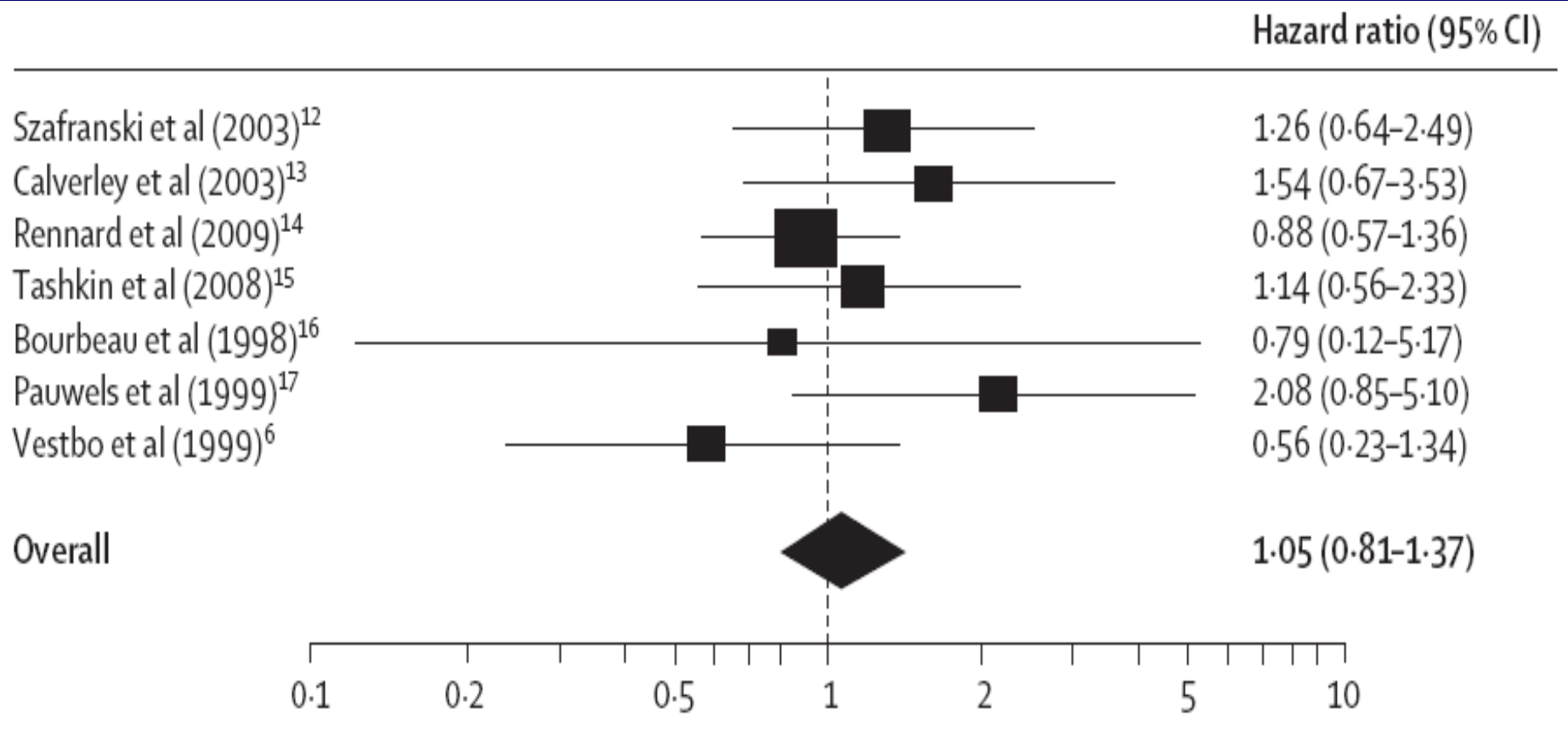
Budesonide risk Pneumonia: Meta-analysis

- **Pooled analysis patient data**
- **7 Large randomized clinical trials - use Budesonide 320 – 1280 µg/day vs FOR or placebo.**
- **Primary analysis: risk pneumonia**
- **Data 7042 patients**
- **Exposure: 5212 patient/year**

