

Exacerbation de BPCO – Approche EBM

Pierre-Olivier Bridevaux

« The greater our knowledge increases, the greater our ignorance unfolds »

John F. Kennedy

Plan

BPCO:

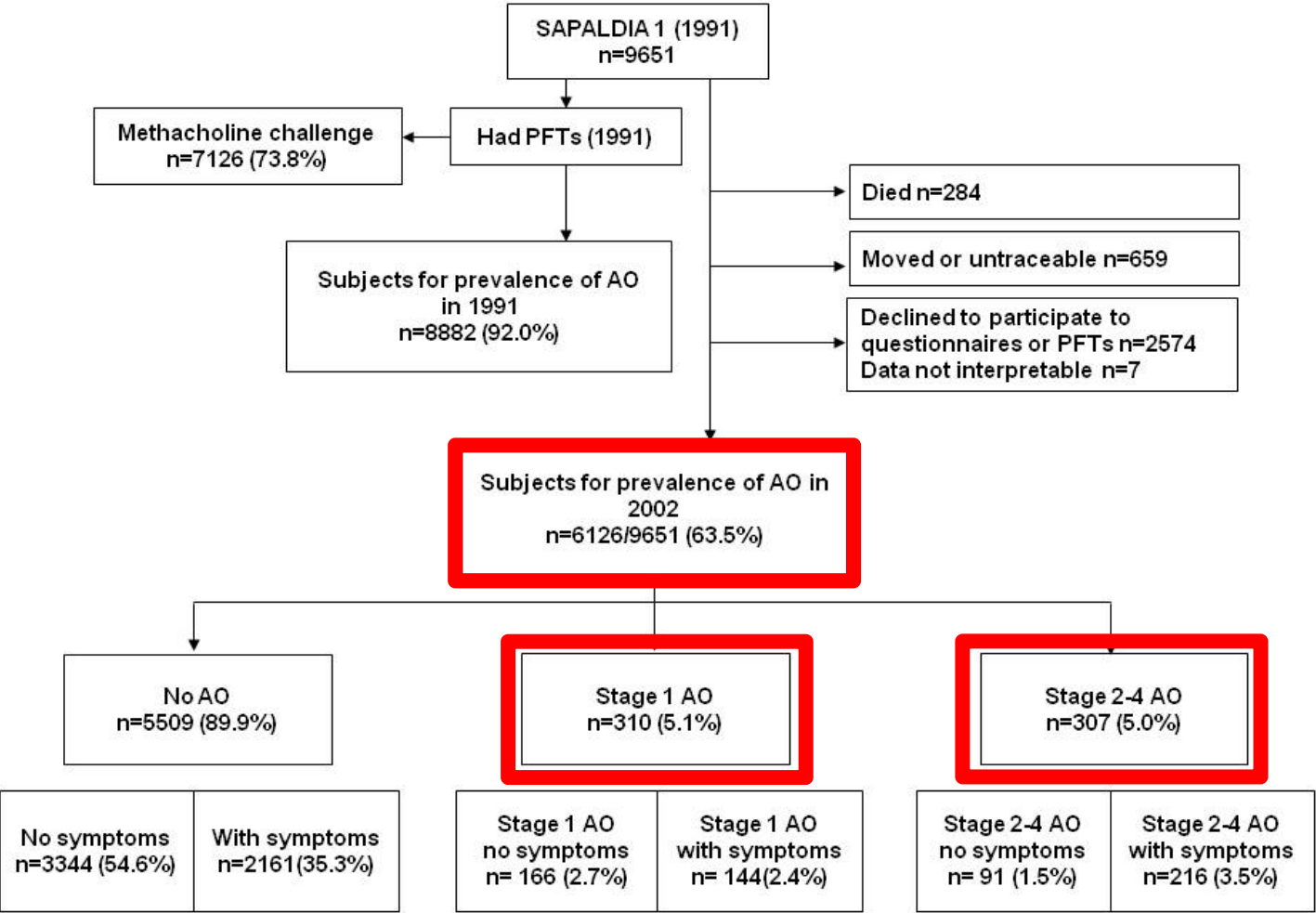
- Epidémiologie générale de la BPCO
- Fréquence des exacerbations

Exacerbation de de BPCO (articles publiés de 2005 à juin 2010)

- Interventions pharmacologiques
- Interventions non pharmacologiques (patient)
- Interventions non pharmacologiques (système de soins)

Prevalence of Airflow Obstruction in Smokers and Never Smokers in Switzerland

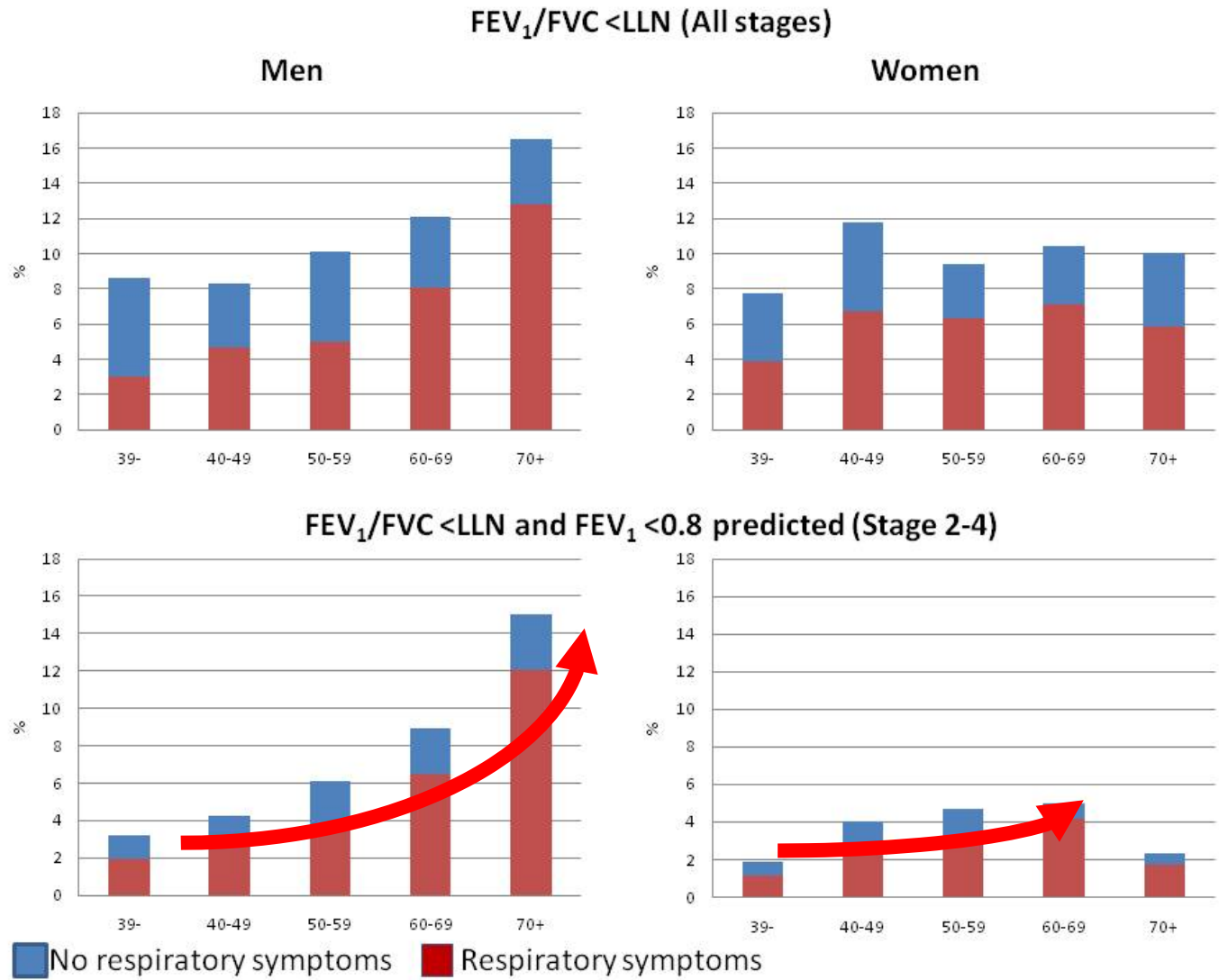
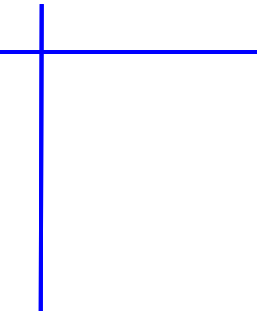
Results from the SAPALDIA cohort study (European Resp J 2010 april 22)



AO: airflow obstruction; PFTs : Pulmonary functions tests; Obstruction: $FEV_1/FVC < LLN$; Stage 1: $FEV_1 \geq 0.8$ predicted; Stage2-4: $FEV_1 < 0.8$ predicted

