Maintenance ICS in severe COPD: Can reduce exacerbation of COPD?

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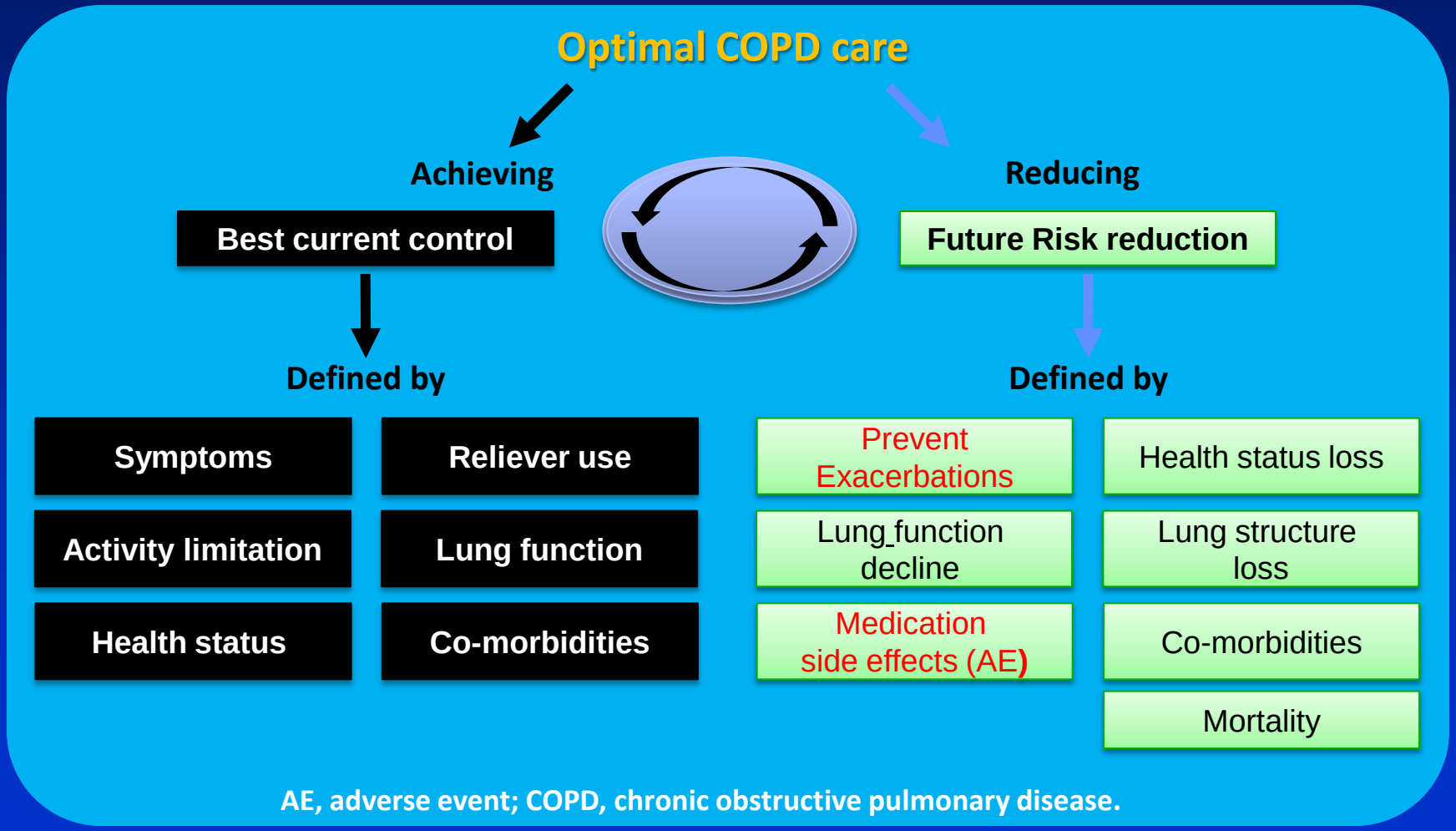
질문

- 67세 남자로 호흡곤란으로 내원 2011년 COPD(emphysematous type) 진단받은 분으로 폐기능 검사상 FEV1 0.9L(32%) FVC/FEV1 60%, CAT score 22점, mMRC 2 인 환자로 흡입약제로 Tiotropium+fluticasone+salmeterol 의 흡입약제로 triple Tx를 사용하는 분입니다.

  향후 이 환자의 장기간 치료 계획으로 생각하는 것을 선택해 주세요

1. 지속적으로 Triple Tx 를 사용할 것이다
2. ICS를 step down 하면서 제외하고 나머지 LAMA, LABA,LABA+LAMA 를 사용할 것이다.

The Goal of COPD Management



AE, adverse event; COPD, chronic obstructive pulmonary disease.

Adapted from: Postma et al. Prim Care Respir J 2011 & GOLD 2011

Ideal Characteristics of COPD Drugs

- Reduces symptoms
- Improves lung function
- Reduces exacerbations & hospitalizations
- Relatively free of side effects
- Prolongs survival

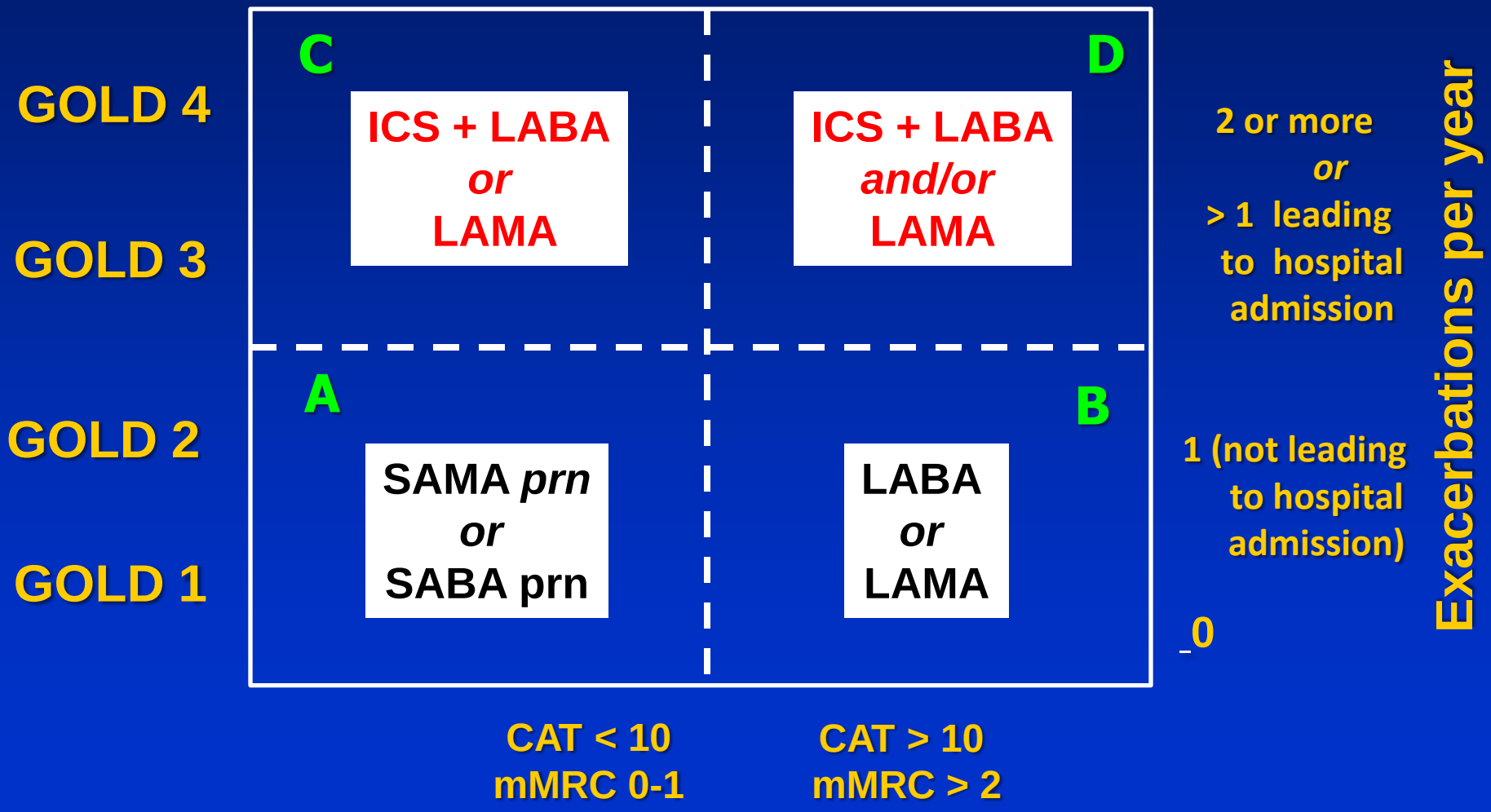
Global Strategy for Diagnosis, Management and Prevention of COPD
Therapeutic Options: Inhaled Corticosteroids

- Regular treatment with inhaled corticosteroids improves symptoms, lung function and quality of life and reduces frequency of exacerbations for COPD patients with an FEV_1 < 60% predicted.
- Inhaled corticosteroid therapy is associated with an increased risk of pneumonia.
- Withdrawal from treatment with inhaled corticosteroids may lead to exacerbations in some patients.

Global Strategy for Diagnosis, Management and Prevention of COPD

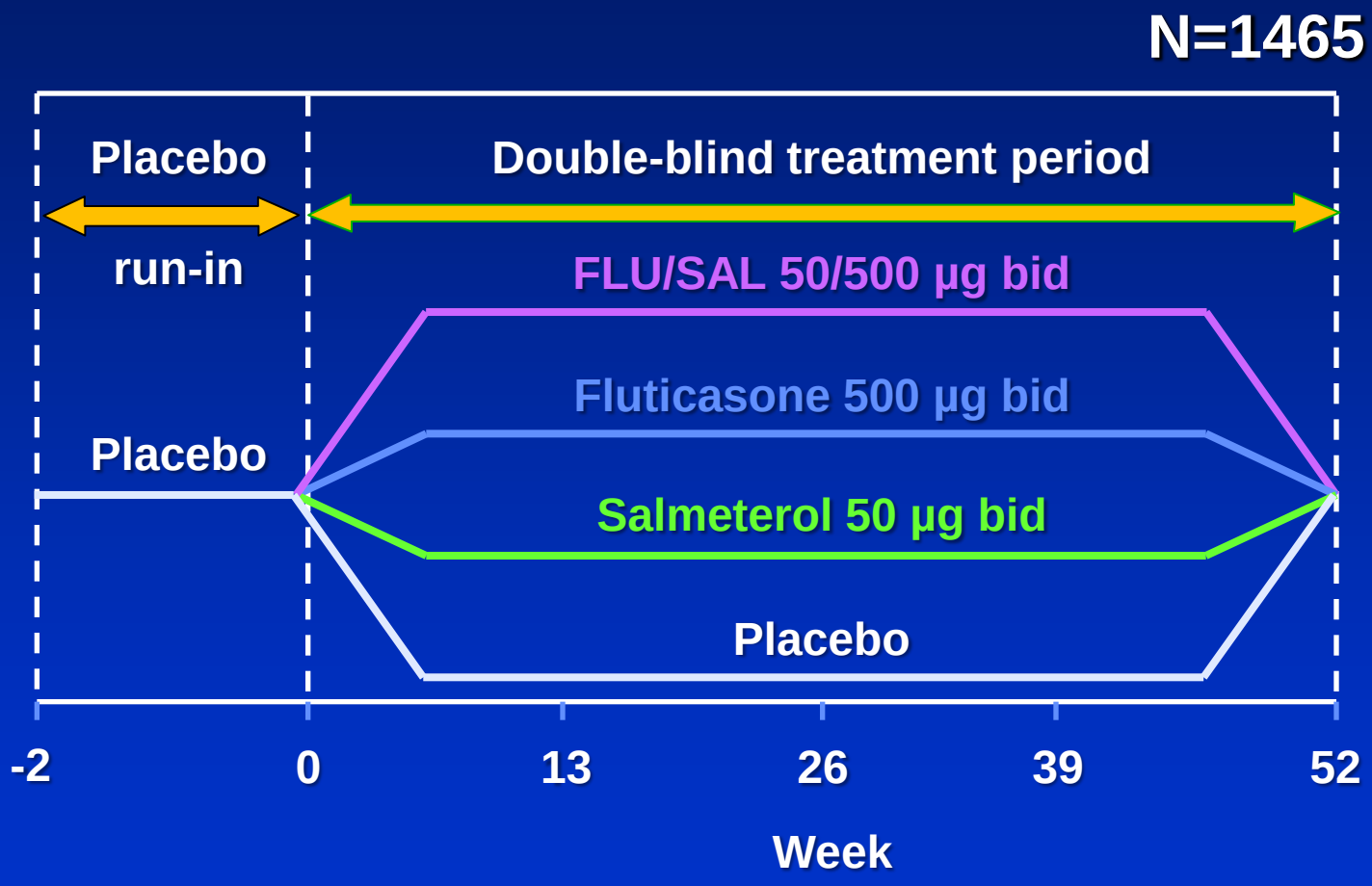
Manage Stable COPD: Pharmacologic Therapy