Kaplan-Meier Estimate to first Pneumonia



Adjusted Risk of Pneumonia



Budesonide risk Pneumonia: Limitations

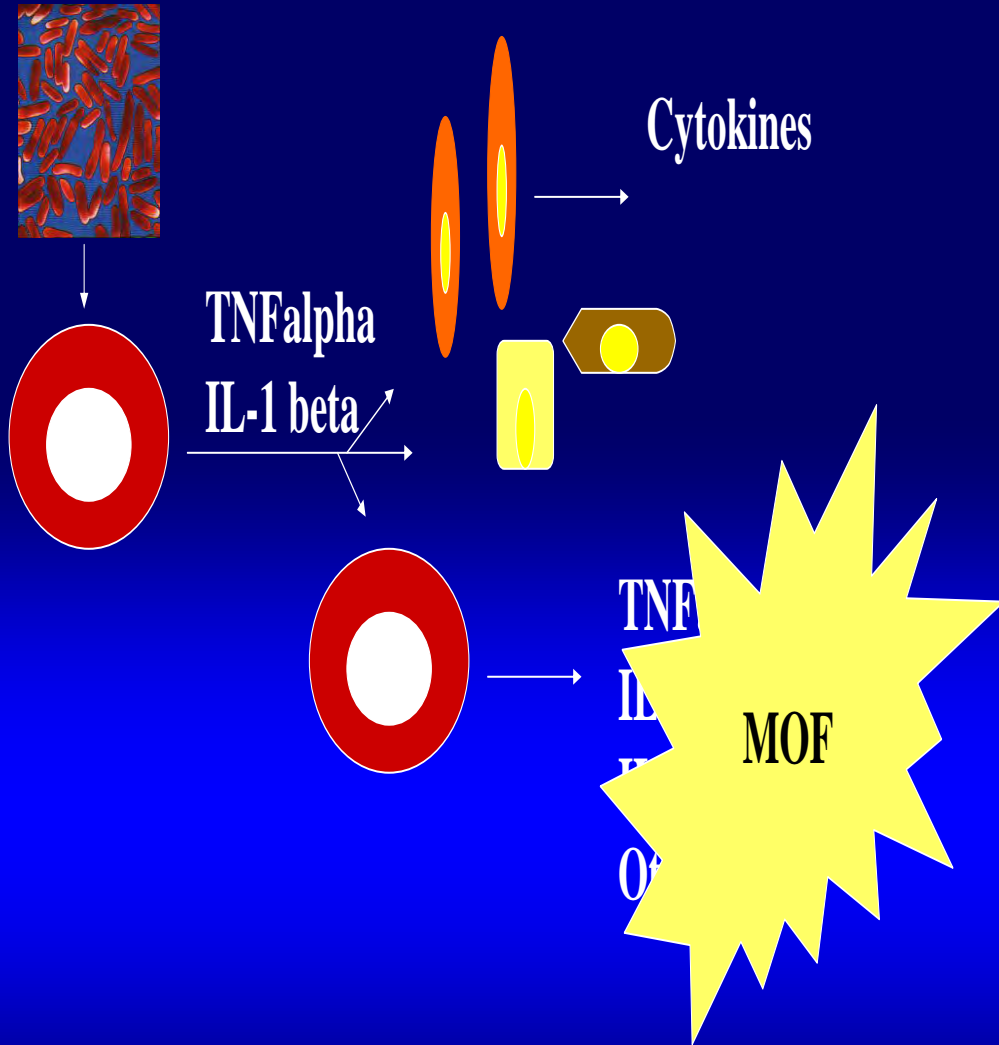
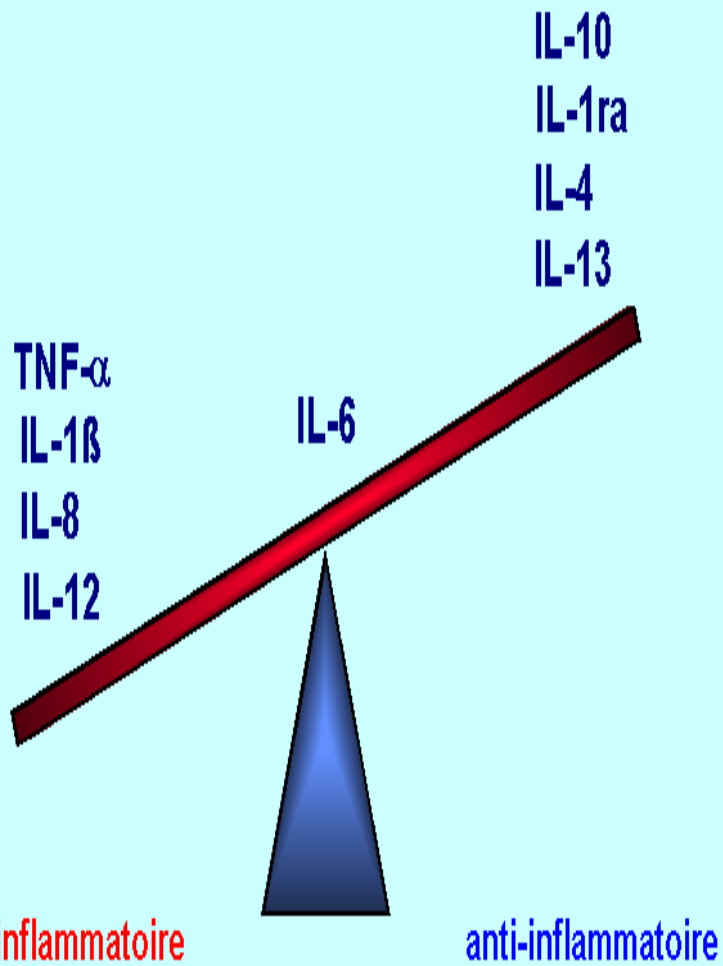
- **Studies not powered or intended to study pneumonia.**
- **Studies duration – 1 yrs**
- **Diagnosis of Pneumonia was reported by investigators and was not systematically validated.**