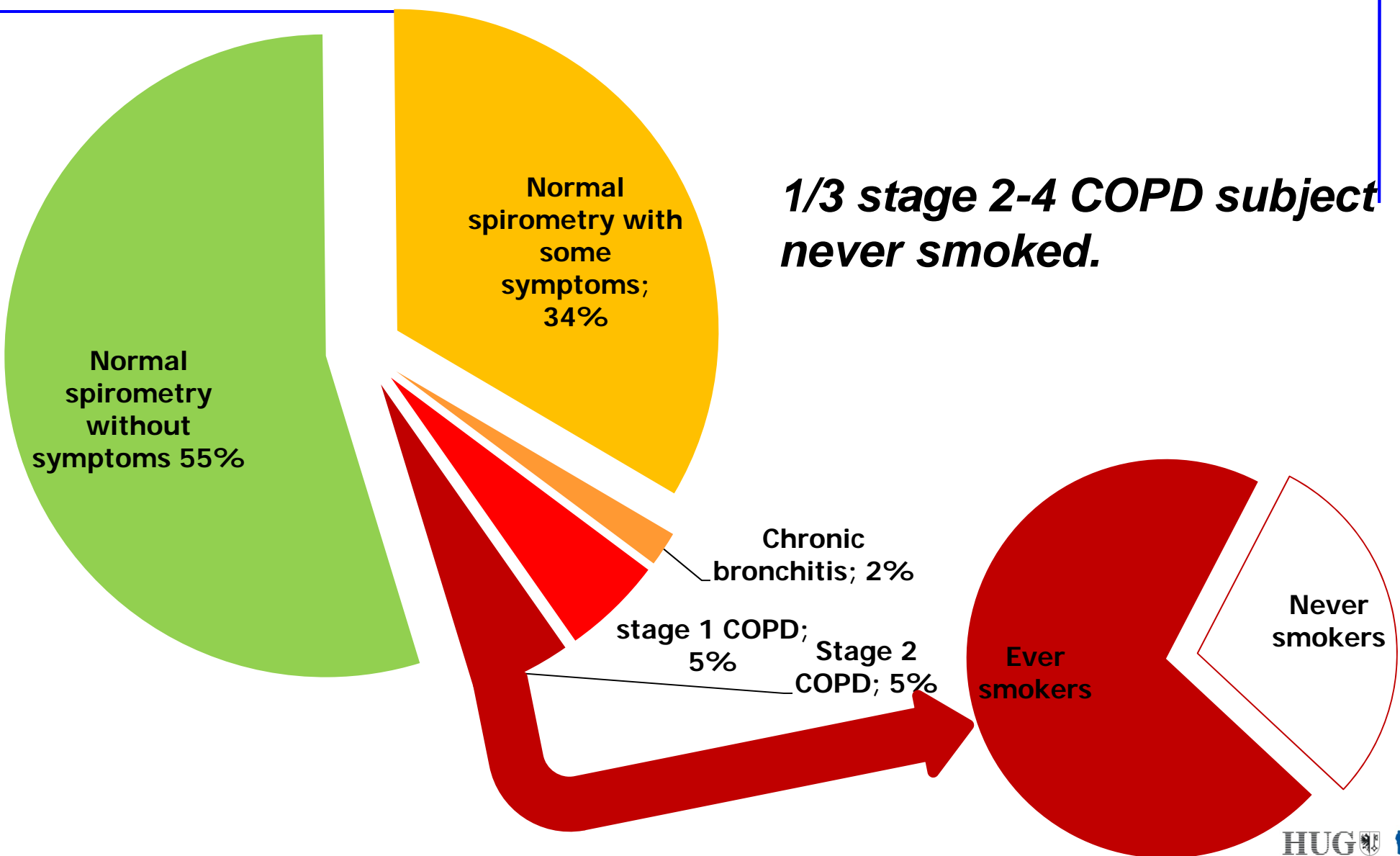
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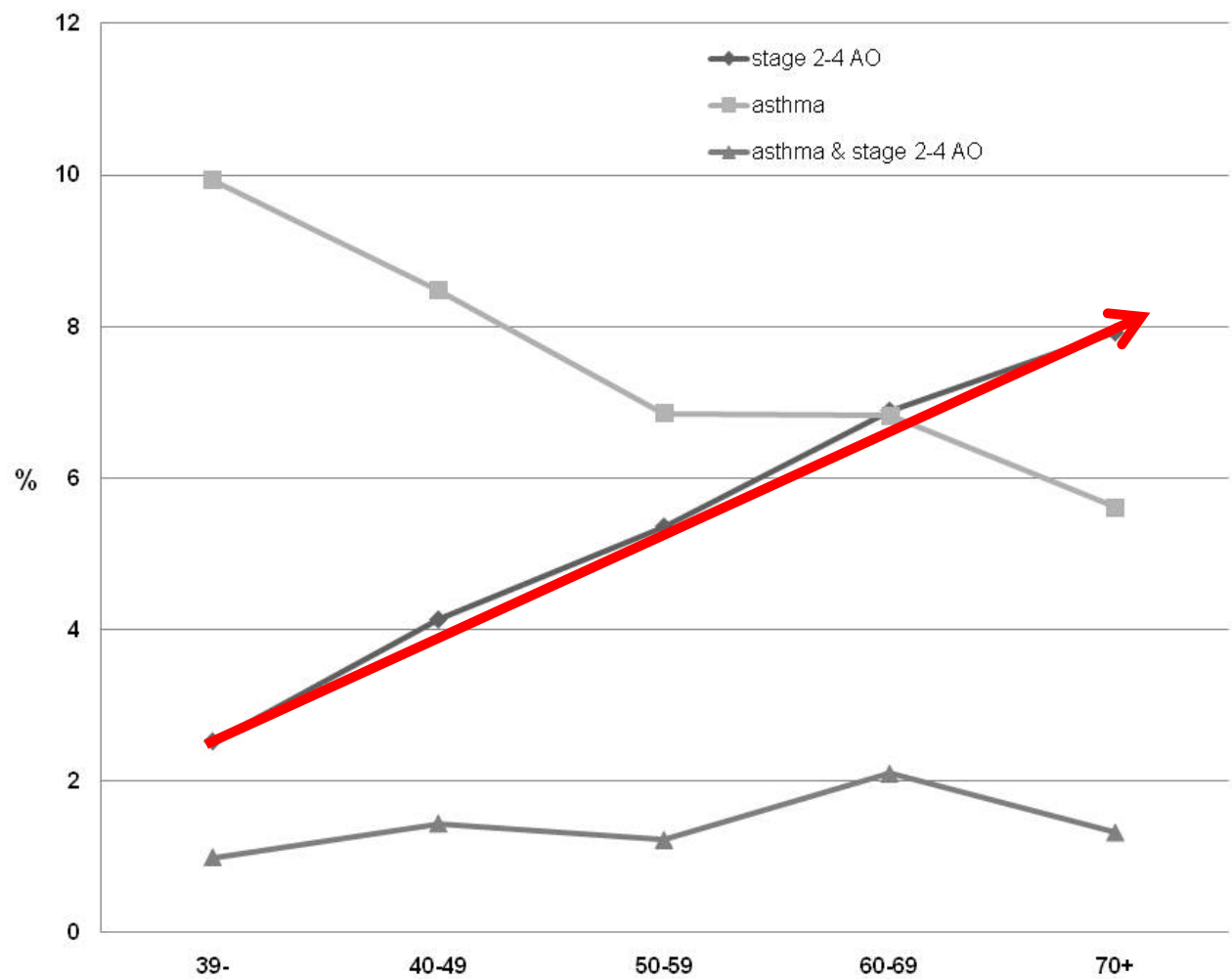
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Prevalence of Airflow Obstruction in Smokers and Never Smokers in Switzerland

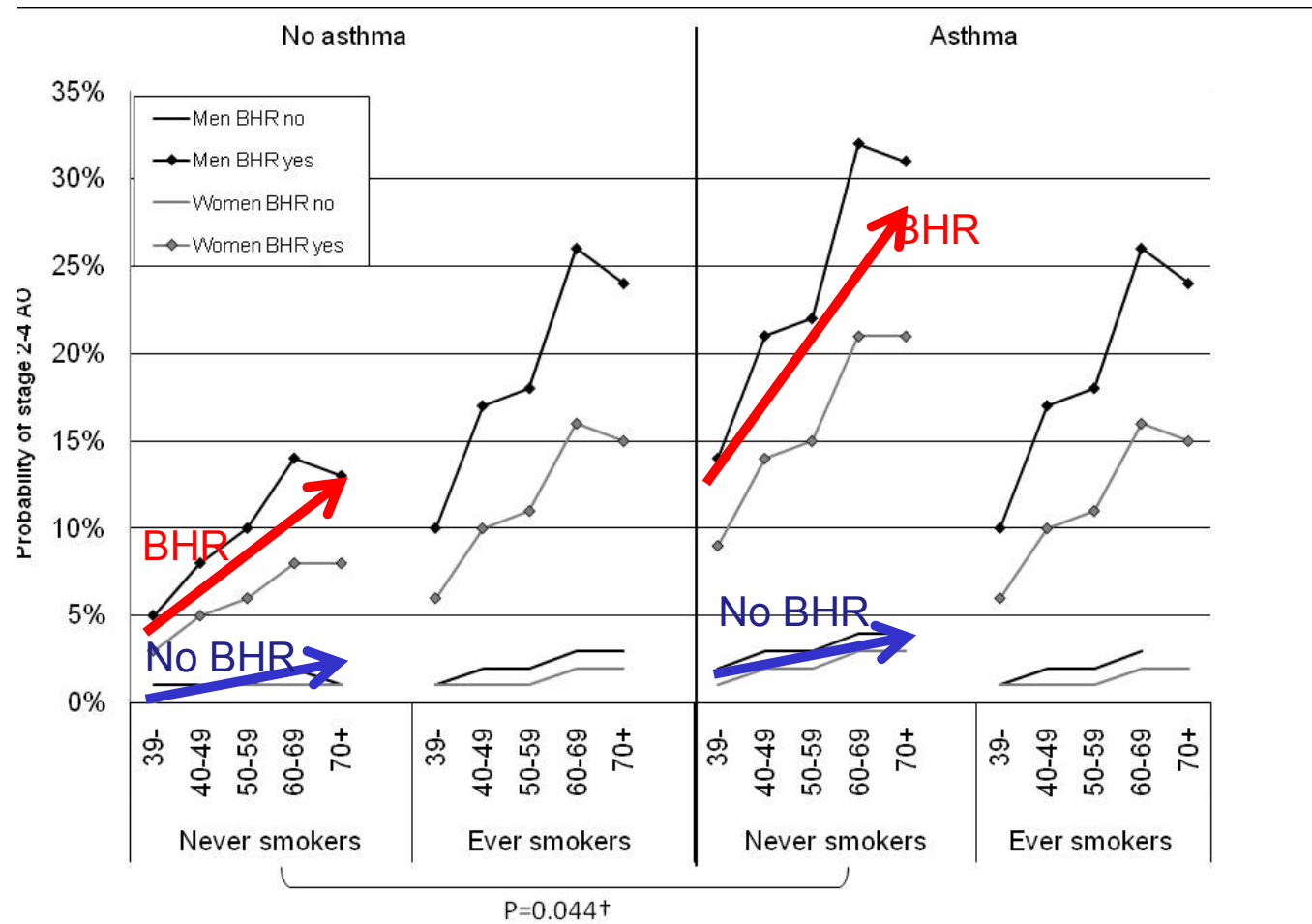
Results from the SAPALDIA cohort study (European Resp J 2010 april 22)



P-O Bridevaux N Probst-Hensch, CSchindler , I Curjuri, DFelber Dietrich , O Braendli , M Brutsche, L Burdet , M Frey , M Gerbase, U Ackermann-Liebrich· M Pons· J-M Tschopp, T Rochat E W Russi

Prevalence of Airflow Obstruction in Smokers and Never Smokers in Switzerland

Results from the SAPALDIA cohort study (European Resp J 2010 april 22)



Prevalence of Airflow Obstruction in Smokers and Never Smokers in Switzerland
Results from the SAPALDIA cohort study (European Resp J 2010 april 22)