RECOMMENDED FIRST CHOICE



ICS/LABA

TRISTAN study design



Calverley et al, Lancet 2003

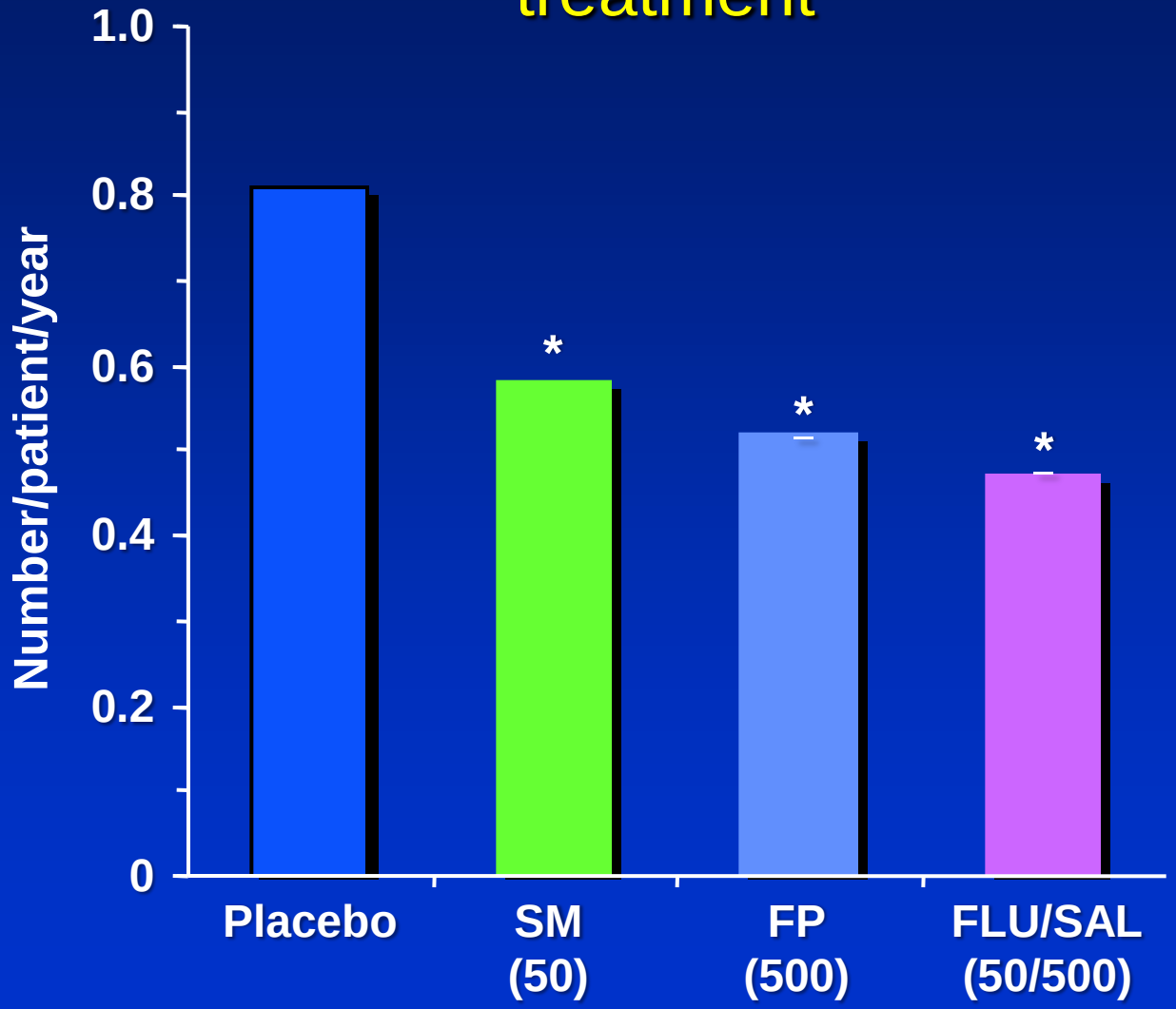
Primary Outcome

- The primary outcome was the pretreatment FEV1 after 12 months treatment and after patients had abstained from all bronchodilators for at least 6 h and from study medication for at least 12 h.

- Exacerbations: a worsening of COPD symptoms that required treatment with antibiotics, oral corticosteroids, or both

Calverley et al, Lancet 2003

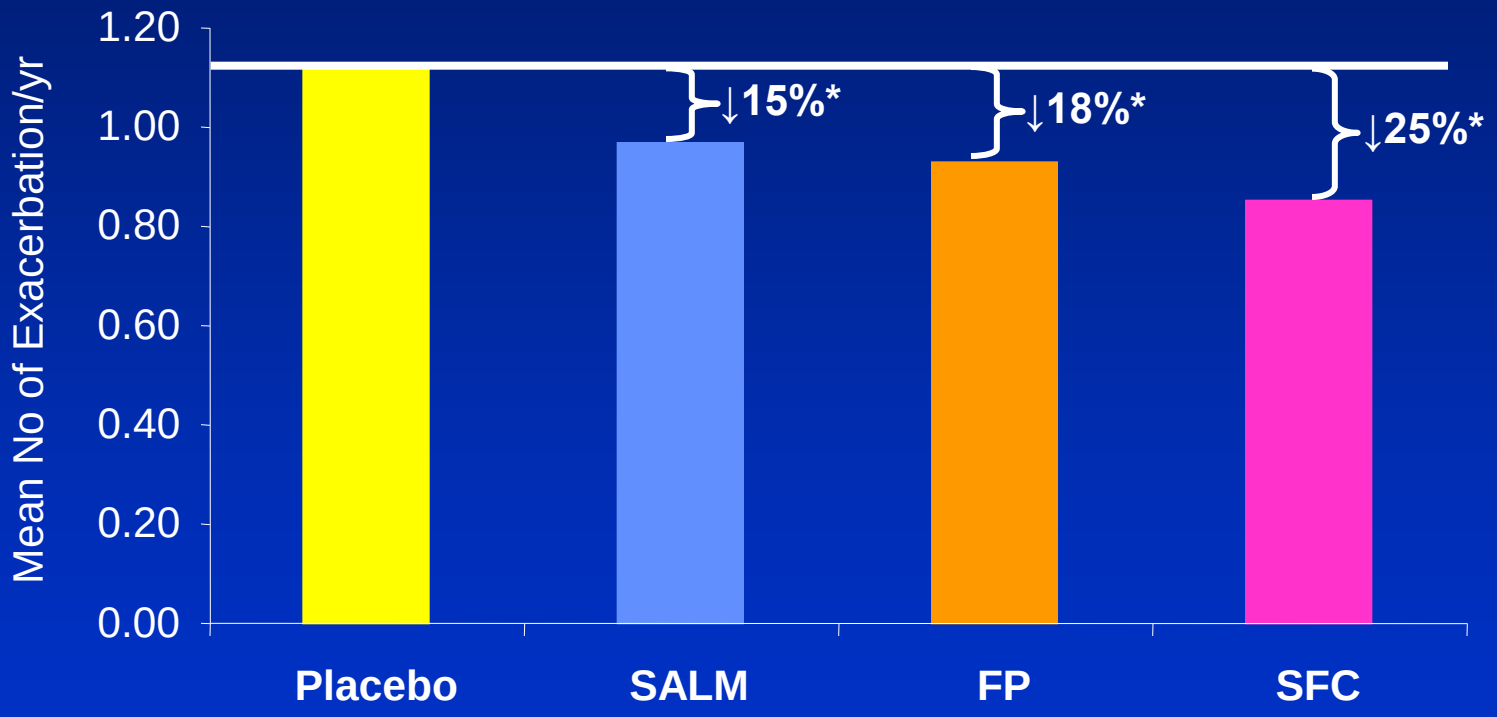
The effect of combination therapy on exacerbations requiring oral corticosteroid treatment



*p<0.001 vs placebo

Calverley et al, Lancet 2003

SFC Reduces Exacerbations



*P<0.05

Calverley et al NEJM 2007

TORCH

3-yr Trial
SFC (50/500 bid) vs FP (500 bid) vs
SALM (50 bid) vs placebo

Age, 65; FEV_1, <60% of predicted

The NEW ENGLAND JOURNAL of MEDICINE

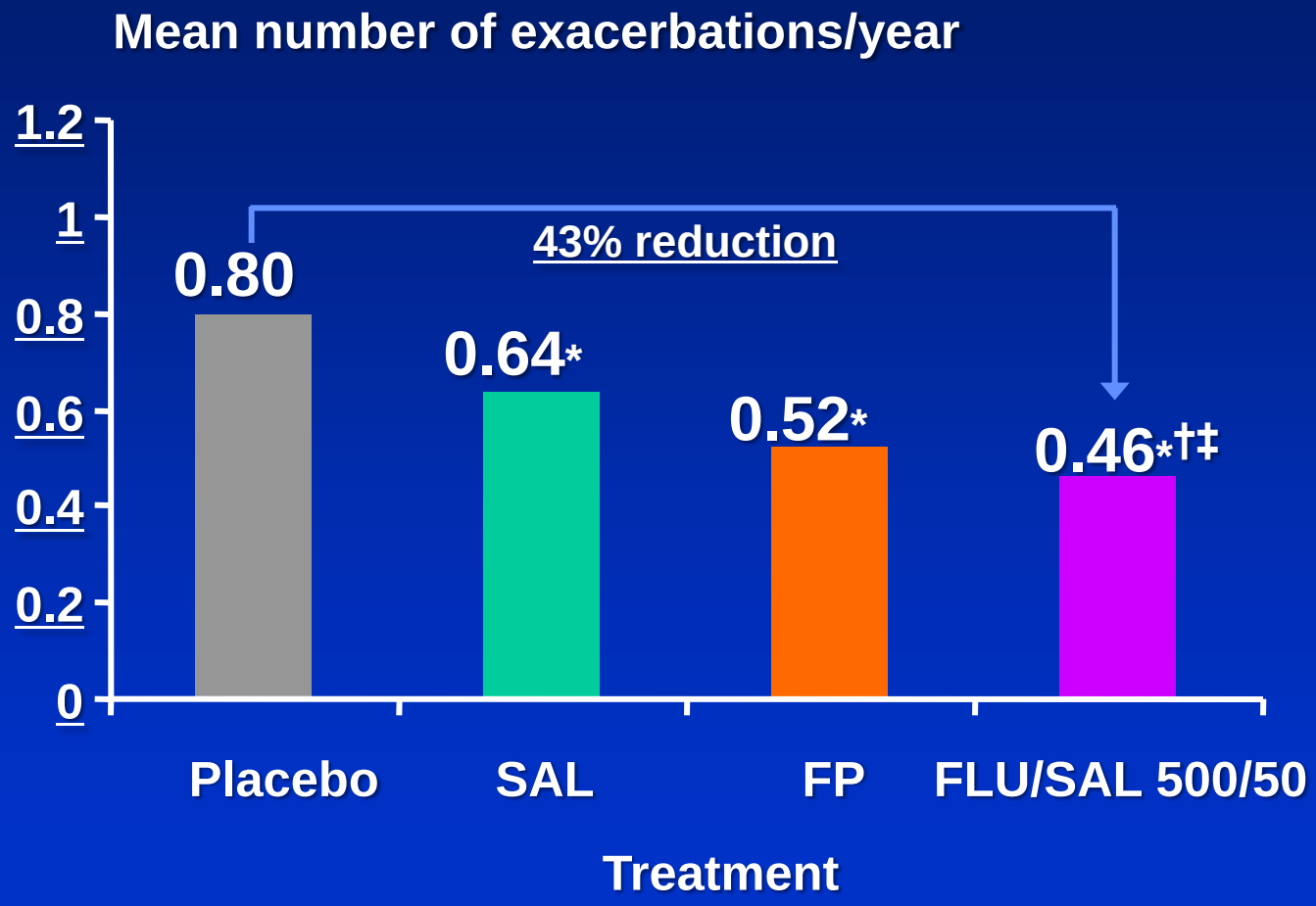
ESTABLISHED IN 1812 FEBRUARY 22, 2007 VOL. 356 NO. 8

Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

Peter M.A. Calverley, M.D., Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D., Paul W. Jones, M.D., Julie C. Yates, B.S., and Jørgen Vestbo, M.D., for the TORCH investigators*

N Engl J Med 2007;356:775-89.