Issues to address

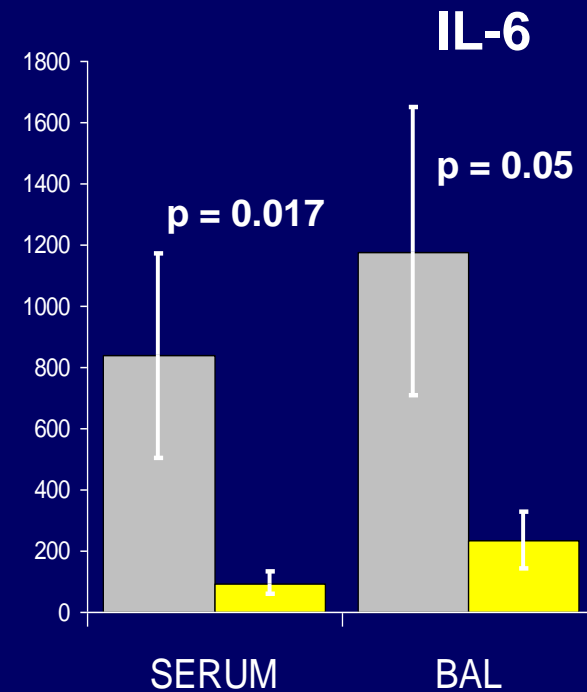
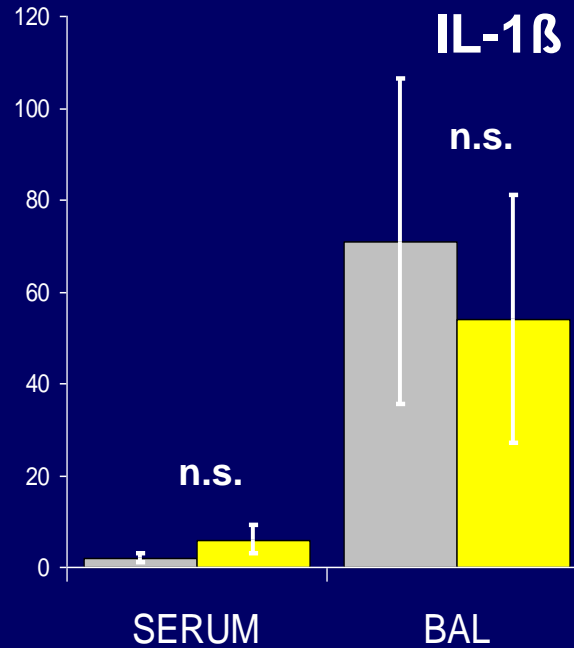
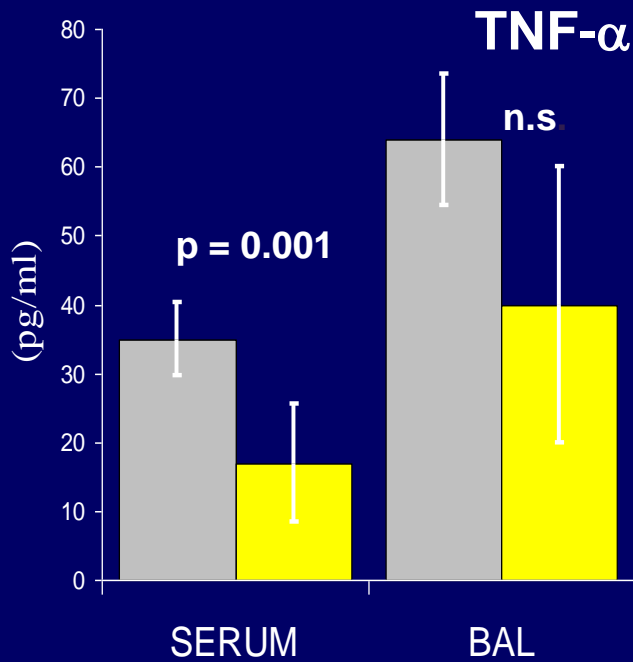
- CAP cohort impact of COPD
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- **Impact ICS use in CAP outcome**