Risk factors for airflow obstruction (2002) in never smokers

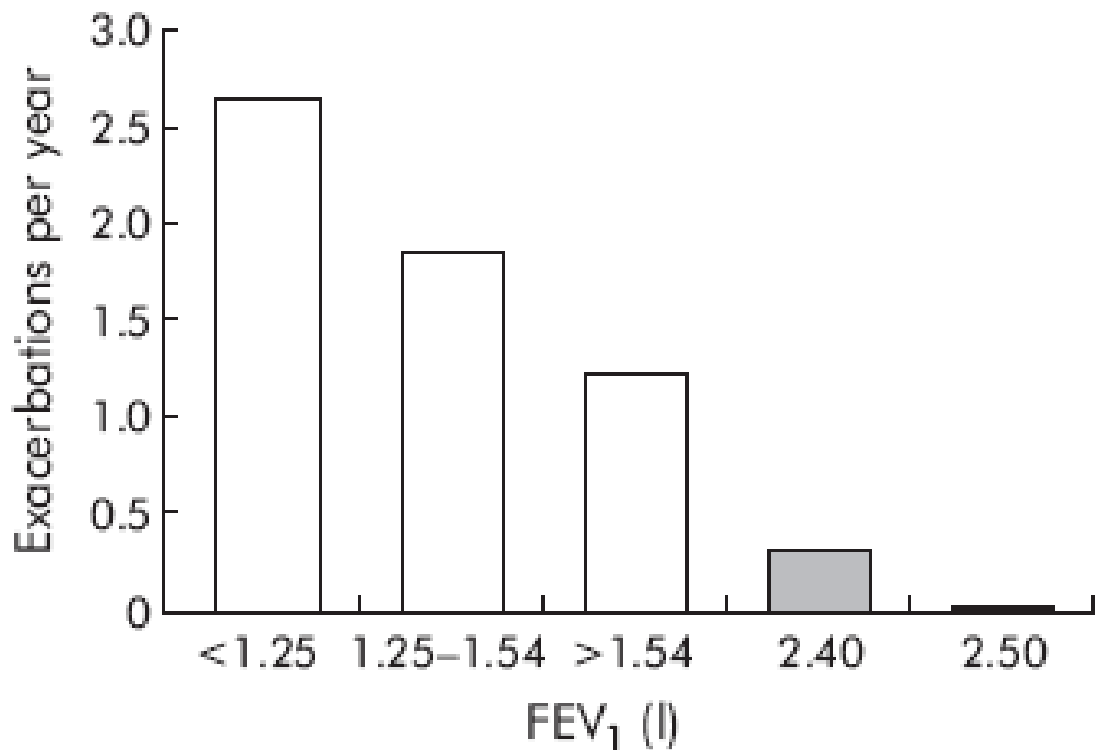
	OR AO in 2002 (95% CI)
Positive Metacholine challenge (1991)	8.2 (4.2 - 16.2)
Asthma (1991)	3.3 (1.5 – 7.3)
Passive smoking (1991)	1.5 (0.4 – 5.3)

Epidémiologie des exacerbations de BPCO

- USA (310 mio habitants) ~600'000 admissions ¹
 - CH (7.7 mio habitants) ~ 15'000 admissions
 - GE (453 241 habitants) ~ 870 admissions
-
- Exacerbation de BPCO = 2.4 % des admissions en urgence ²
 - La plupart des exacerbations sont traitée en ambulatoire ³
 - 50 % des exacerbations ne sont pas rapportée ^{3 4}

1 Snow et al Evidence based guideline for management of COPD acute exacerbation, Ann Intern Med 2001
2 Donaldson & Wedzicha, COPD exacerbations: Epidemiology Thorax 2006,
3 Seemungal et al, Time course and recovery of exacerbation in patients with COPD AJRCCM 2000
4 Miravitles et al, Effect of exacerbation on QoL Thorax 2004

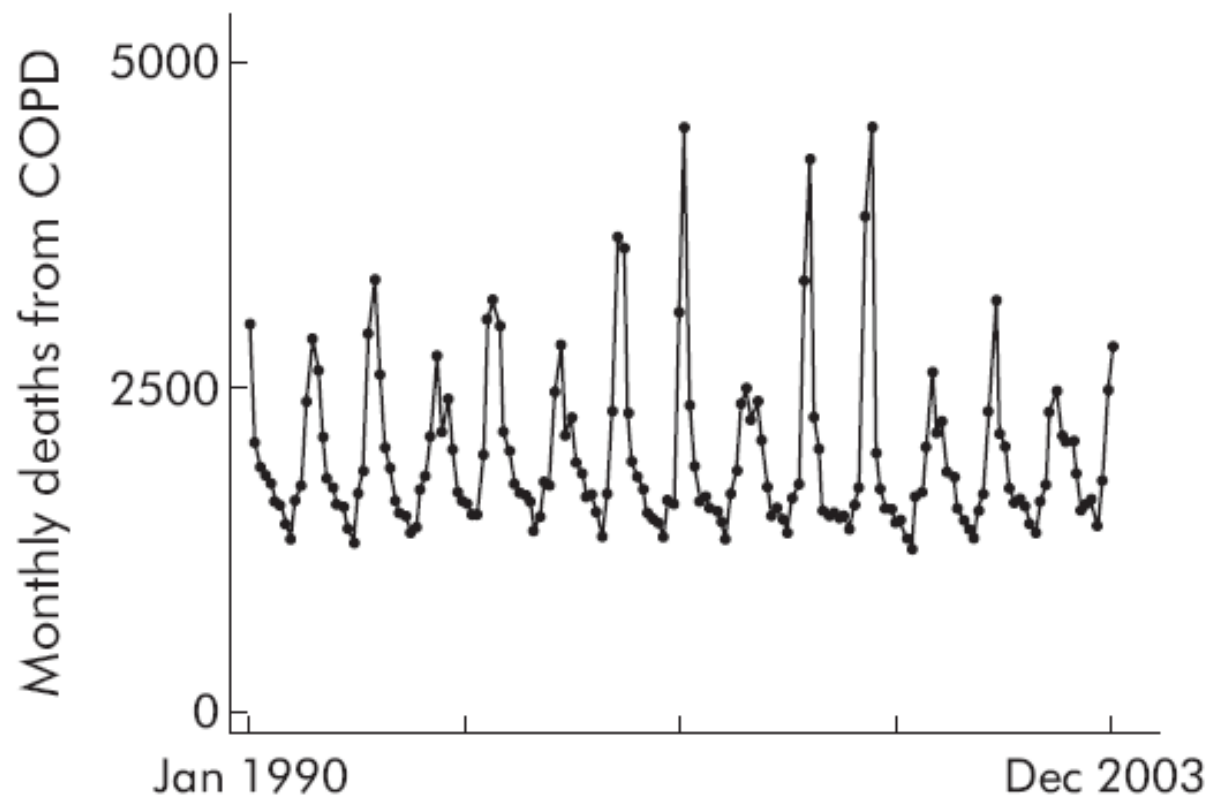
Epidémiologie des exacerbations de BPCO



GOLD III : 3.4 exacerbations / an
GOLD II : 2.7 exacerbations / an

COPD Monthly mortality

Men and women living in England and Wales



ICD9 490-492 and 496 (ad 2001)
ICD10 J40-J44 (2001-2003)

Sélections des articles

Flow chart

Sélections des articles

Flow chart

Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review)



Ram FSE, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

Systematic review and meta-analysis of 11 RCT (917 patients with COPD exacerbations)

Outcomes: mortality, treatment failure

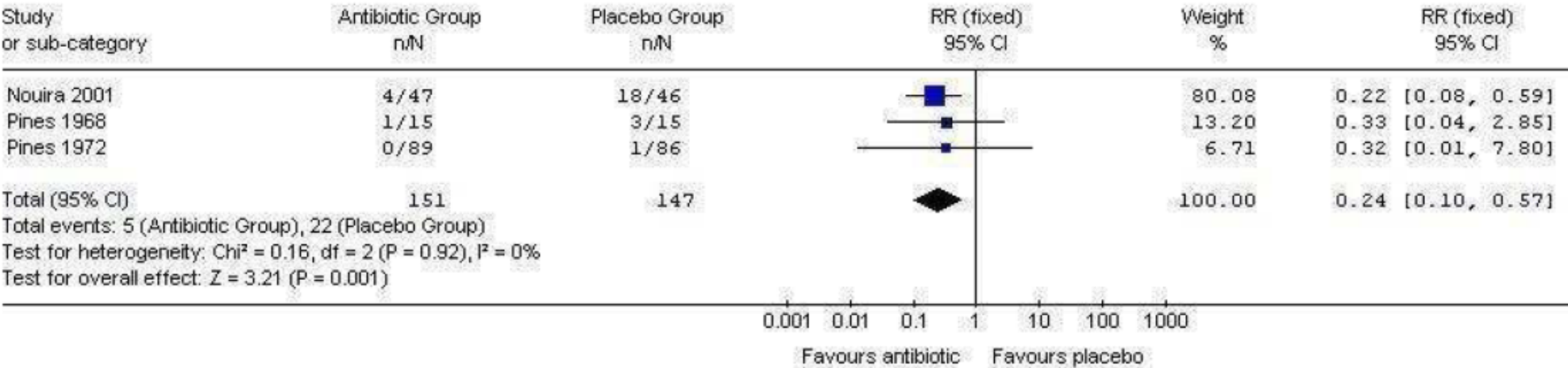
Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review)



Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

Mortality (short term)

Review: *Antibiotics for exacerbations of chronic obstructive pulmonary disease
Comparison: 01 Antibiotics versus Placebo
Outcome: 01 Mortality



RR 0.23 (CI95% 0.10 - 0.52) NNT: 8 (6 to 17) in favor of antibiotics.