Rate of exacerbations requiring systemic corticosteroids



*p < 0.001 vs placebo;
†p < 0.001 vs SAL; ‡p = 0.017 vs FP

Carlverley PM. NEJM 2007;356:775

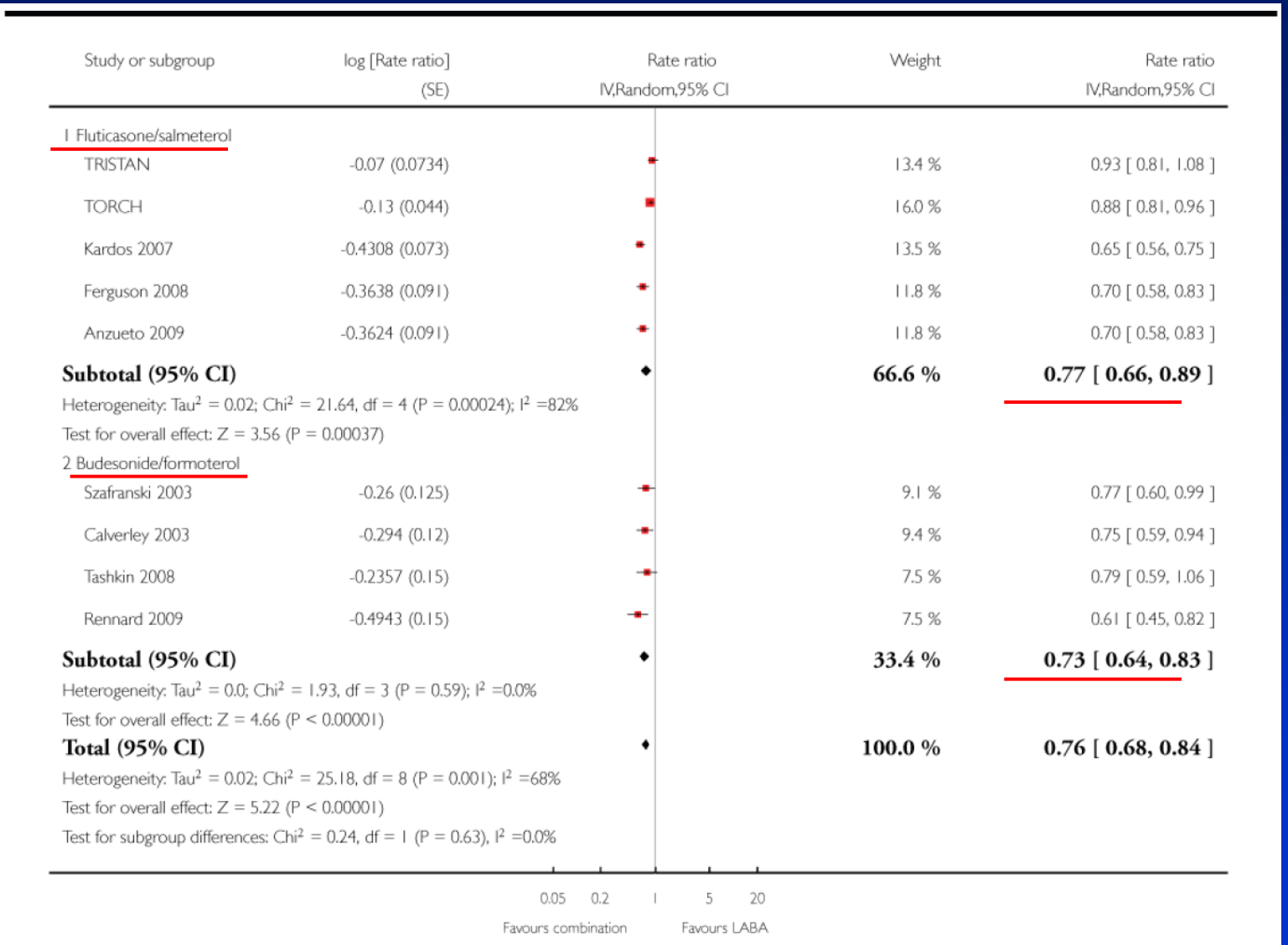
Efficacy analysis for exacerbation Annual rate	Placebo Group (N=1524)	Salmeterol Group (N=1521)	Fluticasone Group (N=1534)	Combination-Therapy Group (N=1533)		Rate Ratio (95% CI)	
Moderate or severe	1.13	0.97	0.93	0.85	Combination therapy vs. placebo	0.75 (0.69–0.81)	<0.001
					Combination therapy vs. salmeterol	0.88 (0.81–0.95)	0.002
					Combination therapy vs. fluticasone propionate	0.91 (0.84–0.99)	0.02
					Salmeterol vs. placebo	0.85 (0.78–0.93)	<0.001
					Fluticasone propionate vs. placebo	0.82 (0.76–0.89)	<0.001
Requiring systemic corticosteroids	0.80	0.64	0.52	0.46	Combination therapy vs. placebo	0.57 (0.51–0.64)	<0.001
					Combination therapy vs. salmeterol	0.71 (0.63–0.79)	<0.001
					Combination therapy vs. fluticasone propionate	0.87 (0.78–0.98)	0.02
					Salmeterol vs. placebo	0.80 (0.72–0.90)	<0.001
					Fluticasone propionate vs. placebo	0.65 (0.58–0.73)	<0.001
Severe (requiring hospitalization)	0.19	0.16	0.17	0.16	Combination therapy vs. placebo	0.83 (0.71–0.98)	0.03
					Combination therapy vs. salmeterol	1.02 (0.87–1.20)	0.79
					Combination therapy vs. fluticasone propionate	0.95 (0.82–1.12)	0.56
					Salmeterol vs. placebo	0.82 (0.69–0.96)	0.02
					Fluticasone propionate vs. placebo	0.88 (0.74–1.03)	0.10

* Only the primary comparison was adjusted because interim analyses were performed. Unadjusted data for the primary end point are provided for comparison.
† The adjusted probability of death was calculated with the use of a Cox proportional-hazards model.
‡ Cause of death was adjudicated by the clinical end-point committee.

Carlverley PM. NEJM 2007;356:775

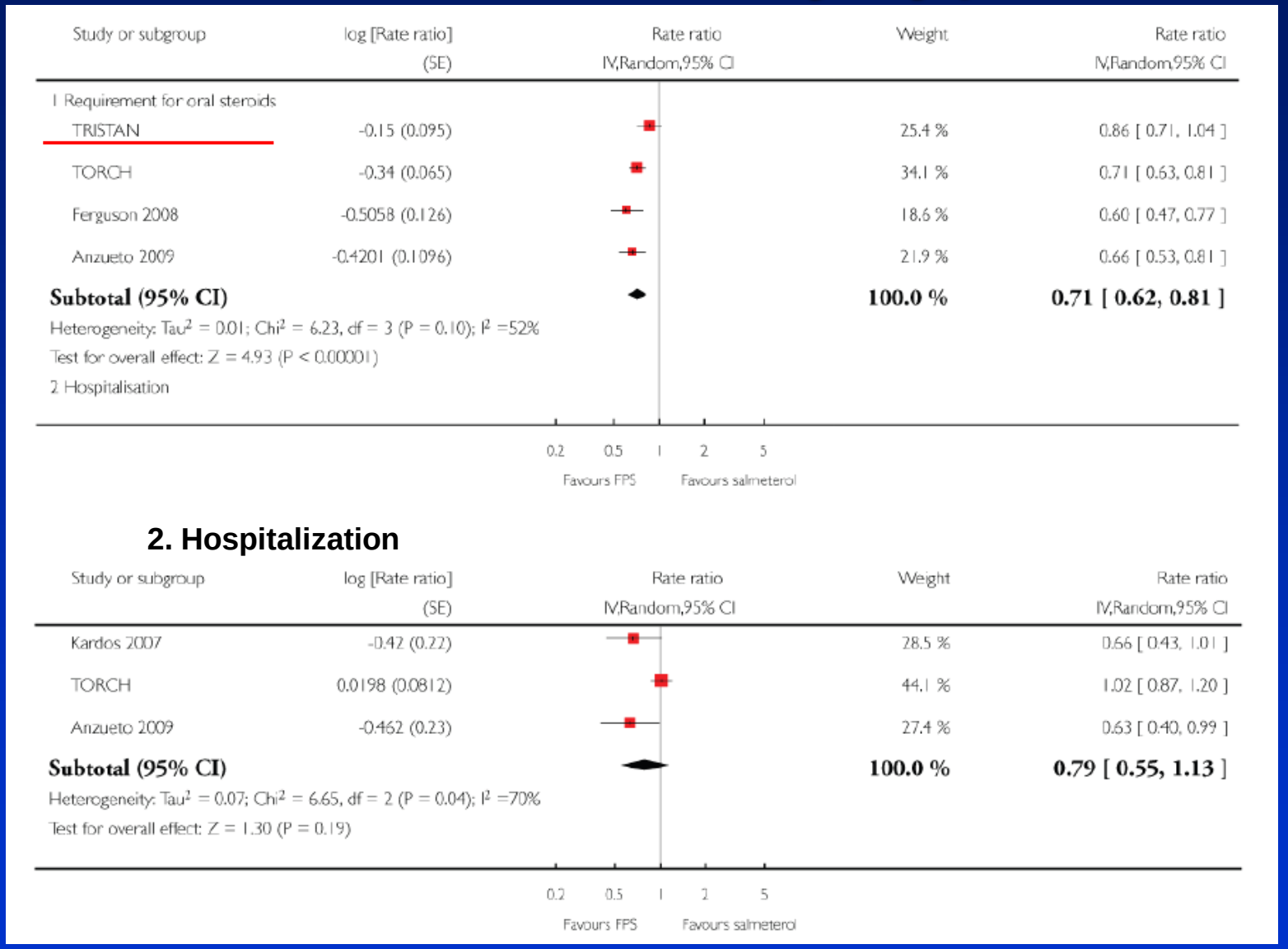
Meta-analysis of ICS/LABA vs. LABA

Exacerbations rates
(per person per year)



Nannini LJ, Cochrane Database Syst Rev. 2013;8

Exacerbation by type



2. Hospitalization

Nannini LJ, Cochrane Database Syst Rev. 2013;8

How about long-acting anticholinergic (tiotropium)?