PATIENTS WITH SEVERE CAP MAY DIE DESPITE EARLY AND APROPIATE ANTIBIOTIC THERAPY

Inflammatory Response



Cytokines in severe Pneumonia



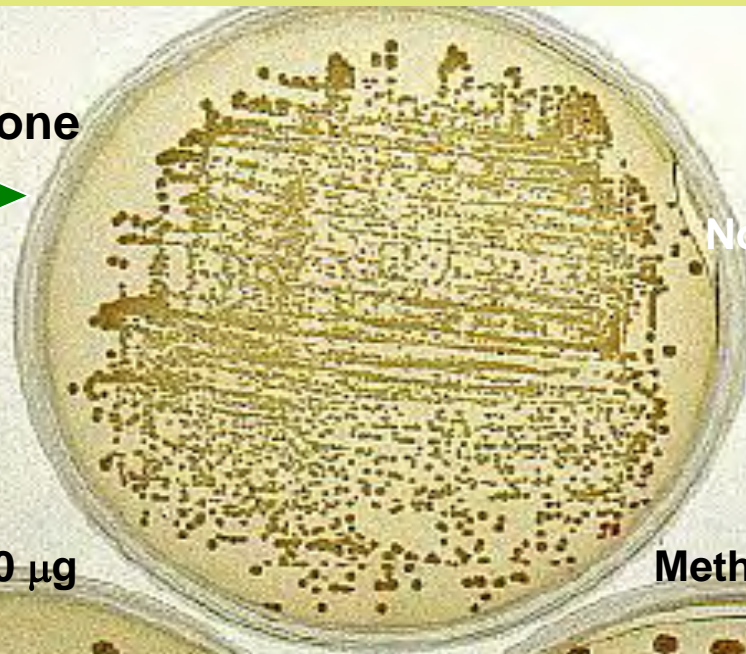
Hydrocortisone Infusion for Severe Community-acquired Pneumonia

A Preliminary Randomized Study

Marco Confalonieri, Rosario Urbino, Alfredo Potena, Marco Piattella, Piercarlo Parigi, Giacomo Puccio, Rossana Della Porta, Carbone Giorgio, Francesco Blasi, Reba Umberger, and G. Umberto Meduri