Comment: All 3 studies included only hospitalized patients

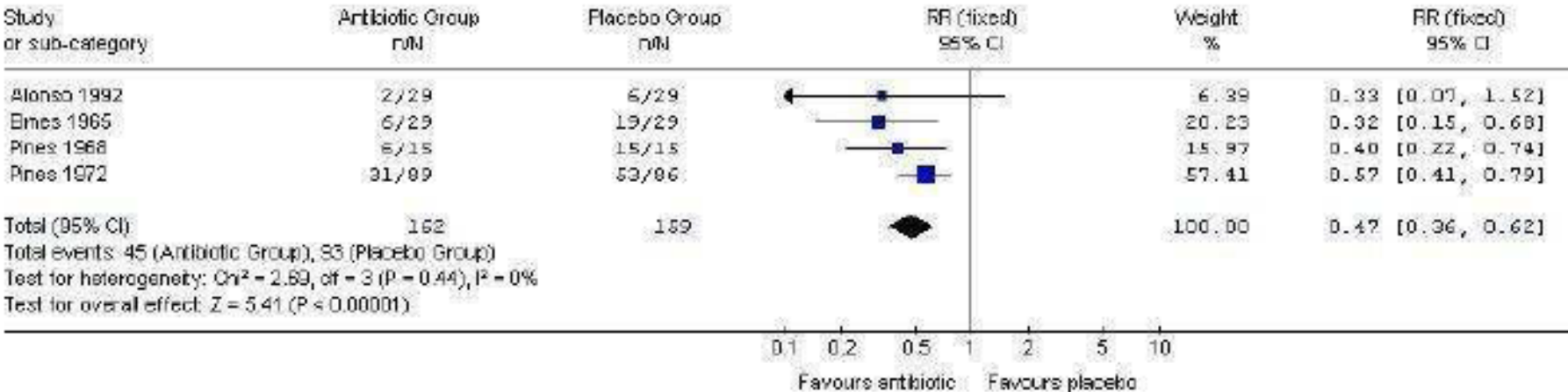
Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review)



Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

Treatment failure (No resolution of symptoms or deterioration)

Review: *Antibiotics for exacerbations of chronic obstructive pulmonary disease
Comparison: 01 Antibiotics versus Placebo
Outcomes: 02 Treatment Failure (no resolution or deterioration of symptoms after trial medication or death)



RR 0.47 (CI95% 0.26 - 0.62) NNT: 3 (3 to 5) in favor of antibiotics.

Comment: All 4 studies included only hospitalized patients

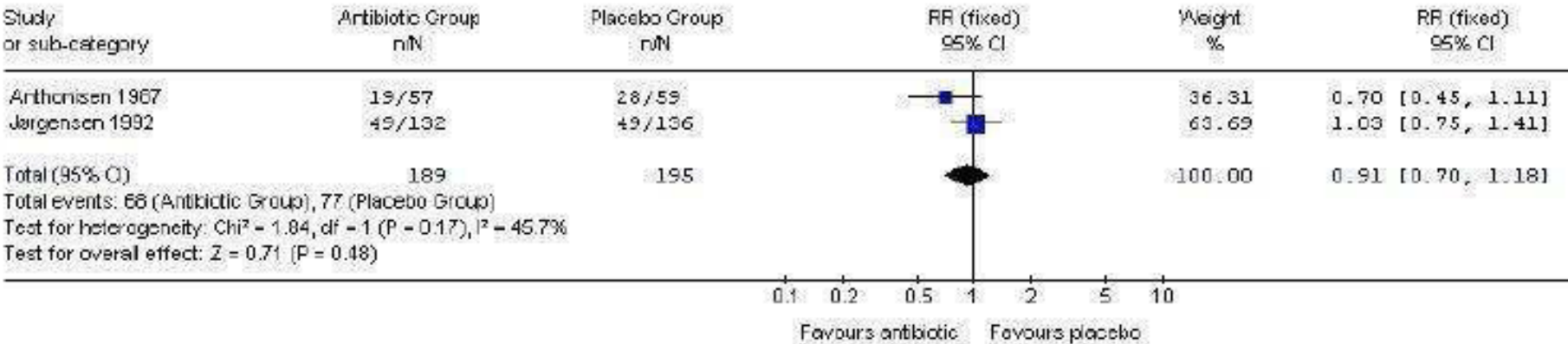
Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review)



Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

Treatment failure (No resolution of symptoms or deterioration)

Review: *Antibiotics for exacerbations of chronic obstructive pulmonary disease (Wiley incorporated)
Comparison: 01 Antibiotics versus placebo
Outcome: 02 Treatment failure (no resolution or deterioration of symptoms after trial medication of any duration or death)



RR 0.91 (CI95% 0.70 – 1.18)

Comment: No benefit of antibiotics for ambulatory patients

Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review)



Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

Conclusions:

- 1) Antibiotics decrease mortality, treatment failure and sputum purulence
- 2) In agreement with S. Saint (1995)
- 3) No effect of specific antibiotics

Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review)



Ram FSE, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

Systematic review and meta-analysis of 11 RCT (917 patients with COPD exacerbations)

Outcomes: mortality (3 studies), treatment failure

Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review)



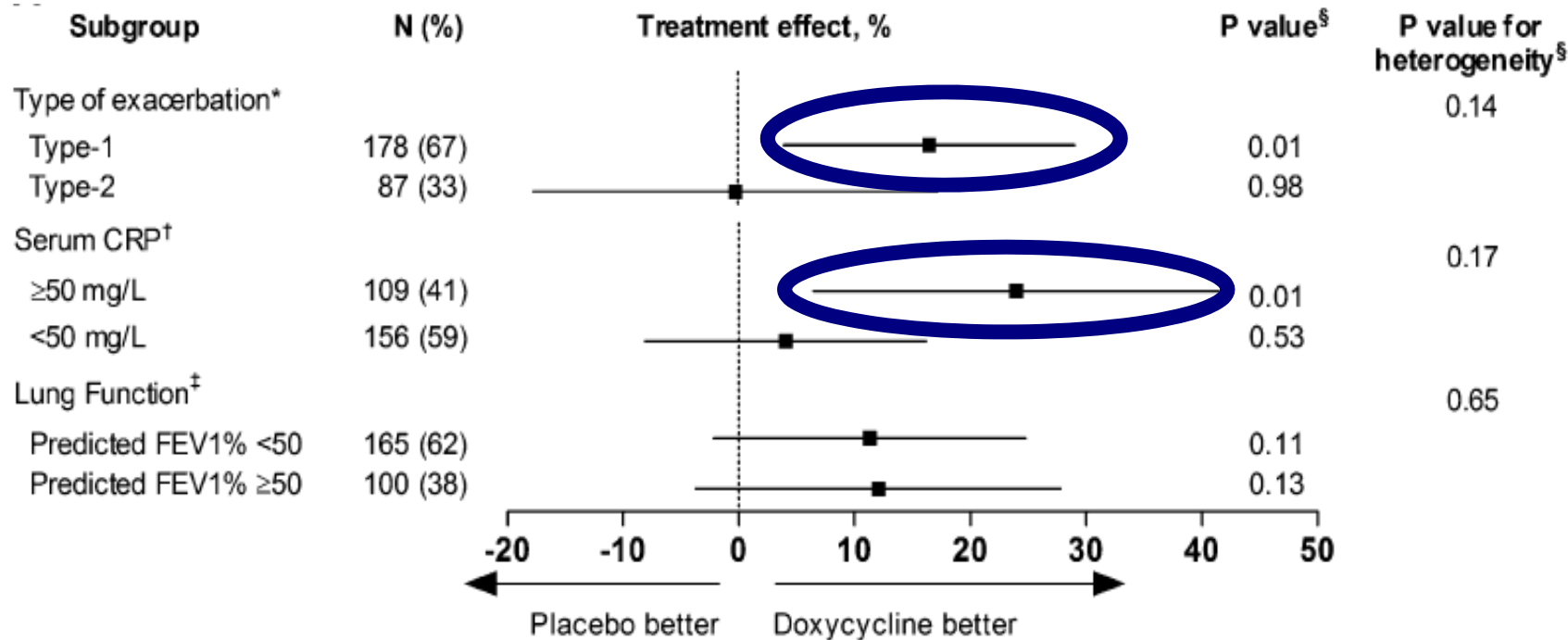
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Systematic review and meta-analysis of 11 RCT (917 patients with COPD exacerbations)

Outcomes: mortality (3 studies), treatment failure

Antibiotics in Addition to Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease AJRCCM 2010

Patients: 265 severe exacerbations (inpatients)
Intervention: Placebo vs doxycycline
Outcomes: time to failure, symptom score, CRP
Results: day 10, clinical success (OR 1.9 CI95% 1.1 3.2)
day 30 , similar



Levofloxacin 500 mg once daily vs cefuroxime 250 mg twice daily in patients with acute exacerbations of COPD.

(Int J of antimicrobial agents 2007)

Background: 50% AECOPD are positive for bacteria. Do antibiotics increase time to relapse?

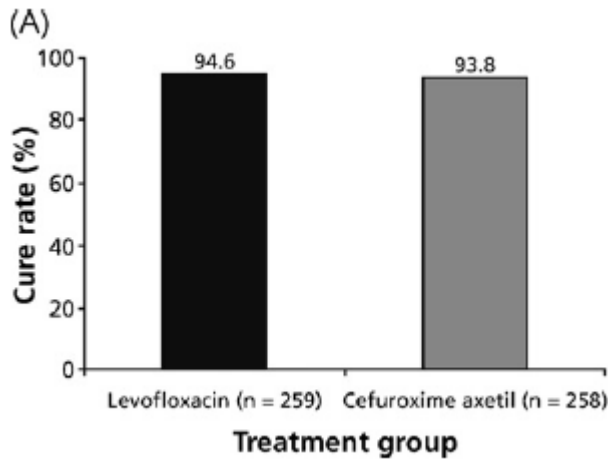
Patients: 689 outpatients FEV1 52%,

Intervention: multicentric (F, B, D, A, Tunisia & Turkey, Sanofi-Aventis sponsored levofloxacin 500 mg od vs cefuroxime 250 bid (10 days)

Outcomes: microbiological cure at 17-21 days. Time to relapse

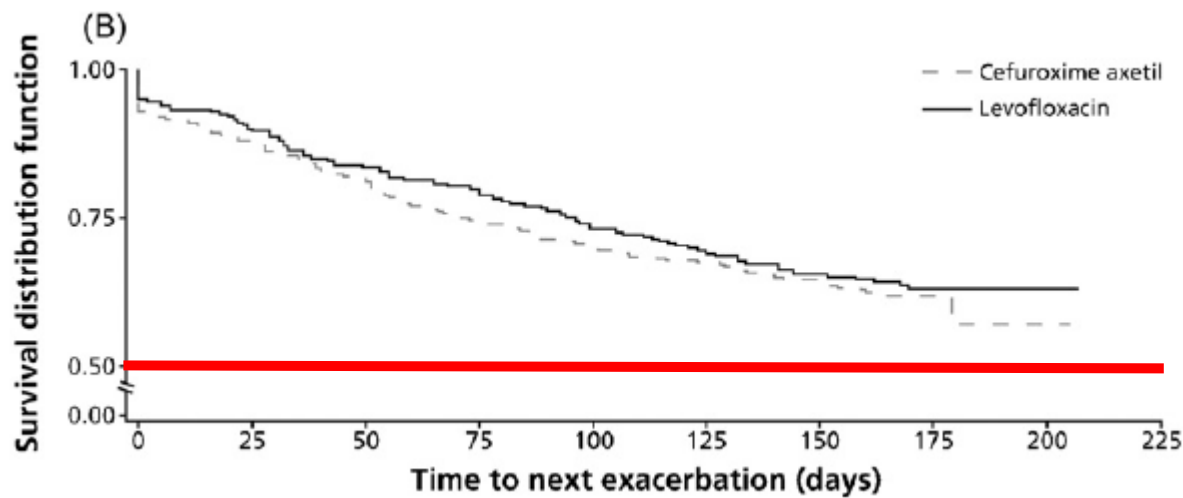
Results: ...