UPLIFT study

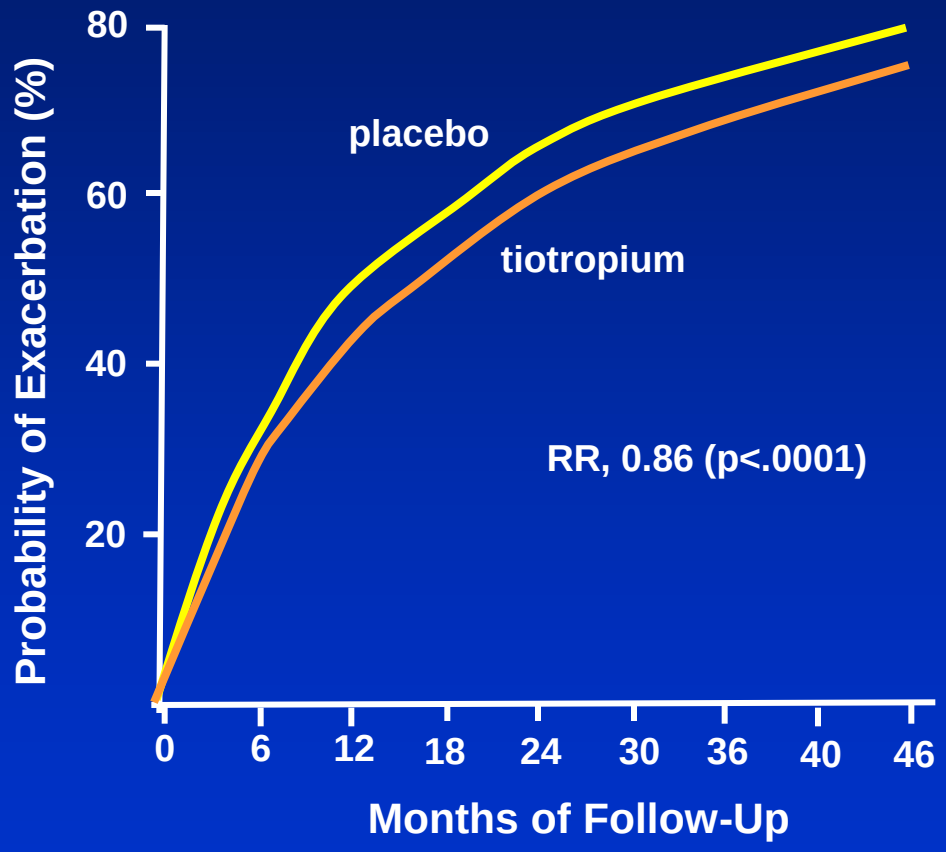
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 9, 2008 VOL. 359 NO. 15

A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

Donald P. Tashkin, M.D., Bartolome Celli, M.D., Stephen Senn, Ph.D., Deborah Burkhart, B.S.N., Steven Kesten, M.D., Shailendra Menjoge, Ph.D., and Marc Decramer, M.D., Ph.D., for the UPLIFT Study Investigators*

Tiotropium Reduces Exacerbation



Tashkin et al.NEJM 2008;359:1543-54

Table 3. Exacerbations of COPD and Related Hospitalizations.*

Variable	Tiotropium	Placebo	Relative Risk for Tiotropium vs. Placebo (95% CI)	P Value
Exacerbation†				
Per patient-year — no.	0.73±0.02	0.85±0.02	0.86 (0.81–0.91)	<0.001
Leading to hospitalization — no. per patient-year	0.15±0.01	0.16±0.01	0.94 (0.82–1.07)	0.34
Days per patient-year	12.11±0.32	13.64±0.35	0.89 (0.83–0.95)	0.001
Hospitalization days per patient-year	3.17±0.17	3.13±0.17	1.01 (0.87–1.18)	0.86

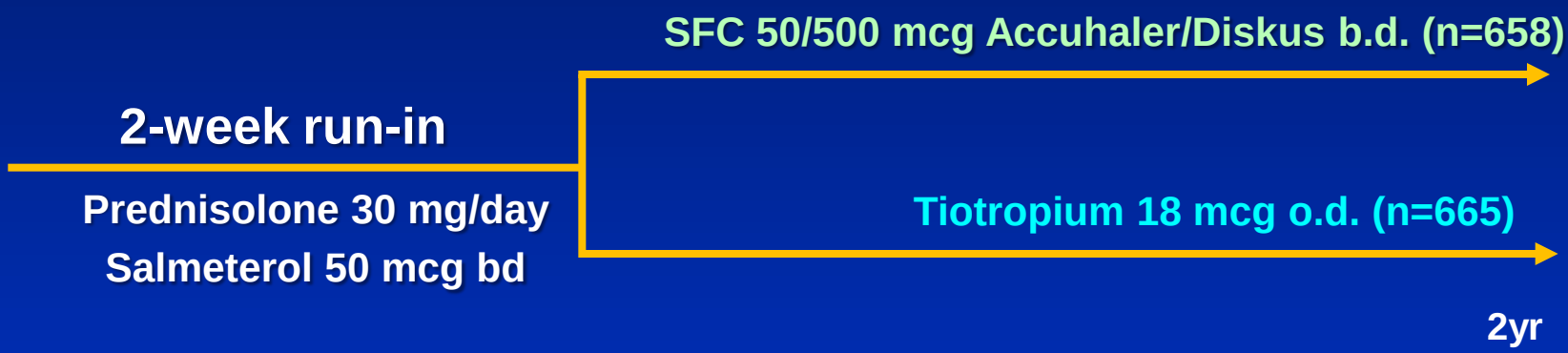
How about tiotropium
vs
SFC?

INSPIRE

2-yr Trial
SFC (50/500 bid) vs Tiotropium (18 ug QD)

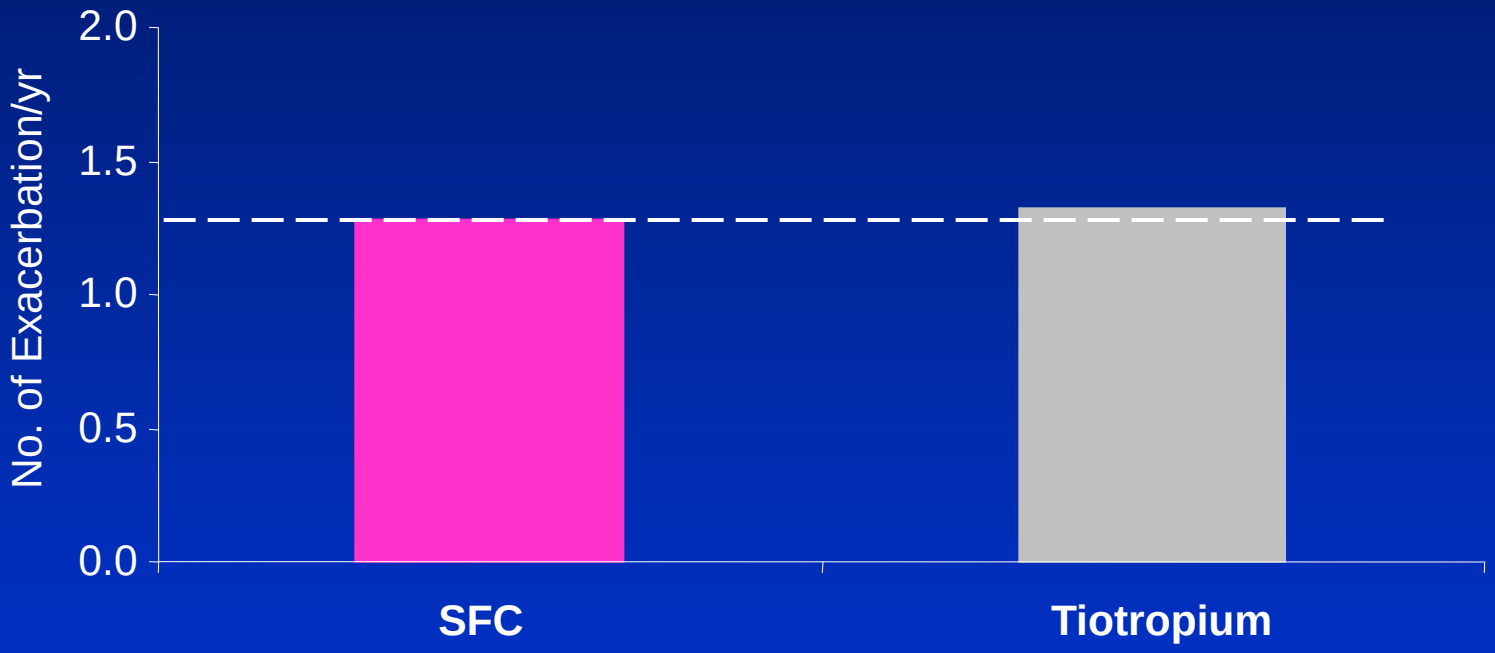
Age, 64; FEV_1, 50-80% of predicted (GOLD2)

INSPIRE study design



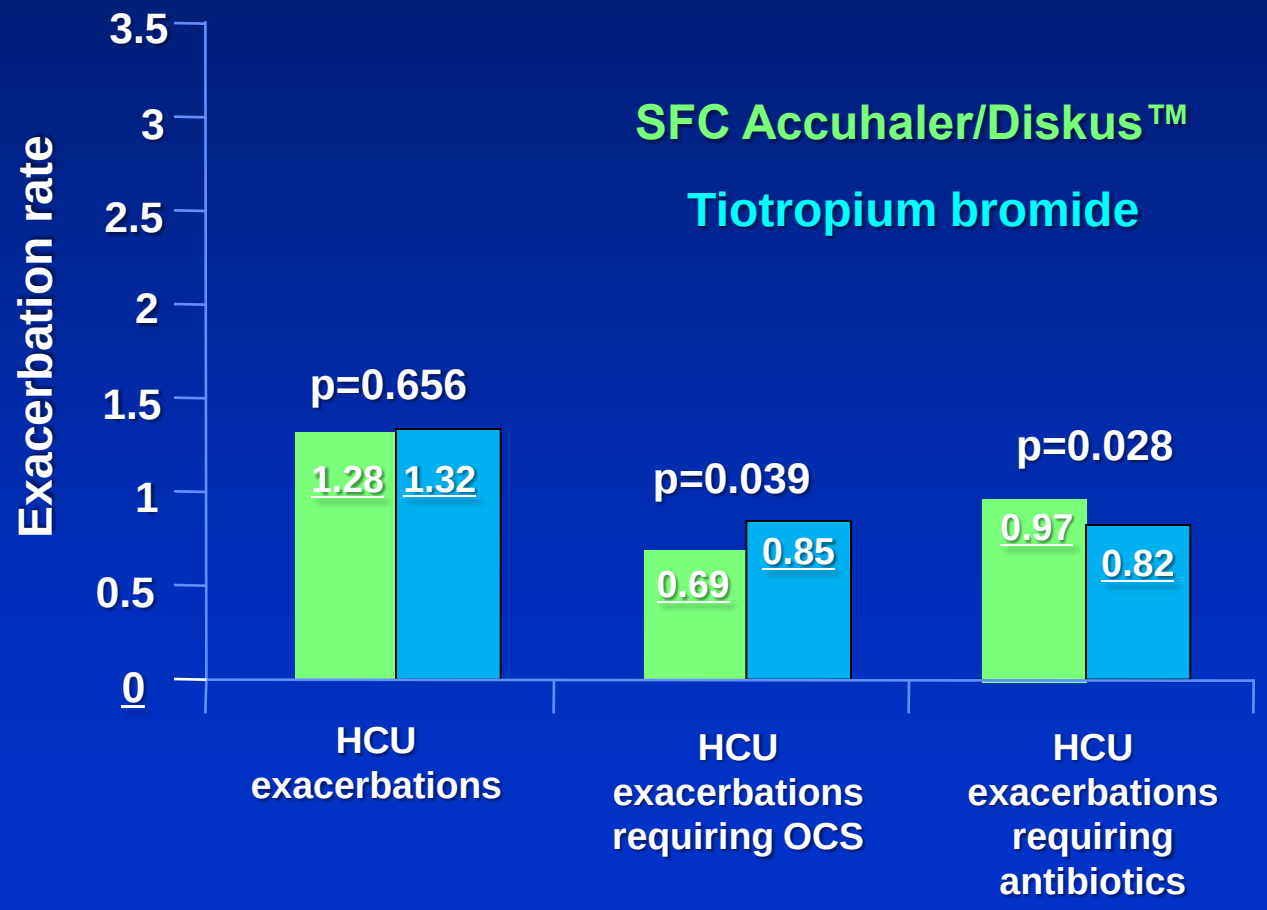
Wedzicha JA et al. Am J Crit Care Med 2008; 177: 19–26

No Difference Between SFC vs Tio In Exacerbation



INSPIRE

SFC healthcare utilisation exacerbation rates



Wedzicha JA et al. *Am J Crit Care Med* 2008; 177: 19–26.