	Placebo	Hydrocort
PaO₂/FIO₂	237+92	332+80
Chest-X ray score	2.6+1.3	1.1+0.7
MOF score	1.0+0.9	0.3+0.5
CRP mg/dl	34 (0-225)	18 (0-44)
Patients on MV	65%	26%
Length of stay (days)	18 (3-45)	13 (10-53)
60 day mortality	38%	0%

No Methylprednisolone

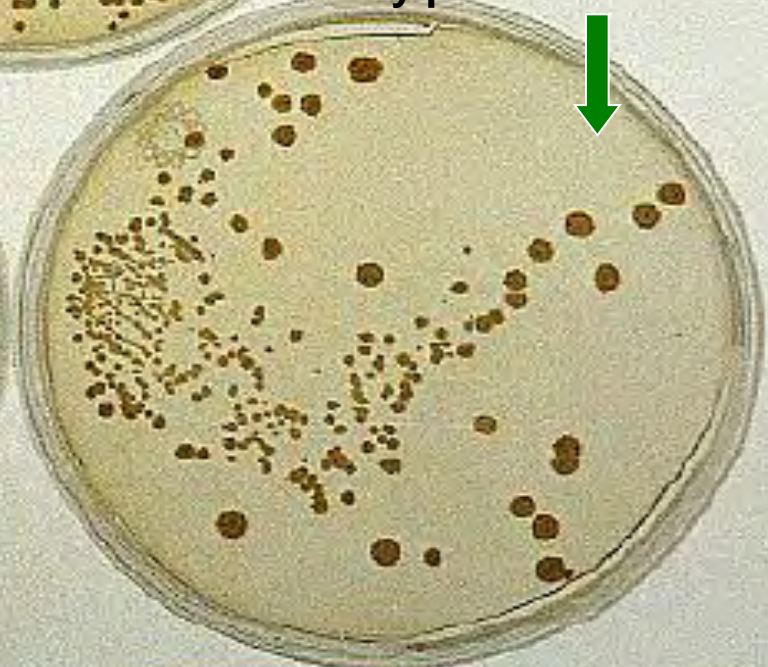