Levofloxacin 500 mg once daily vs cefuroxime 250 mg twice daily in patients with acute exacerbations of COPD.
(Int J of antimicrobial agents 2007)



Conclusions:
No difference between levofloxacin and Cefuroxime

Comments:
Industry driven



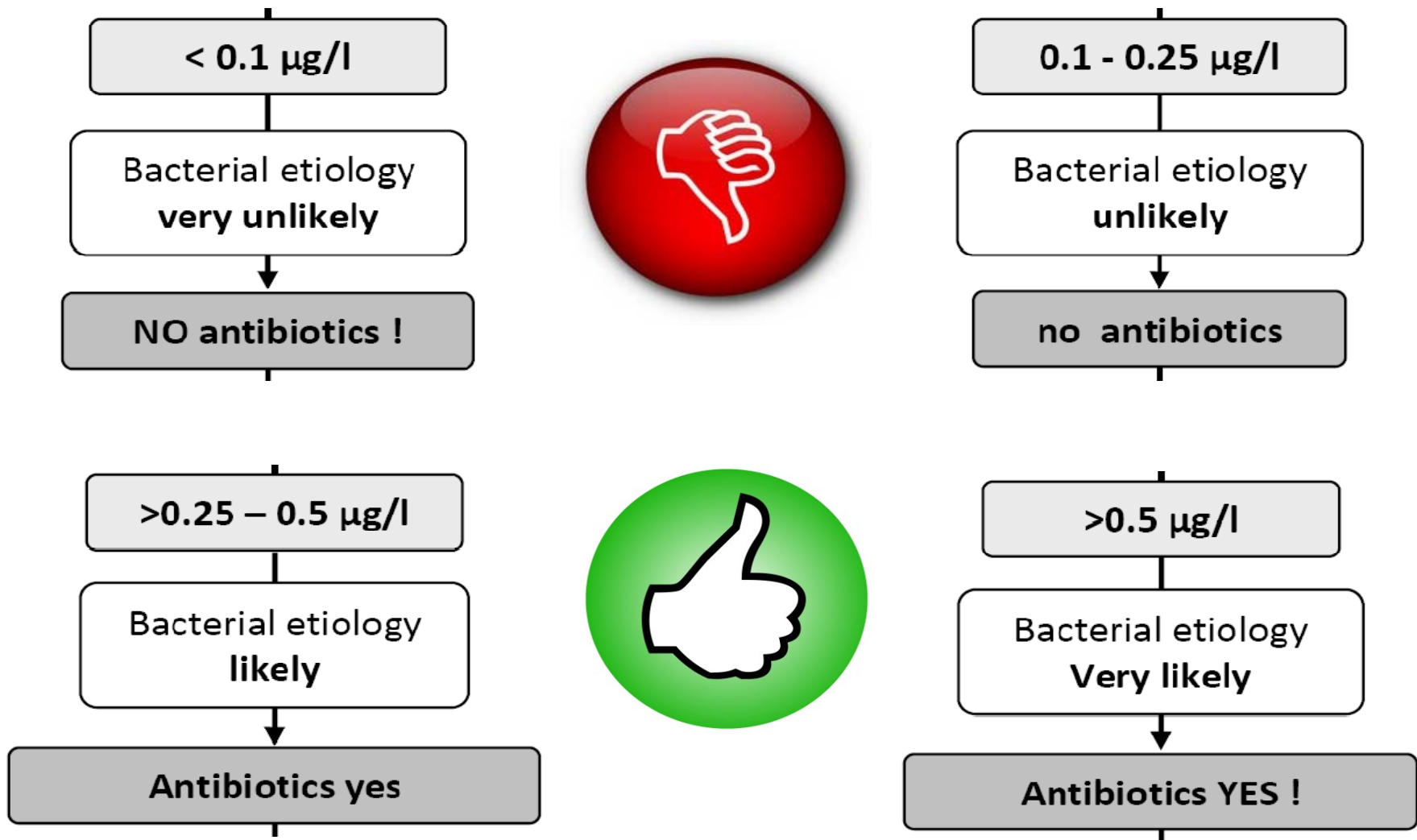


Usefulness of Procalcitonin for targeting the use of antibiotics?

- **Pragmatic study comparing two strategies**
 - Treatment recommendations based on pro-CT values
 - Standard care
- **228 patients with acute exacerbation of COPD**

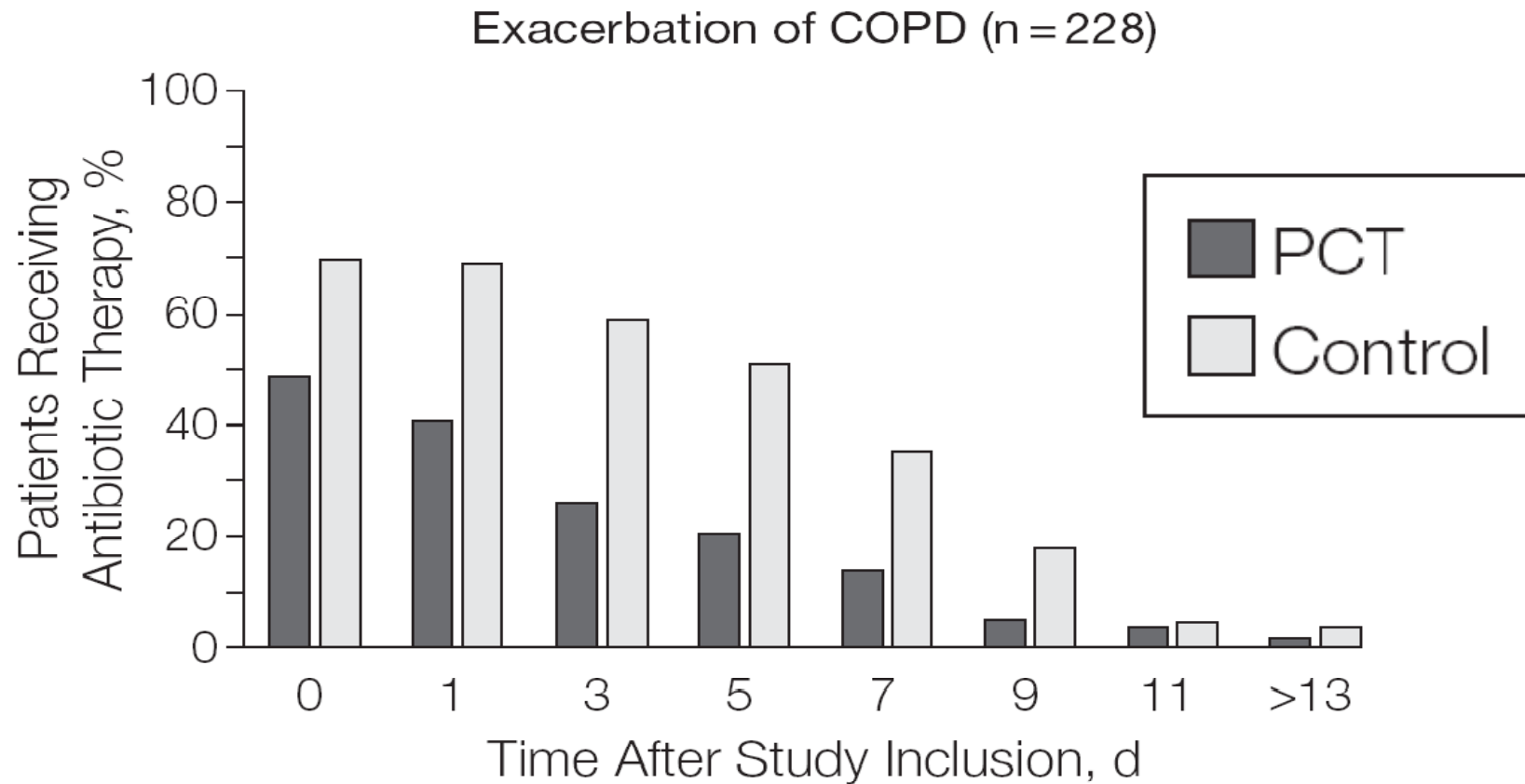


ProCT guided antibiotherapy





ProCT guided antibiotherapy



No. of patients

PCT	56	47	30	23	16	6	4	2
Control	79	78	67	58	40	20	5	4



ProCT guided antibiotherapy : limitations

$$\text{Prob [bact inf]} = [\text{COPD stage}] + [\text{acute symptoms}] + [\text{chest Xray}] + [\text{CRP}] + [\text{ProCT}] ?$$

In outpatient setting...