Triple therapy vs. LAMA

CLIMB vs. OPTIMAL,

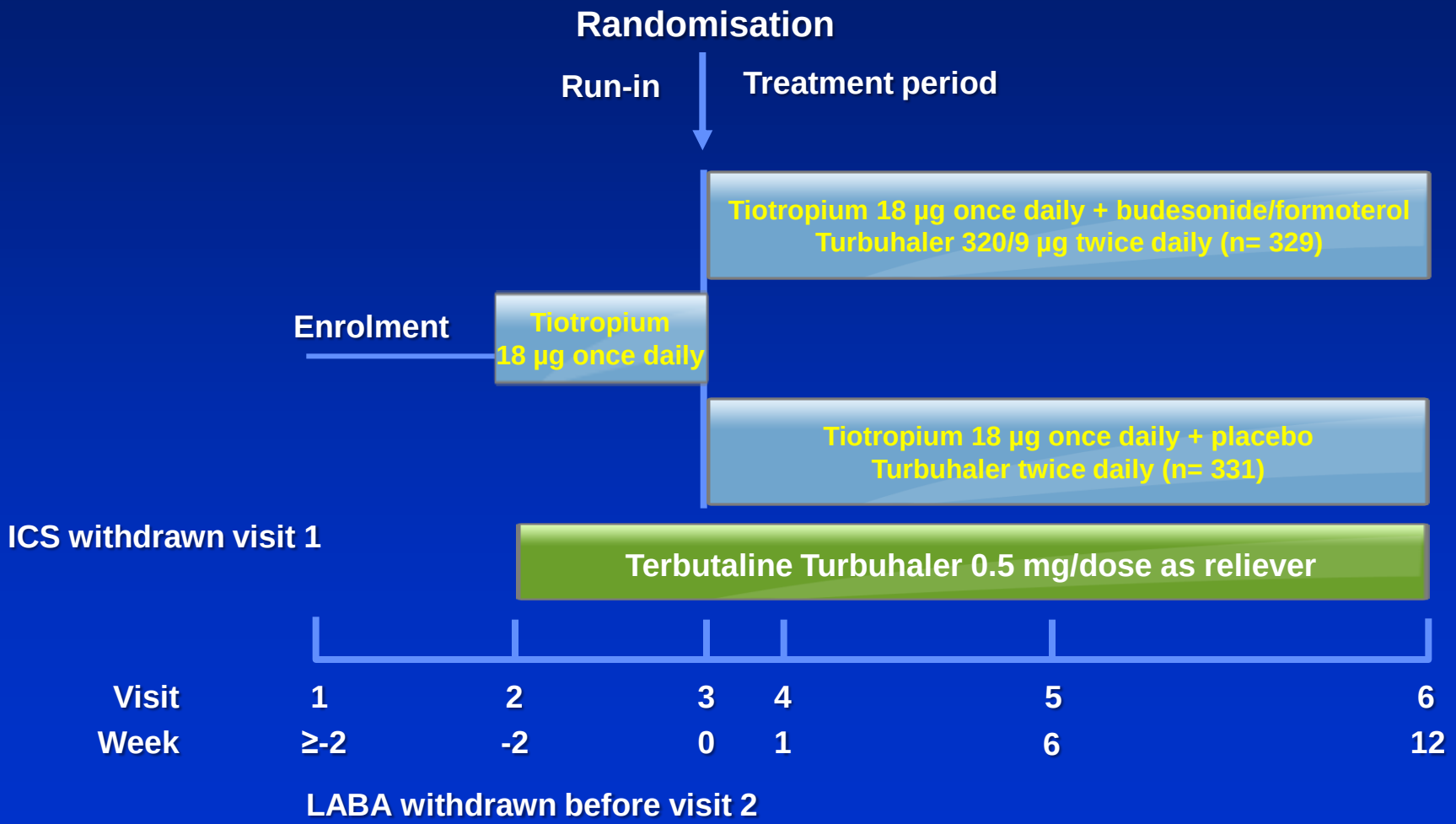
CLIMB study

- N=660
- Primary endpoint
  - **Change in morning pre-dose FEV_1** from randomisation to study completion assessed by spirometry at each clinic visit (weeks 1, 6 and 12)
- Secondary endpoints
  - Morning pre- and post-dose spirometry measurements (pre-dose FVC and IC, and post-dose FEV_1, FVC and IC)
  - Morning PEF
  - GSSQ
  - SGRQ-C
  - First to severe exacerbation
- Severe exacerbations were defined as worsening of COPD requiring systemic corticosteroids (oral or parenteral) and/or hospital/emergency room visits

Welte T et al. Am J Respir Crit Care Med 2009; 180: 741–750

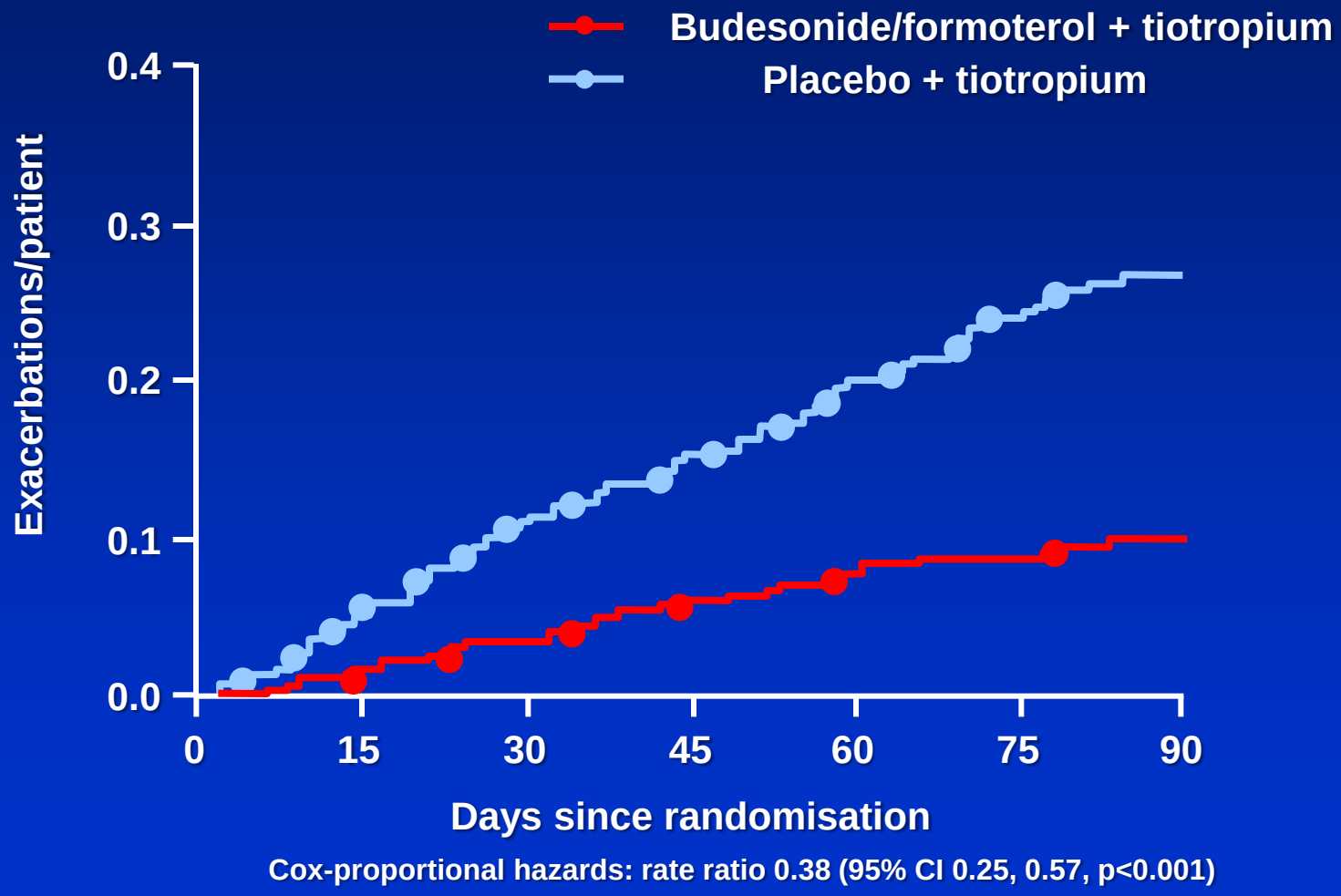
The CLIMB study design

A 12-week randomised double-blind parallel-group study



Welte T et al. Am J Respir Crit Care Med 2009; 180: 741–750.

Rate of severe exacerbations reduced by 62% with budesonide/formoterol plus tiotropium compared with tiotropium alone



Cox-proportional hazards: rate ratio 0.38 (95% CI 0.25, 0.57, p<0.001)

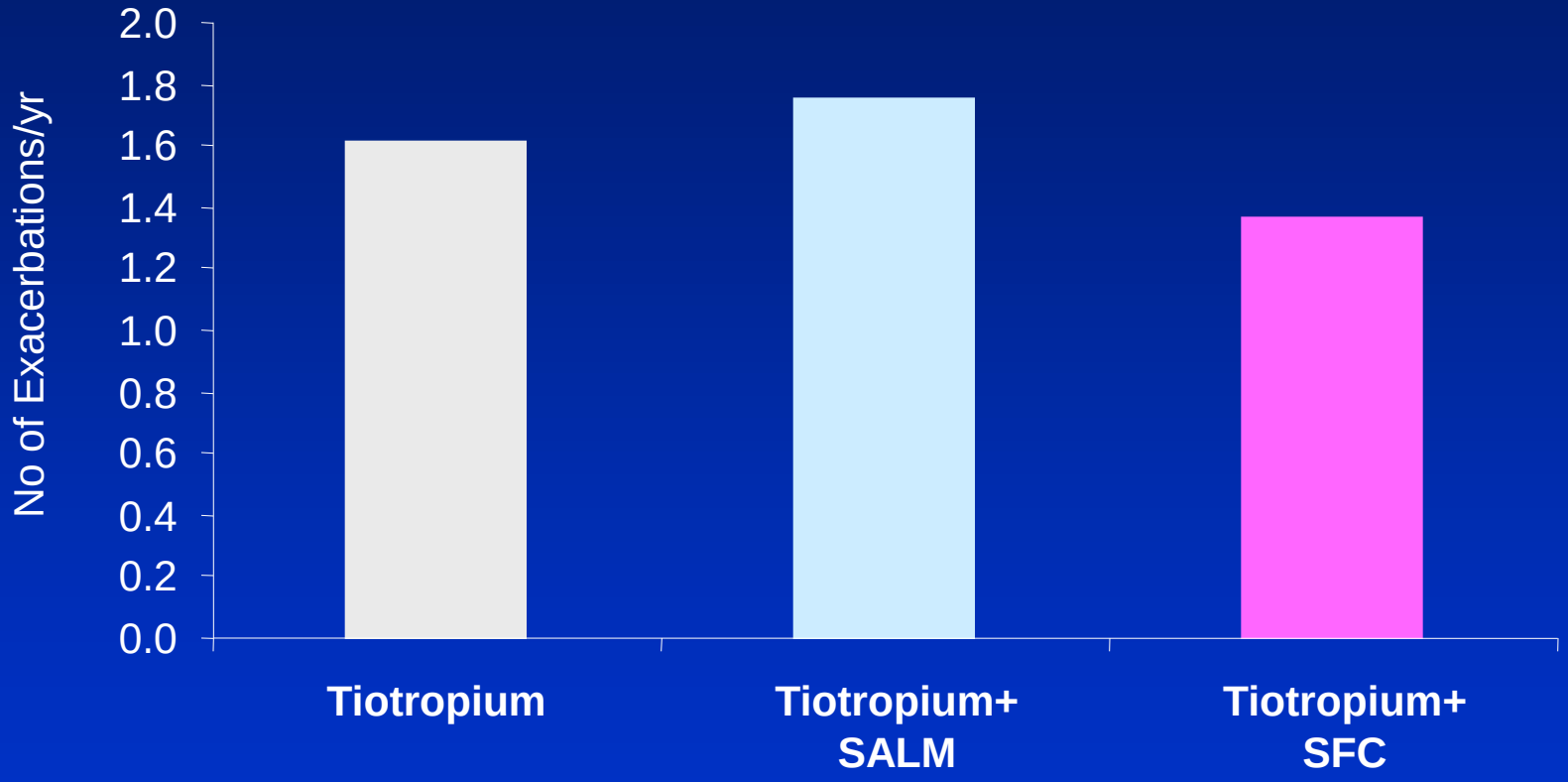
Welte T et al. Am J Respir Crit Care Med 2009; 180: 741–750

Canadian OPTIMAL Study

- Treatment arm
  a. Tiotropium 18 μg od
  b. Tiotropium 18 μg od and Salmeterol 50 μg bid
  c. Tiotropium 18 μg od and Flu/ Sal 500 / 50 μg bid
- Duration: 12 months
- N: 449 (Mean FEV1: 38%)
- Key endpoint: Proportion of COPD exacerbation / number of COPD exacerbations, urgent visits to a health care provider or ED, hospitalizations,HRQL, symptoms, lung function
- Exacerbation: physician-directed, short-term use of oral or intravenous steroids, oral or intravenous antibiotics, or both therapies.