No methylprednisolone

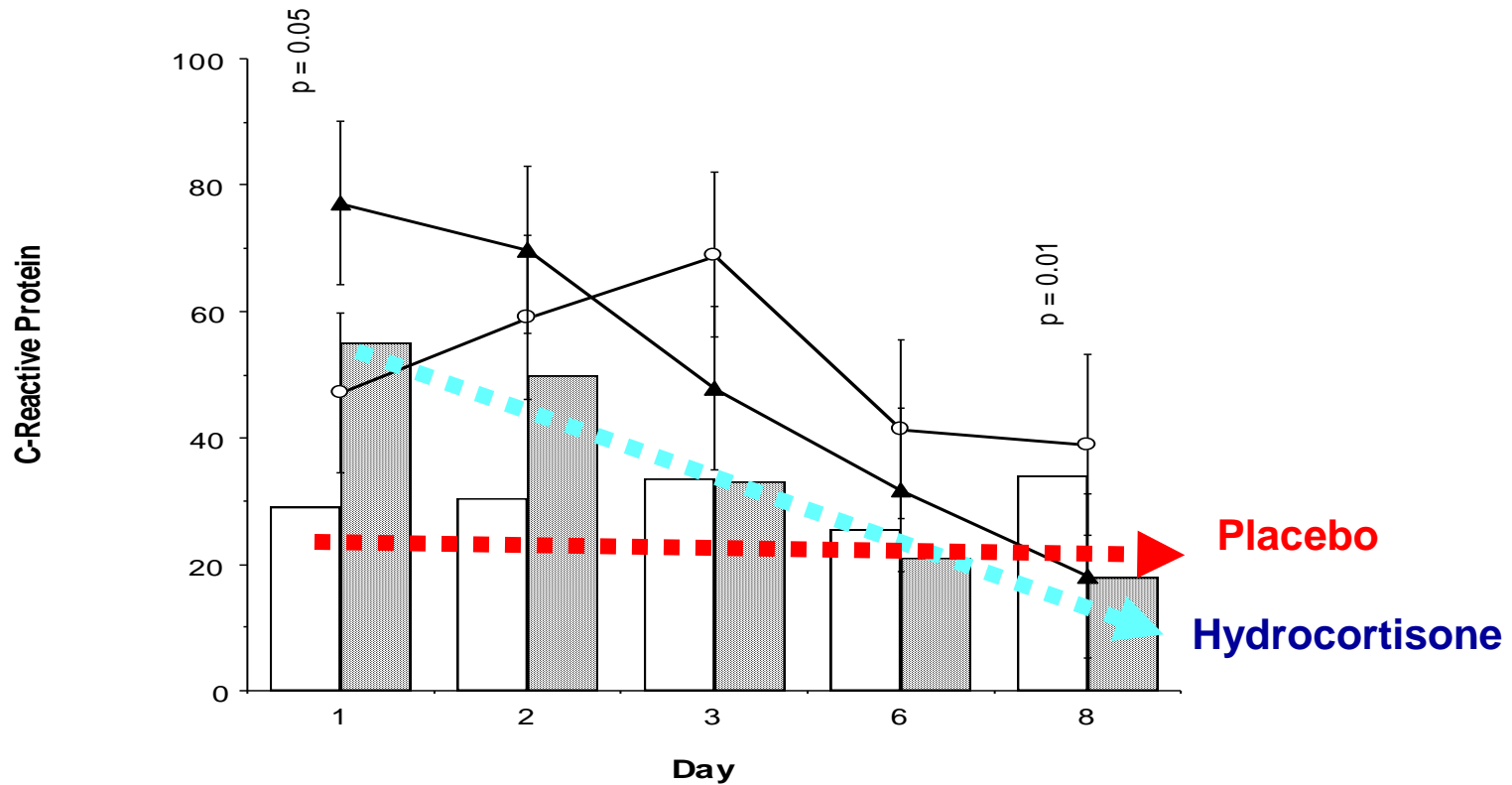
Methylprednisolone 150 μ g



Methylprednisolone 250 μ g



Serum CRP Over Time



The impact of outpatient inhaled corticosteroid therapy on disease severity in hospitalized patients with CAP