1. ATB is delayed while waiting for test result
2. False negative result (too early?)
3. No outpatient studies – Lower specificity to be expected in outpatient setting

Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease (Review)

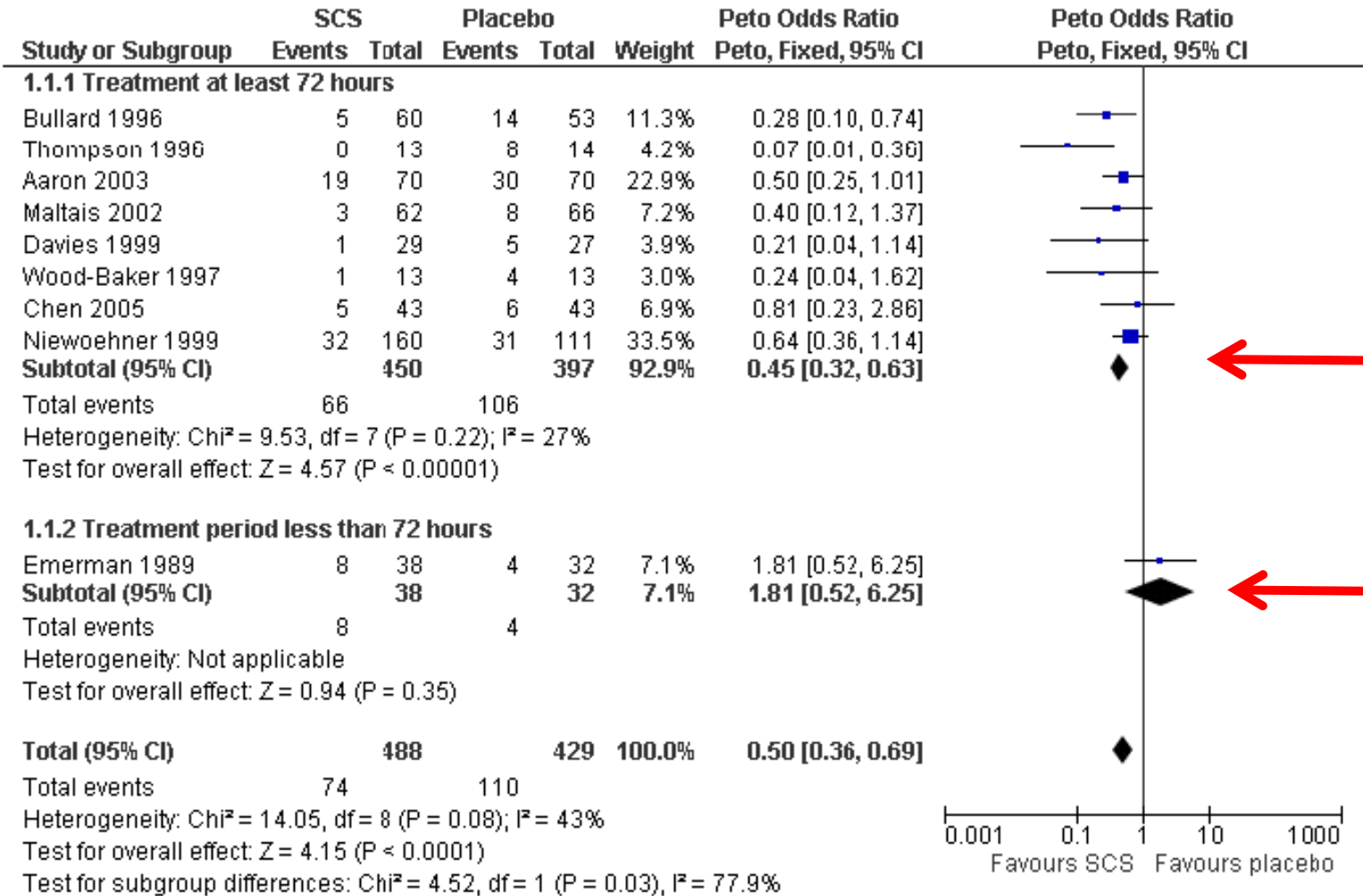
Walters JAE, Gibson PG, Wood-Baker R, Hannay M, Walters EH



Systematic review and meta-analysis of 10 RCT (1051 patients with COPD exacerbations)

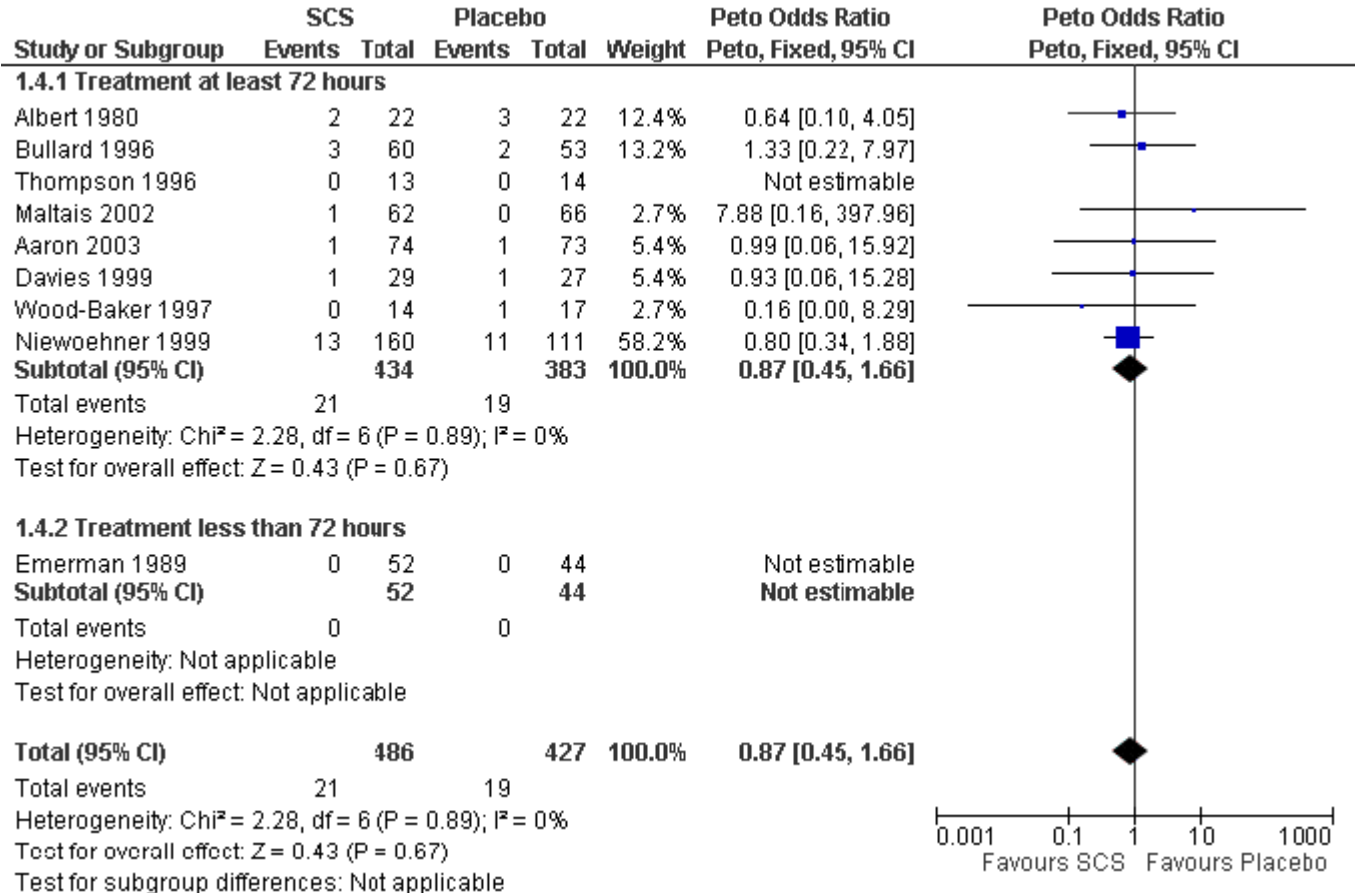
Outcomes: treatment failure, duration of hospitalisation, mortality, adverse events

Systemic steroids: Treatment failure (Therapy intensification or change or ICU admission or NIV)



Comment: Heterogeneity related to therapy duration
NNT: 10 (7 – 16)

Systemic steroids: Mortality



Comment: No change in mortality

Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease (Review)



Walters JAE, Gibson PG, Wood-Baker R, Hannay M, Walters EH

Hospitalization duration

2 studies (n=295 patients)

-1.22 days (CI95% -2.26 -0.18)

Adverse events (hyperglycemia, insomnia)

7 studies

OR 2.33 (CI95% 1.60-3.40)

1/6 patients

Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease (Review)



Walters JAE, Gibson PG, Wood-Baker R, Hannay M, Walters EH

Conclusions

- 1) Lower risk of treatment failure (NNT 10)
- 2) Shorter LoS
- 3) No effect on mortality
- 4) Higher risk of minor adverse event (NNH 6)
- 5) Cannot conclude about dosage (recommended 30 to 40 mg) and duration (recommended <10 days)



Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease (Review)

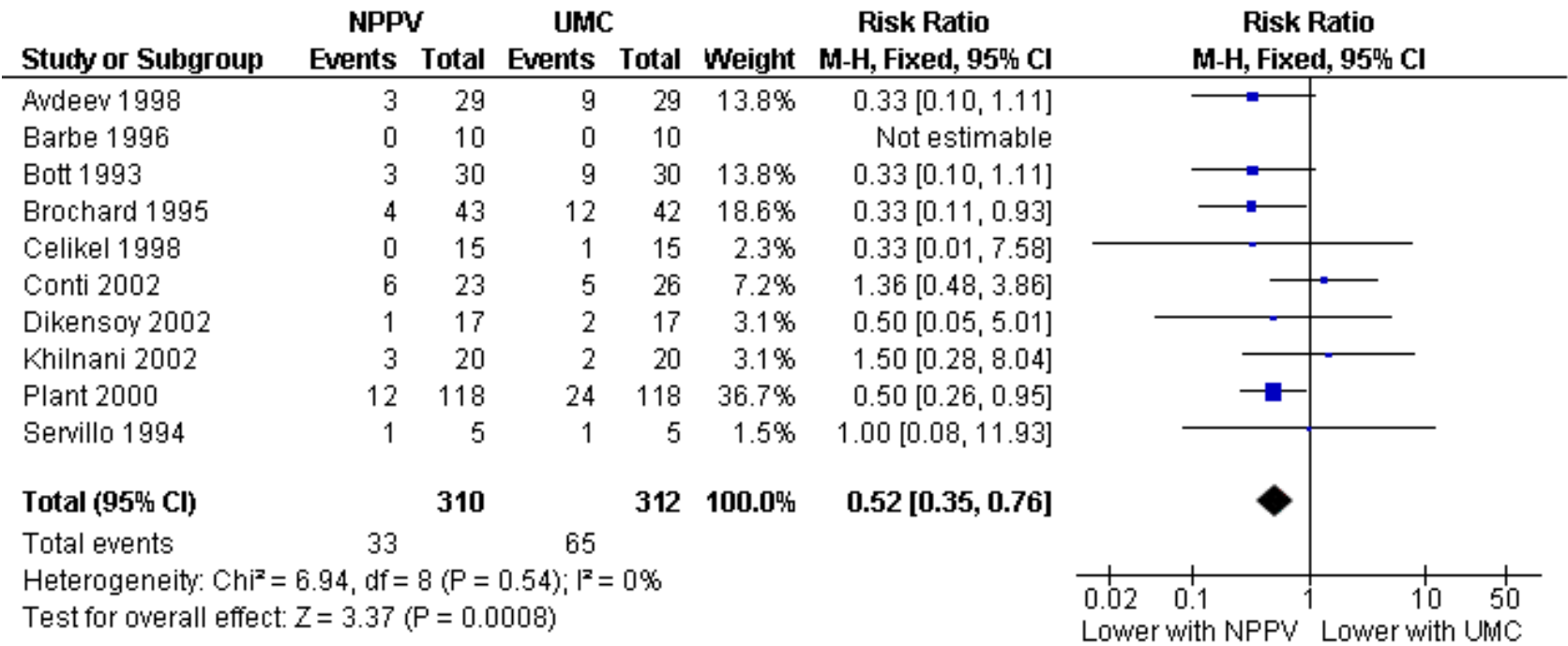
Ram FSE, Picot J, Lightowler J, Wedzicha JA