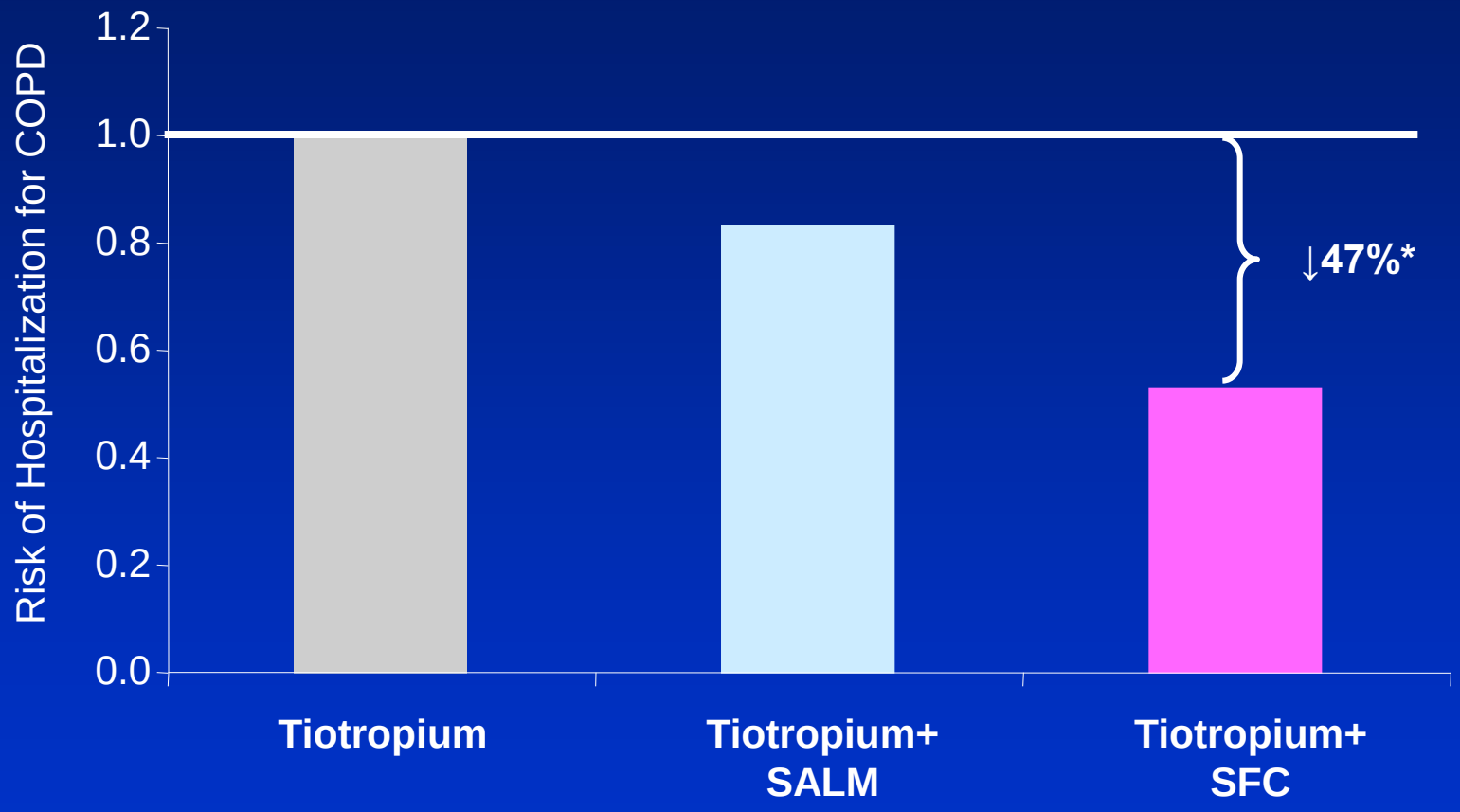
Aaron et al. Ann Int Med 2007;146:545-55

Exacerbations



Aaron et al. OPITMAL 2007

Hospitalizations for COPD



*P<0.05

Aaron et al. OPITMAL 2007

Meta analysis of triple therapy vs. LAMA

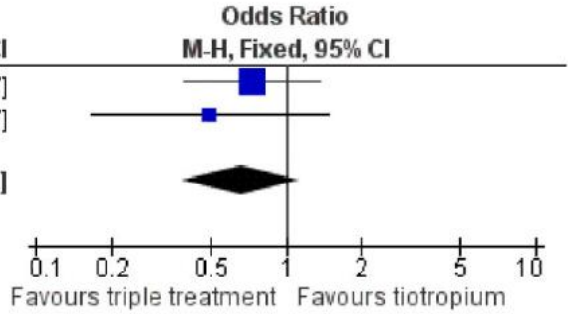
Triple vs. tiotropium

Hospital admission (exacerbation)

Study or Subgroup	tiotropium+LABA/ICS Events	Total	tiotropium+placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aaron 2007	20	145	28	156	70.3%	0.73 [0.39, 1.37]
Welte 2009	5	329	10	331	29.7%	0.50 [0.17, 1.47]
Total (95% CI)		**474**		**487**	**100.0%**	**0.66 [0.39, 1.13]**
Total events	25		38			

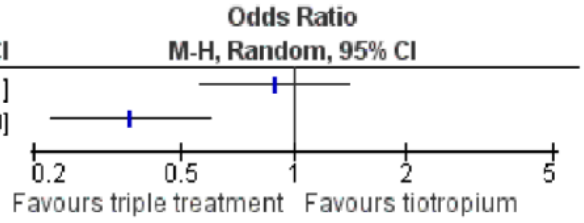
Heterogeneity: Chi² = 0.37, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.50 (P = 0.13)

OPTIMAL CLIME



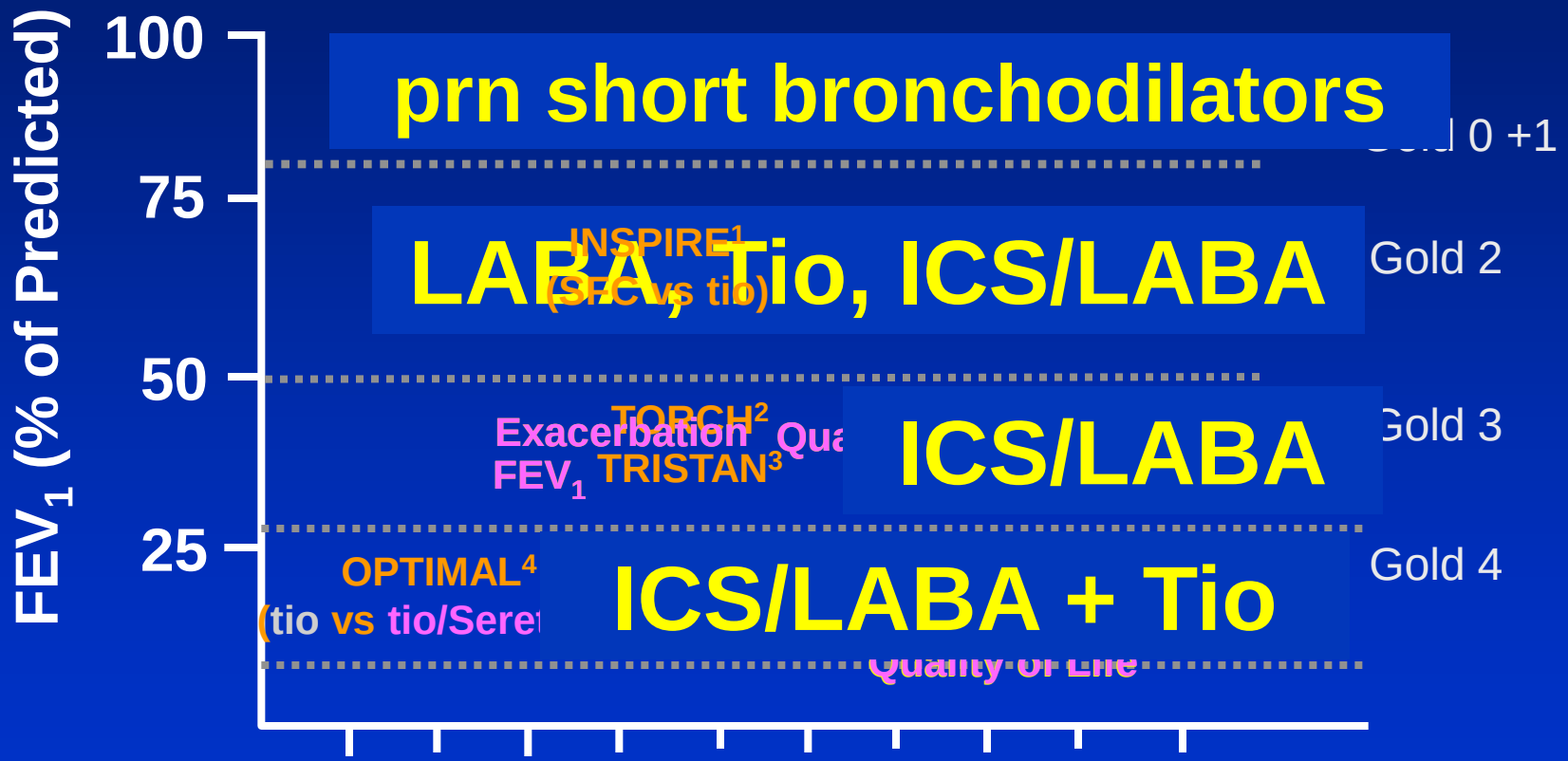
Exacerbation

Study or Subgroup	tiotropium+LABA/ICS Events	Total	tiotropium+placebo Events	Total	Odds Ratio M-H, Random, 95% CI
Aaron 2007	87	145	98	156	0.89 [0.56, 1.41]
Welte 2009	25	329	61	331	0.36 [0.22, 0.60]



Karner C, Cochrane Database Syst Rev. 2013: 5

An Approach To COPD Based on New "Facts"



[1]INSPIRE. AJRCCM 2007
[2]TORCH. N Engl J Med 2007
[3]TRISTAN. Lancet 2003
[4]OPTIMAL. Ann Intern Med 2007

WISDOM study

The NEW ENGLAND JOURNAL of MEDICINE

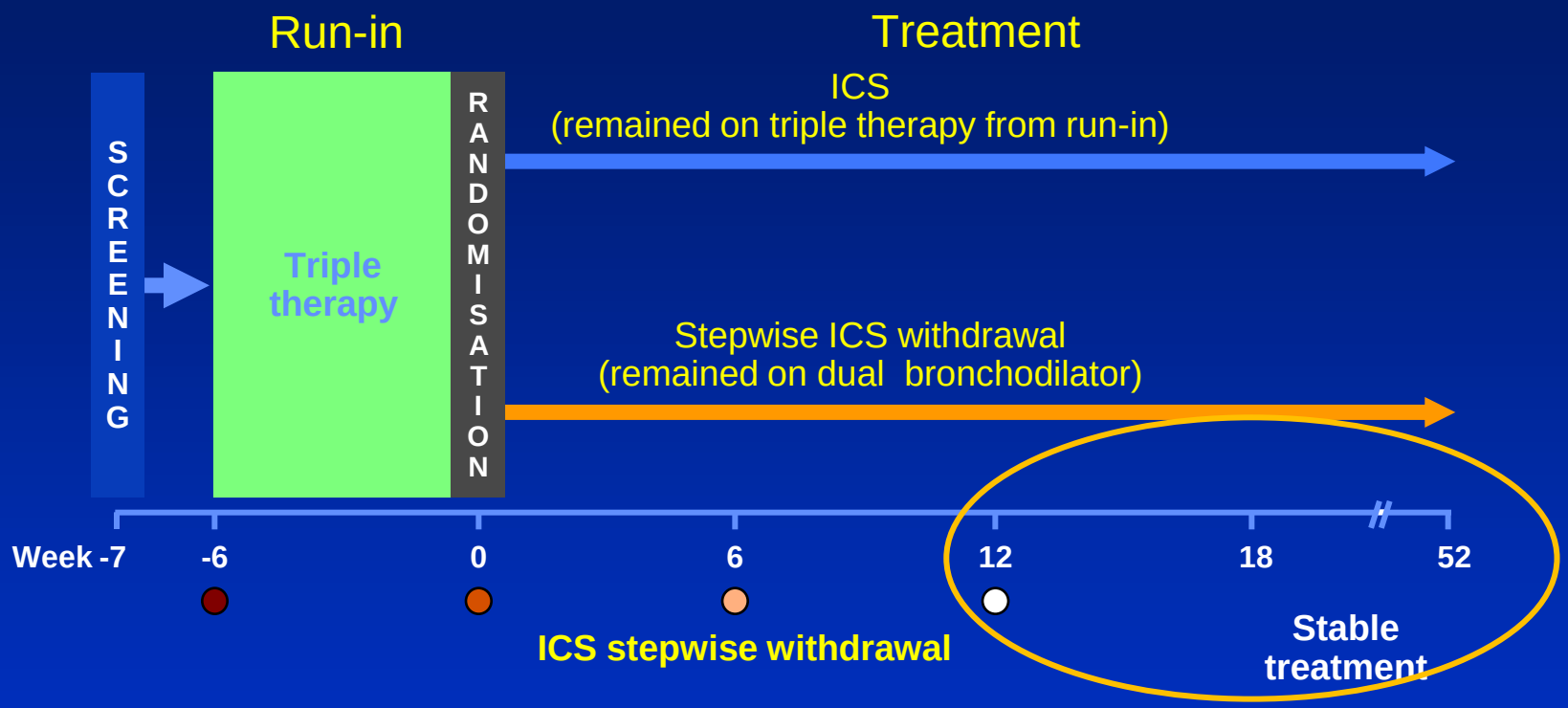
ORIGINAL ARTICLE

Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

Helgo Magnussen, M.D., Bernd Disse, M.D., Ph.D., Roberto Rodriguez-Roisin, M.D., Anne Kirsten, M.D., Henrik Watz, M.D., Kay Tetzlaff, M.D., Lesley Towse, B.Sc., Helen Finnigan, M.Sc., Ronald Dahl, M.D., Marc Decramer, M.D., Ph.D., Pascal Chanez, M.D., Ph.D., Emiel F.M. Wouters, M.D., Ph.D., and Peter M.A. Calverley, M.D., for the WISDOM Investigators*