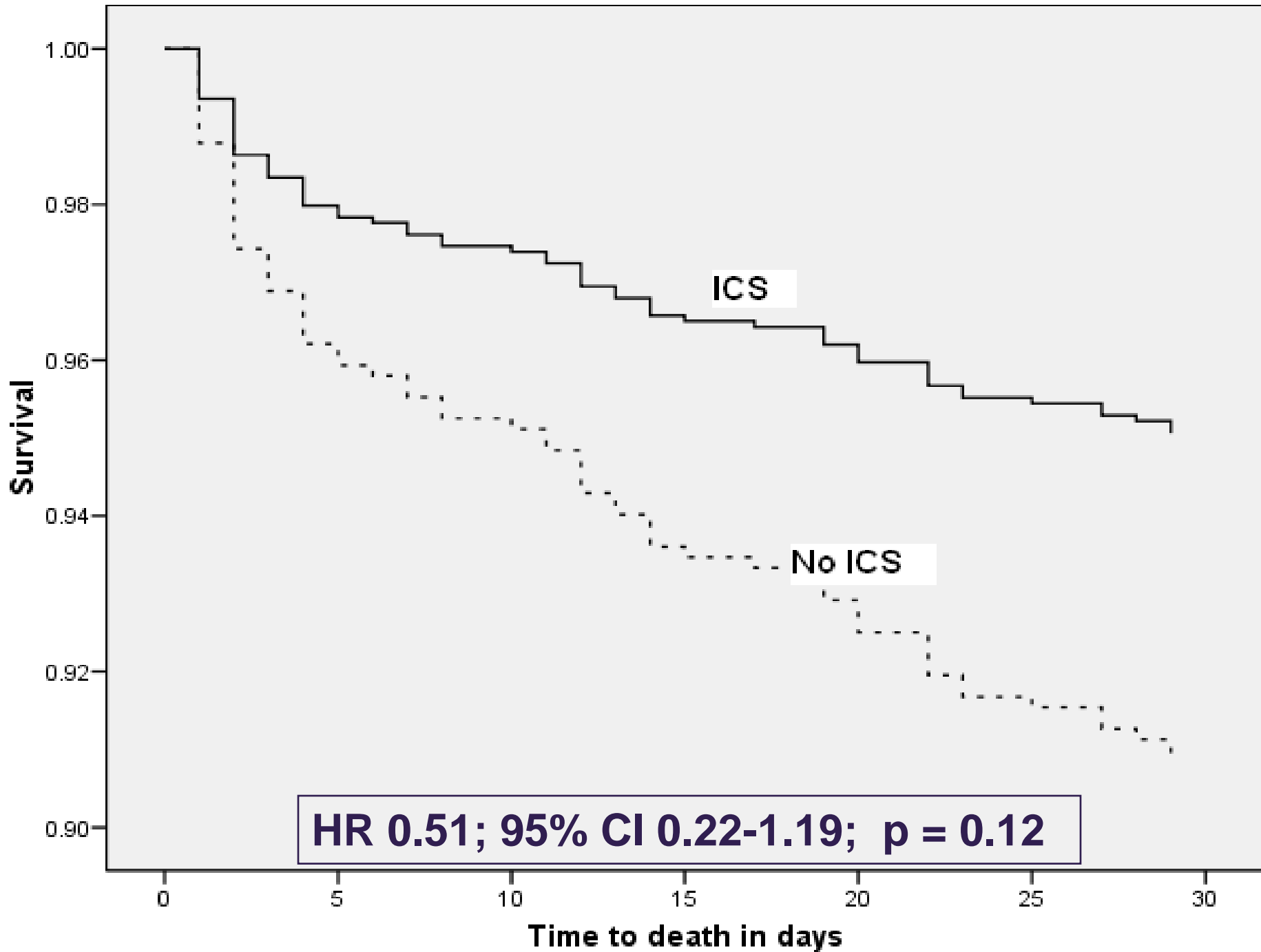
R. Malo de Molina, M.D.; E.M. Mortensen, M.D., M.Sc.; P. Castellanos-Matteus, M.D.; A. Anzueto, M.D.; M.I. Restrepo, M.D, M.Sc.



*VERDICT South TX Veterans Health Care System
and The University of Texas Health Science
Center at San Antonio, Texas*

Methods

- ***Study Design***
 - A retrospective observational cohort study of patients hospitalized at two teaching hospitals in southwestern US
 - VA medical center and county-run referral hospital
 - Admission between Jan 1, 1999 and Dec 31, 2001
 - ❖ Study was approved by the local Institutional Review Board



Secondary Outcomes

Variables	Inhaled CS HR [95%CI]
➤ Severe CAP	0.51 [0.25-1.05] P= 0.06
➤ Severe Sepsis	0.40 [0.22-0.70] P= 0.001

Limitations

- **Retrospective data analysis**
- **Large number of different ICS, unknown if it is a class effect**
- **Unknown duration of prior corticosteroid use**
- **No data on current smoking status, vaccination history and lung function**

COPD in CAP: Conclusions

- **What we know:**
- COPD is a frequent co-morbid condition in patient with CAP.
- Most data are from CAP cohorts: good diagnosis of CAP, limited diagnosis of COPD.
- COPD in CAP may be associated with poor outcome. Need to evaluate co-founded variables.

COPD in CAP: Conclusions

- **What we need to understand:**
- Prevalence and incidence of CAP in COPD cohorts.
- Impact of pharmacotherapy, vaccination etc. on patients' outcomes.
- Impact of COPD exacerbation and CAP.
- Further confirm that ICS may provide different risk of CAP.

"Pneumonia may well be called the friend of the aged. Taken off by it in an acute, short, not often painful illness, the old man escapes those 'cold gradations of decay' so distressing to himself and to his friends."

Sir William Osler, *The Principles and Practices of Medicine*, 1912

Gràcies