Systematic review and meta-analysis of 14 RCT (758 patients with COPD exacerbations)

Outcomes: Mortality, Intubation rate, treatment failure, pH improvement, treatment failure, duration of hospitalisation, adverse events

Non-invasive positive pressure ventilation for treatment of
respiratory failure due to exacerbations of chronic obstructive
pulmonary disease (Review)

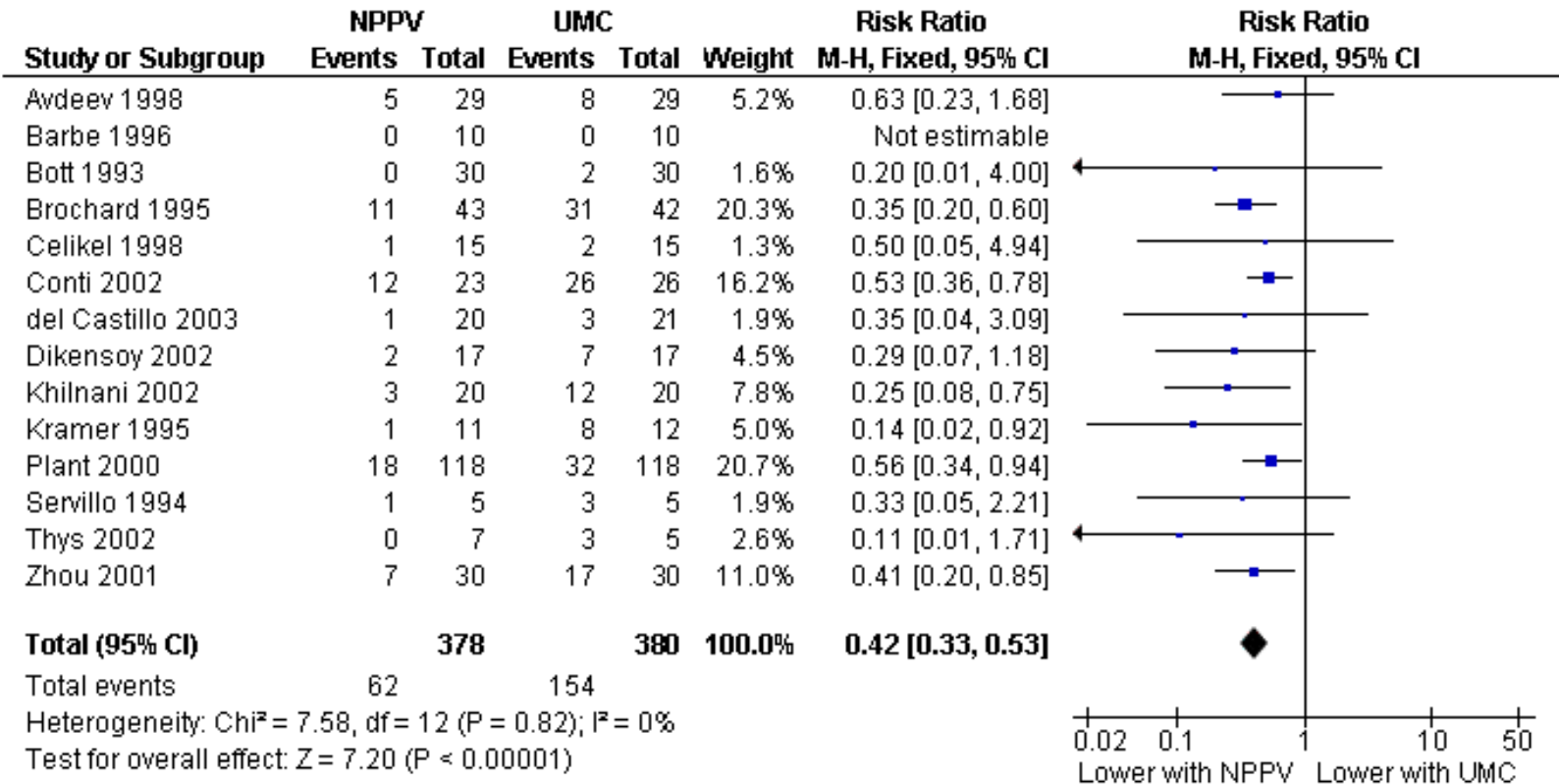
Ram FSE, Picot J, Lightowler J, Wedzicha JA



Mortality: favors NIV 0.52 (CI95% 0.35 - 0.76) NNT 10 (7 – 20)
Comments: No difference between pH subgroup (<7.30 and >=7.30)

Non-invasive positive pressure ventilation for treatment of
respiratory failure due to exacerbations of chronic obstructive
pulmonary disease (Review)

Ram FSE, Picot J, Lightowler J, Wedzicha JA



Intubation: favors NIV 0.42 (CI95% 0.33 - 0.53), NNT 4 (4 – 5)

**Non-invasive positive pressure ventilation for treatment of
respiratory failure due to exacerbations of chronic obstructive
pulmonary disease (Review)**

Ram FSE, Picot J, Lightowler J, Wedzicha JA



Studies	Outcome	Change (CI95%)
7	pH (within first hour)	0.03 (0.02 - 0.04)
7	PaCO2 (kPa)	-0.40 (-0.78 -0.03)
8	LoS (days)	-3.2 (-4.4 -2.1)

Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease (Review)

Ram FSF, Picot J, Lightowler J, Wedzicha JA



Conclusions

- 1) NIV reduces mortality, need for intubation, and LoS, improves pH and PaCO₂
- 2) No differences between pH subgroup
- 3) No differences in studies conducted in ICU or outside

Iron Lung vs Mask Ventilation in acute exacerbation of COPD: A Randomized crossover study (Intensive care med 2009)

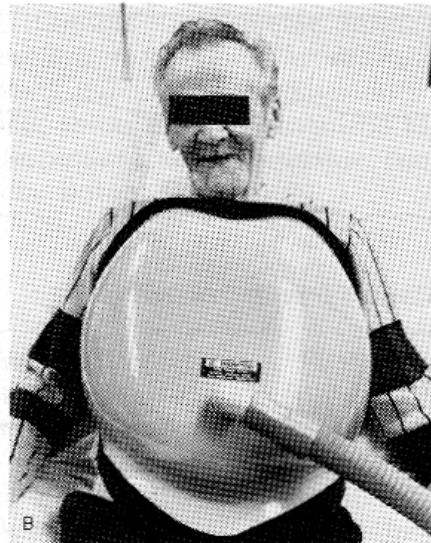
Background: NIPPV vs medical therapy: less intubation & mortality

Patients: 141 patients (PaCO_2 90 mm Hg!; pH 7.25)

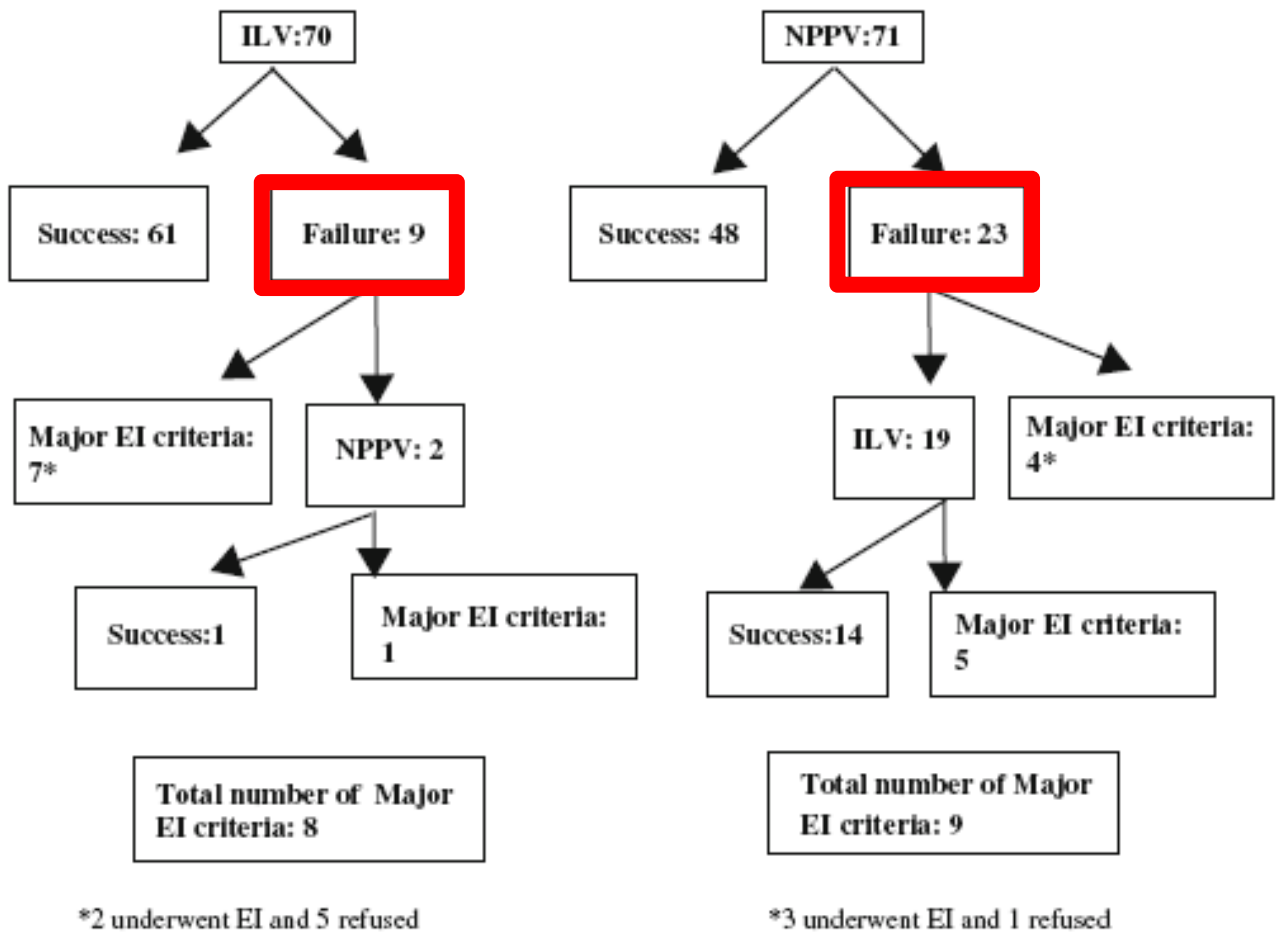
Intervention: Intermediate respiratory ICU
IRON LUNG (inspiration -30 to -40 cm & exp. 10 to 15 cm H_2O)
vs NIPPV (BiPAP EPAP 4-5 IPAP 12 to 20, goal VT 6 ml/min/kg)

Outcomes: Intubation rate, treatment failure on first treatment, LoS

Results: ...