Magnussen NEJM 2014: 5

Study design



Triple therapy regimen

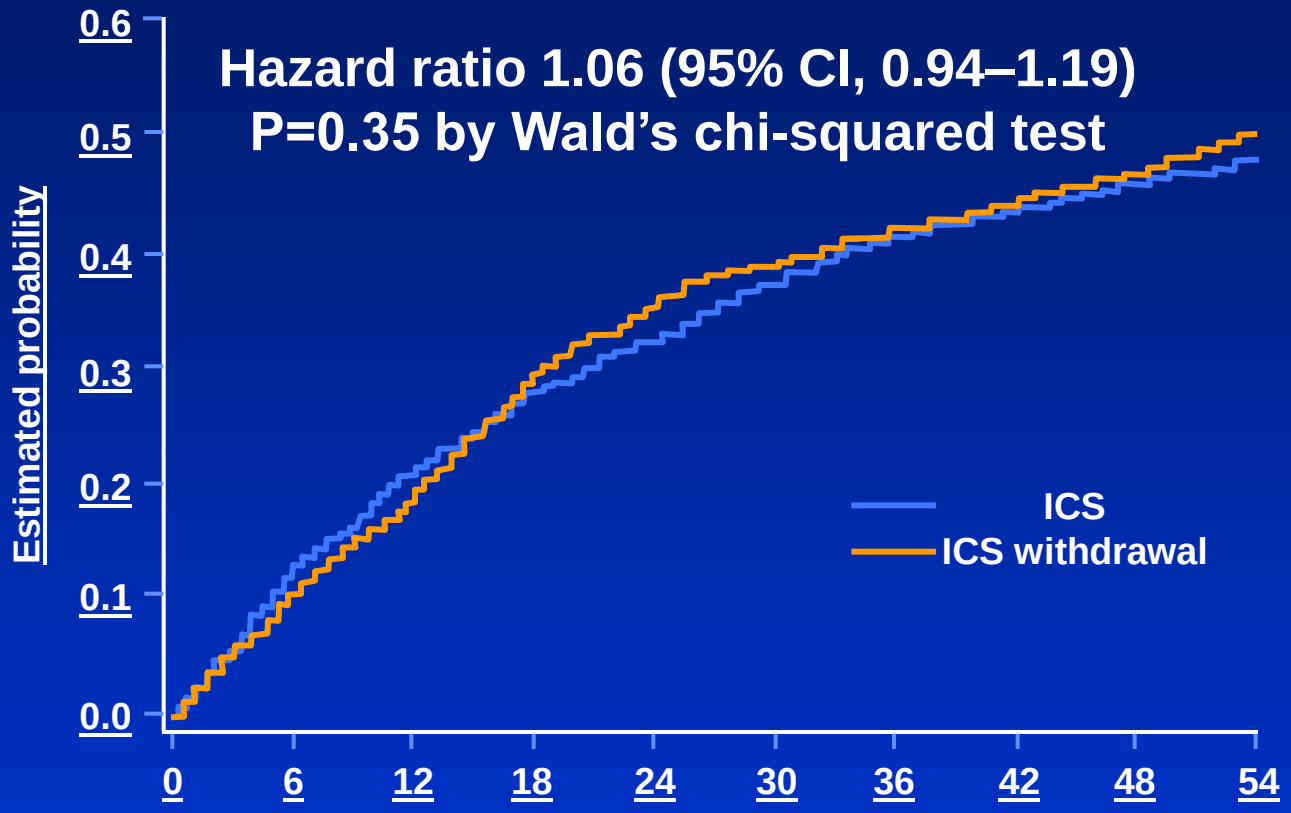
- Tiotropium 18 µg QD
- Salmeterol 50 µg BID
- Fluticasone propionate 500 µg BID

Fluticasone propionate 12-week withdrawal schedule

- 500 µg BID
- Reduced to 250 µg BID
- Reduced to 100 µg BID
- Reduced to 0 µg (placebo)

Magnussen H et al. N Engl J Med. 2014 Oct 2;371(14):1285-94

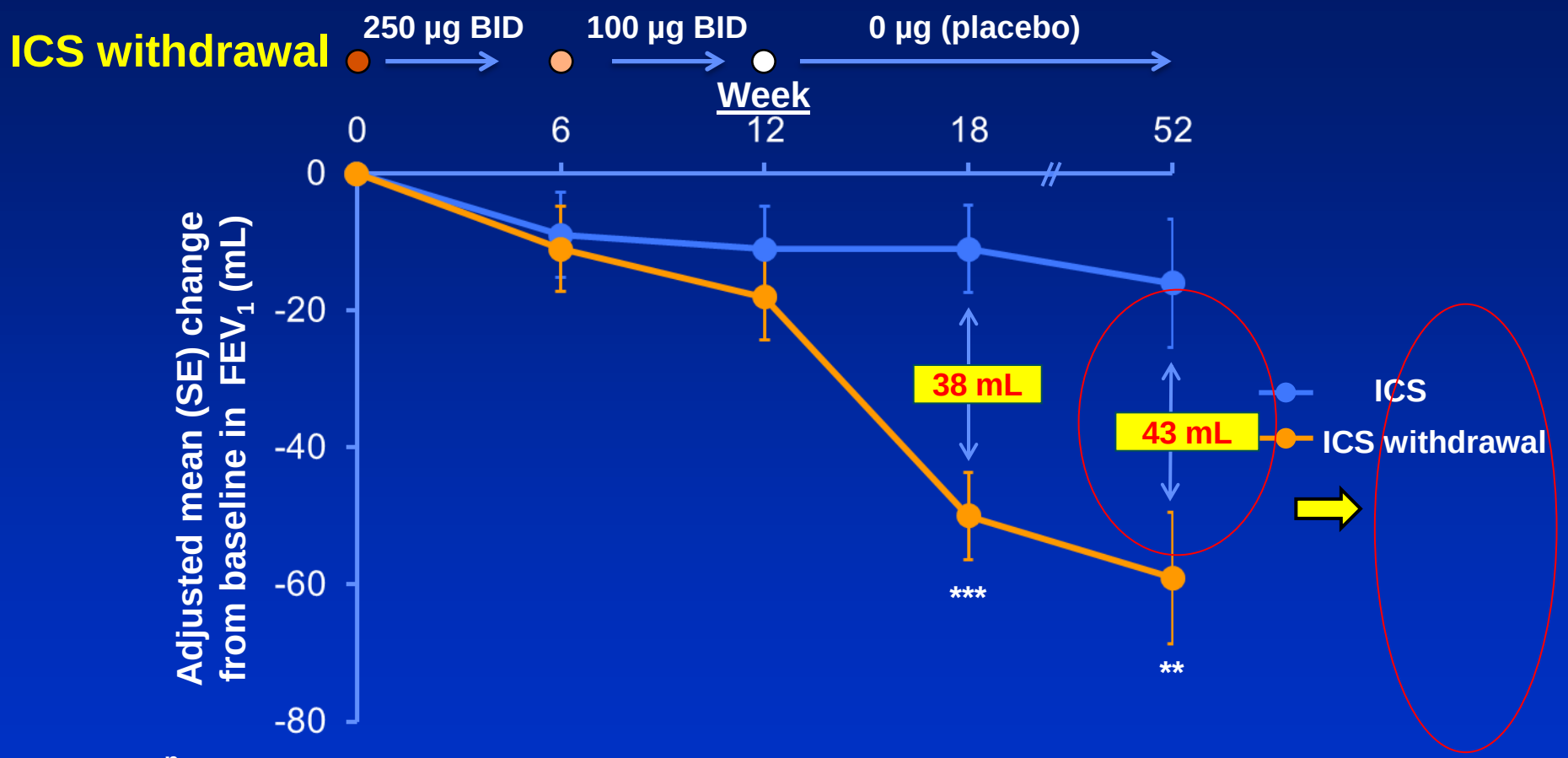
Time to moderate or severe COPD exacerbation



No. at risk										
ICS	1243	1059	927	827	763	694	646	615	581	14
ICS withdrawal	1242	1090	965	825	740	688	646	607	570	19

Magnussen H et al. N Engl J Med. 2014 Oct 2;371(14):1285-94

FEV1 mean change from baseline



n					
ICS withdrawal	1223	1135	1114	1077	970
ICS	1218	1135	1092	1058	935

**p<0.01; ***p<0.0001 vs ICS; restricted maximum likelihood repeated measures model; baseline values 970 mL for ICS, 981 mL for ICS withdrawal

Magnussen H et al. N Engl J Med. 2014 Oct 2;371(14):1285-94

Limitation

- Follow-up of less than 1 year
- Definite trend toward an increase in severe exacerbation after glucocorticoid withdrawal (P=0.08)
- Significant dose- and time-dependent loss of FEV1 and deterioration in QOL after the withdrawal of inhaled corticosteroid

- The decision to exclude from this study patients with no previous exacerbation :

  In no previous exacerbation patients,

  inhaled glucocorticoids may have successfully

  prevented exacerbations

ICS in New LAMA +LABA and New LAMA

Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomized, double-blind, parallel-group study

Section 12. Analysis of moderate to severe COPD exacerbations by ICS use

	Treatment	Annualized Rate (95% CI)	Comparison	Rate Ratio 95% CI	p value
No ICS use	QVA149 (n=183)	0.77 (0.63, 0.95)	QVA149 vs glycopyrronium	1.04 (0·78, 1.38)	0·81
			QVA149 vs tiotropium	0·99 (0·75, 1.30)	0·93
	Glycopyrronium (n=183)	0.75 (0.60, 0.93)	Glycopyrronium vs tiotropium	0·95 (0·72, 1·27)	0·74
	Tiotropium (n=178)	0.78 (0.64, 0.96)			
ICS use	QVA149 (n=546)	0·96 (0·86, 1.08)	QVA149 vs glycopyrronium	0·84 (0·73, 0·97)	0·015
			QVA149 vs tiotropium	0·88 (0·76, 1·01)	0·067
	Glycopyrronium (n=556)	1.14 (1.03, 1.28)	Glycopyrronium vs tiotropium	1·04 (0·91, 1·20)	0·55
	Tiotropium (n=559)	1.10 (0·98, 1·23)			

Wedzicha Lancet Respir Med 2013;1: 199.209

Inhaled steroids in COPD: when should they be used?