Iron Lung vs Mask Ventilation in acute exacerbation of COPD: A Randomized crossover study (Intensive care med 2009)



Iron Lung vs Mask Ventilation in acute exacerbation of COPD: A Randomized crossover study (Intensive care med 2009)

Table 3 Complications in patients treated as first line with ILV and NPPV

	ILV	NPPV	<i>P</i>
Back pain	1	0	0.994
Treatment intolerance	5	7	0.782
Vomiting	1	1	0.843
Conjunctivitis	0	1	0.994
VAP	2	0	0.470
Abdominal hyperdistension	2	1	0.99
Skin necrosis	0	6	0.039
Gastrointestinal bleeding	3	2	0.987
Total complications	14	18	0.577

Iron Lung vs Mask Ventilation in acute exacerbation of COPD: A Randomized crossover study (Intensive care med 2009)

Conclusions:

- 1) No difference on intubation rate
- 2) IRON LUNG better on minor criteria (Respiratory rate >35 , pH below 7.3 or deteriorating, decreasing Glasgow)
- 3) No skin necrosis on IRON LUNG

Comments:

Very experienced team; Failure of treatment not blinded (Bias?)

A multicenter RCT of NIV with Helium-oxygen mixture in exacerbations of COPD (Critical Care med 2010)

Background: Heliox (He 65%, O₂ 35%) density lower than air oxygen. Work of breathing reduced. However no proven clinical efficacy.

Patients: 204 patients (PaCO₂ 73 mm Hg)

Intervention: ICU
NIV (EPAP 5 IPAP 17 to 20, FIO₂ 35%, >6h/day)
vs NIV + heliox (idem + heliox)

Outcomes: Intubation rate, treatment failure, LoS, mortality

Results: ...

A multicenter RCT of NIV with Helium-oxygen mixture in exacerbations of COPD (Critical Care med 2010)

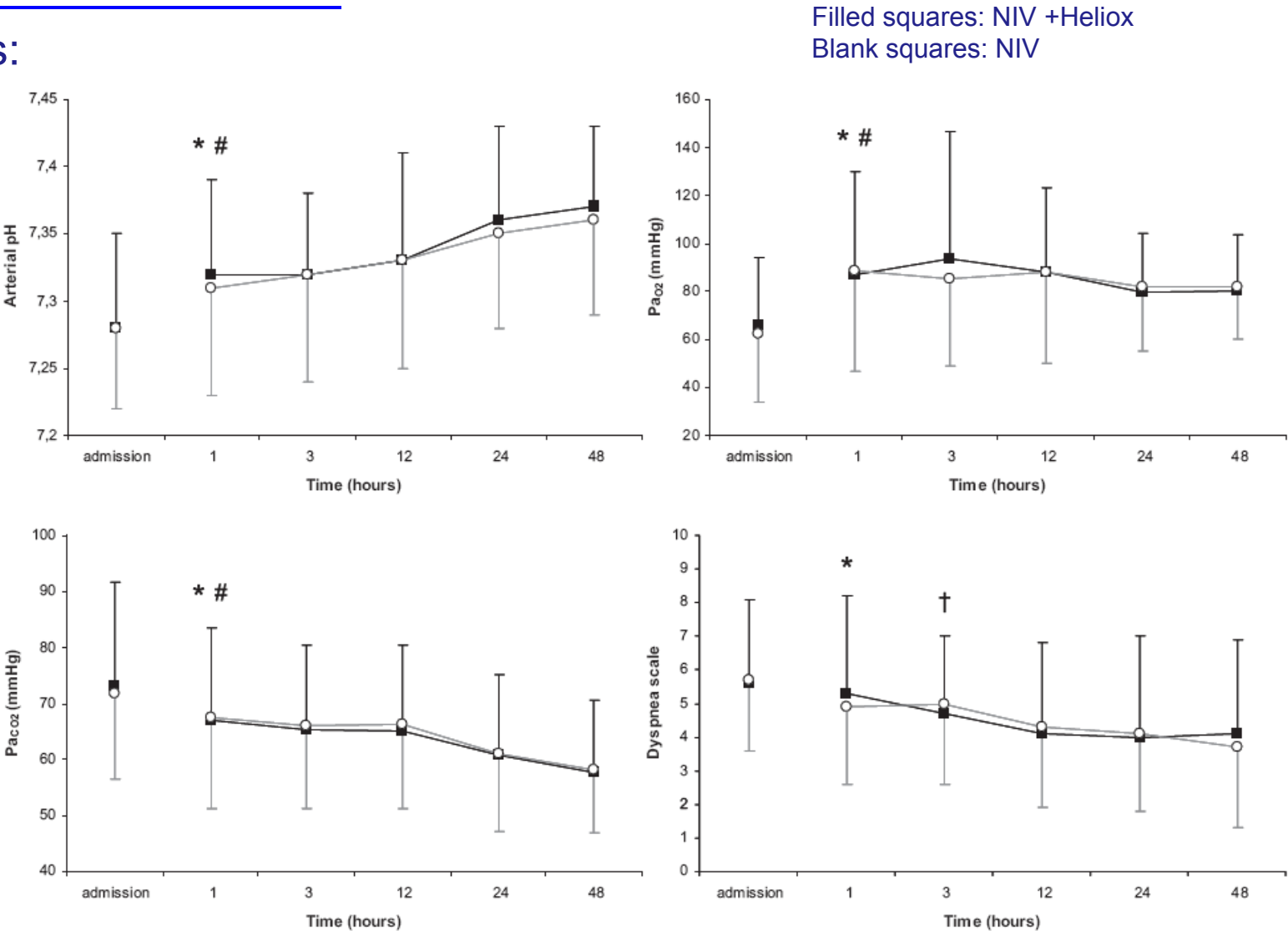
Results:

Table 2. Comparison of outcomes in the two study groups

	Noninvasive Ventilation, HeO ₂ Group (n = 102)	Noninvasive Ventilation, Air-Oxygen Group (n = 102)	<i>p</i>
Duration of noninvasive ventilation, days	3.8 ± 2.9	4.2 ± 3.0	.3
Intubated patients, n; %	25; 24.5	31; 30.4	.35
Time to intubation, days	2.4 ± 1.8	4.6 ± 6.9	.09

A multicenter RCT of NIV with Helium-oxygen mixture in exacerbations of COPD (Critical Care med 2010)

Results:



A multicenter RCT of NIV with Helium-oxygen mixture in exacerbations of COPD (Critical Care med 2010)

Conclusions:

- 1) Similar intubation rate
- 2) Similar LoS and mortality

Comments:

The largest clinical study on heliox, however negative.
« Physiologically sound, clinically useless »

Substitutive « hospital at Home » vs inpatient care for elderly patients with exacerbations of COPD: A randomized controlled trial (A multicenter RCT of NIV with Helium-oxygen mixture in exacerbations of COPD (Journal of the Am Geriatric Soc 2008))

Background: Hospital admission are costly, impacts QoL and maybe dangerous. Effect of Hospital at home on mortality, re-admission rate unknown.

Patients: 104 patients in Emergency Dep., >75 year-old (FEV₁ 42% pred, PaCO₂ 45, pH 7.40)

Intervention: hospital at home after ED evaluation (2 Geriatricians, 1 nurses) vs General Ward

Outcomes: Mortality and readmission rate at 6 months, costs

Results: ...

Substitutive « hospital at Home » vs inpatient care for elderly patients with exacerbations of COPD: A randomized controlled trial
(Journal of the Am Geriatric Soc 2008)

Table 3. Treatments Received by Study Participants

Treatment	Geriatric Home Hospitalization Service (n = 52)	General Medical Ward (n = 52)	P-Value
	n (%)		
Oxygen therapy	30 (58)	38 (73)	.55
Intravenous antibiotics	40 (77)	39 (75)	.95
Intravenous steroids	23 (44)	27 (52)	.77
Beta-agonist bronchodilators	20 (39)	25 (48)	.66
Anticholinergic bronchodilators	26 (50)	21 (40)	.67

Substitutive « hospital at Home » vs inpatient care for elderly patients with exacerbations of COPD: A randomized controlled trial
(Journal of the Am Geriatric Soc 2008)

At 6 months	Hospital at home	General Medical Ward	P value
Readmitted (%)	42	87	.001
Mortality (%)	17	23	0.72
Days to readmission (mean, SD)	78 (55)	37 (29)	.005
Total Costs Costs per day	1176 \$ 101 \$	1391 \$ 152 \$	0.38 0.002
Length of « stay » (mean, SD)	15.5 (9.5)	11.0 (7.9)	0.01

Substitutive « hospital at Home » vs inpatient care for elderly patients with exacerbations of COPD: A randomized controlled trial (Journal of the Am Geriatric Soc 2008)

Conclusions:

- 1) For selected COPD exacerbations, Hospital at home is safe
- 2) At 6 months, lower readmission rate, better QoL
- 3) Lower health care costs
- 4) Similar mortality

Comments:

Effect of geriatric assessment may confound the results.
« Clinical unit » do not exist in CH.

Exacerbation de BPCO

Conclusions 2010

- 1) BPCO dans la population CH de 40 à 70 ans: ~ 5% (lég. plus basse qu'ailleurs)
- 2) Antibiothérapie: à proposer. Pro-CT acceptable en milieu hospitalier.
- 3) Corticothérapie: à proposer.
- 4) VNI: à proposer si $\text{pH} < 7.35$ et $\text{PaCO}_2 > 6$.
 - a) Heliox (pas de preuves d'efficacité)
 - b) Pression négative (possible avantage par des groupes expérimentés)
- 5) Soins intégrés: études prometteuses