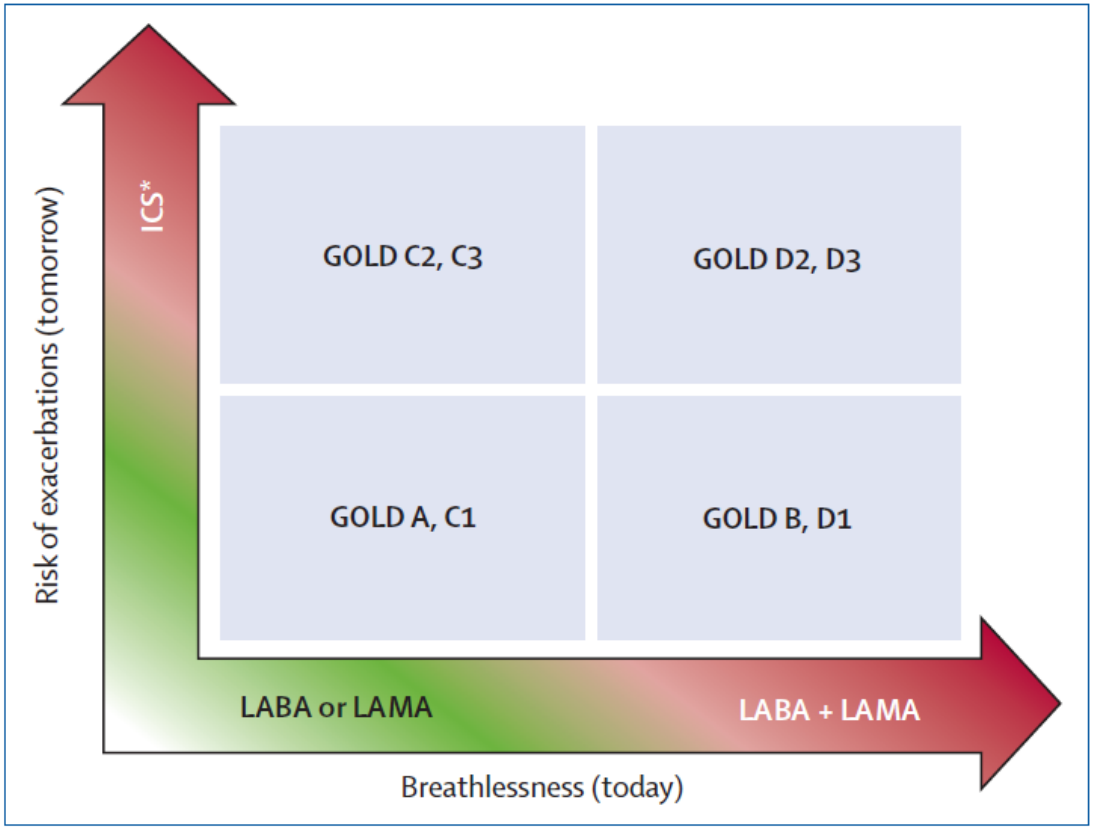


Figure: **Proposed escalation and combination of bronchodilator and inhaled corticosteroid (ICS) in the management of chronic obstructive pulmonary disease**

LABA=long-acting β, agonist. LAMA=long-acting muscarinic antagonist.

*Consider adding roflumilast, azithromycin, theophylline, or antioxidants if COPD is uncontrolled with inhaled corticosteroid.

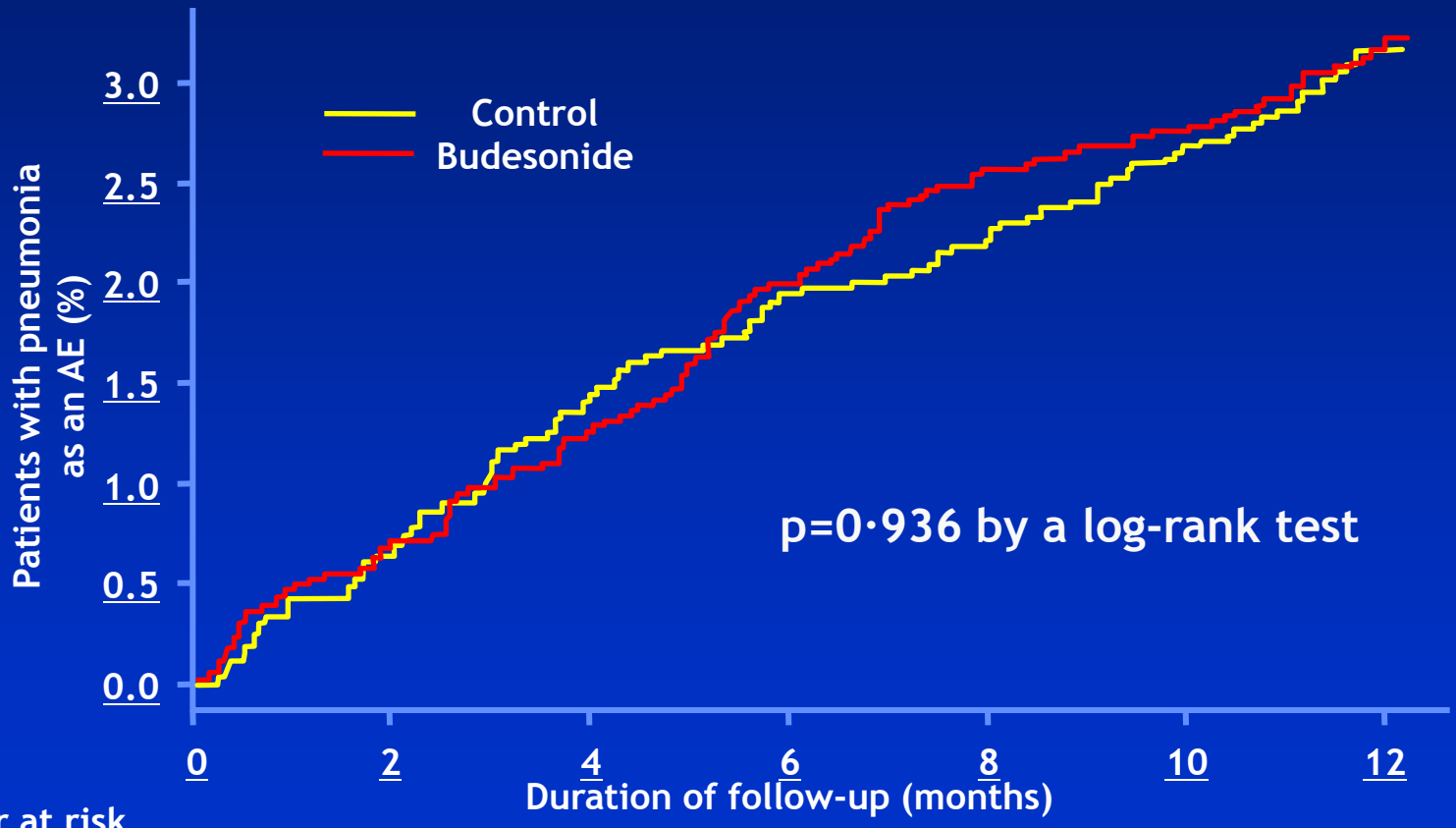
Augusti A Lancet 2014

- The specific inhaled corticosteroid (and dose) :

  matters in terms of efficacy:safety ratio

  Ex. PATHOS

BUDESONIDE & PNEUMONIA

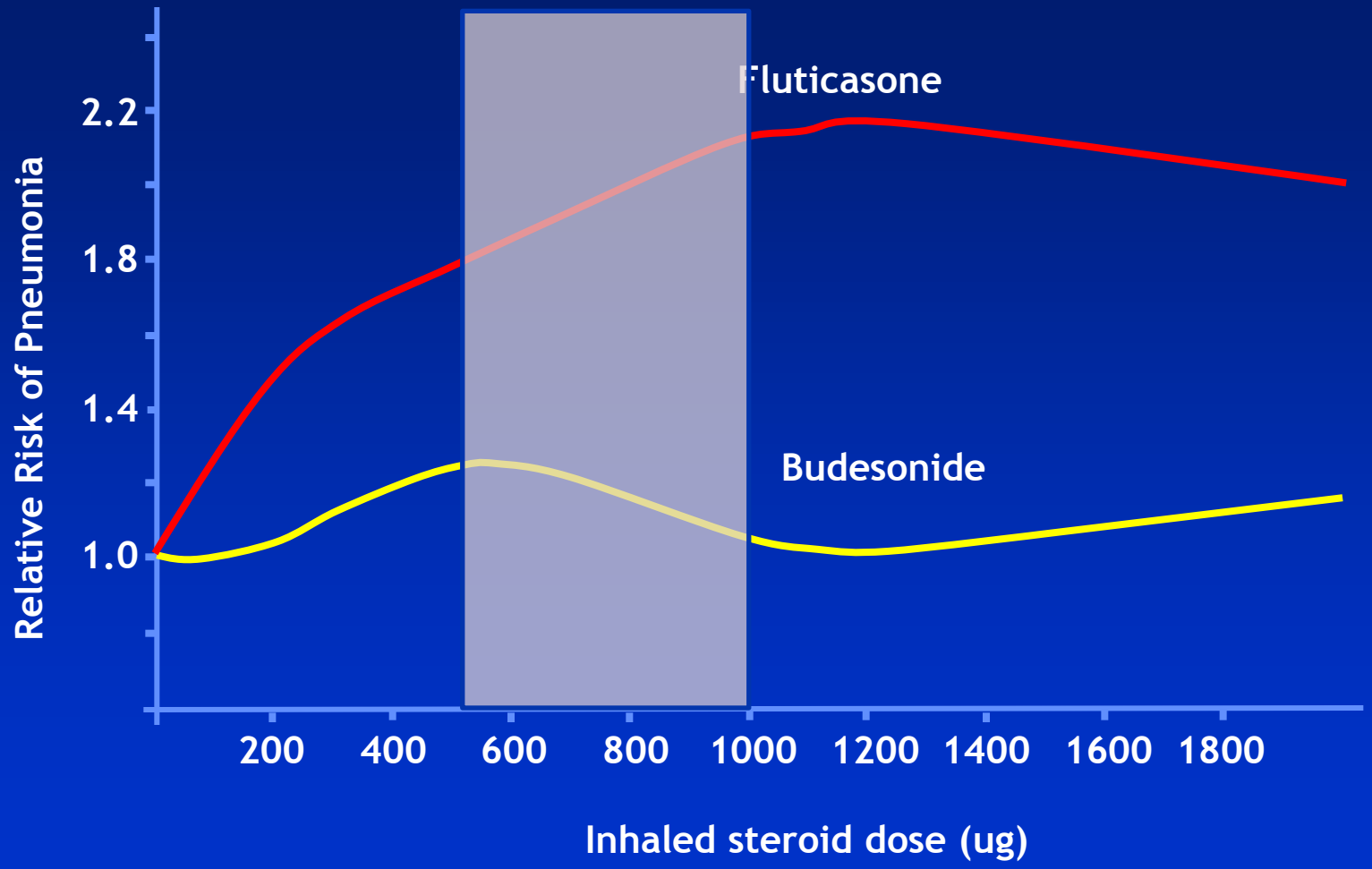


Number at risk							
Budesonide	3801	3543	3293	3105	2031	1945	1860
Control	3241	2877	2617	2487	1903	1810	1724

AE = adverse event.

Sin DD et al. Lancet 2009; 374:712-719.

ICS & PNEUMONIA



Suissa et al. Thorax 2013;68:1029-36

- Identify a subgroup of patients with COPD that respond better to inhaled cortoicosteroids

Those with elevated circulating eosinophils

Asthma-COPD overlap syndrome

Biomarker predicting COPD exacerbation

Blood Parameters as Biomarkers in COPD

Biomarker	Mortality	Exacerbation	FEV1 decline
CRP	Yes	Yes	No
MMP9	No data	Yes	No data
PARC	Yes	Yes	No
Copeptin	No data	Yes	No data
Serum amyloid A	No data	Yes	No data
IP-10	No data	Yes	No data
IL-6	Yes	Yes	No
fibrinogen	Yes	Yes	No
Surfactant Protein D	Yes	Yes(high Con)	No
CC-16	Yes	No data	Possibly
TNF-α	No data	No data	No

Kim JW, Sin Chest magazine 2012 Pulmonary perspective

Conclusion

- Regular treatment with inhaled corticosteroids improves symptoms, lung function and quality of life and reduces frequency of exacerbations for COPD patients with an FEV_1 < 60% predicted.
- Withdrawal from treatment with inhaled corticosteroids may lead to exacerbations in some patients. Ex. Asthma-COPD overlap syndrome, exacerbation Hx , Subgroup of patients that respond ICS

- Severe and very severe COPD patients with previous exacerbation Hx and future exacerbation risk factor may use of ICS with LAMA or LABA and LAMA+LABA

- 67세 남자로 호흡곤란으로 내원하여 2011년 COPD(emphysematous type) 진단받은 분으로 폐기능검사상 FEV1 0.9L(32%) FVC/FEV1 60%, BR(+), CAT score 22점, mMRC 2 인 환자로 흡입약제로 Tiotropium+fluticasone+salmeterol의 흡입약제 triple Tx를 사용하는 분입니다. 환자는 금년에 두차례 급성악화로 응급실 내원 입원한 기왕력이 있으며 지난 4년간 5차례 악화로 입원한 병력이 있는 분입니다. 향후 이 환자의 장기간 치료 계획을 선택해주세요

1. 지속적으로 Triple Tx 를 사용할 것이다
2. ICS를 step down 하면서 제외하고 LABA, LAMA, LABA+LAMA 복합제를 사용할 것이다.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