De-escalation of Triple Therapy in COPD

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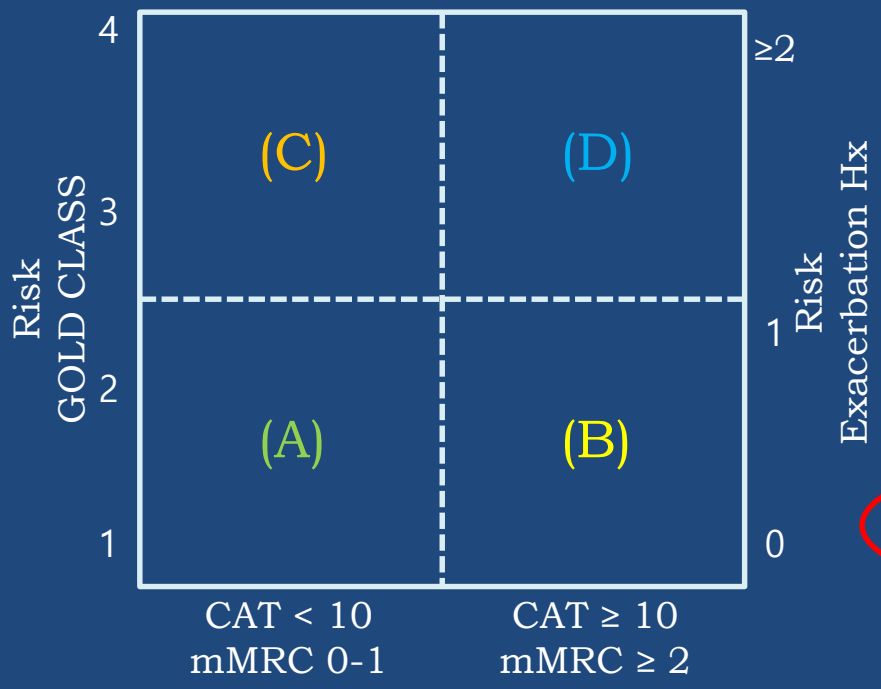
GOLD Recommendation

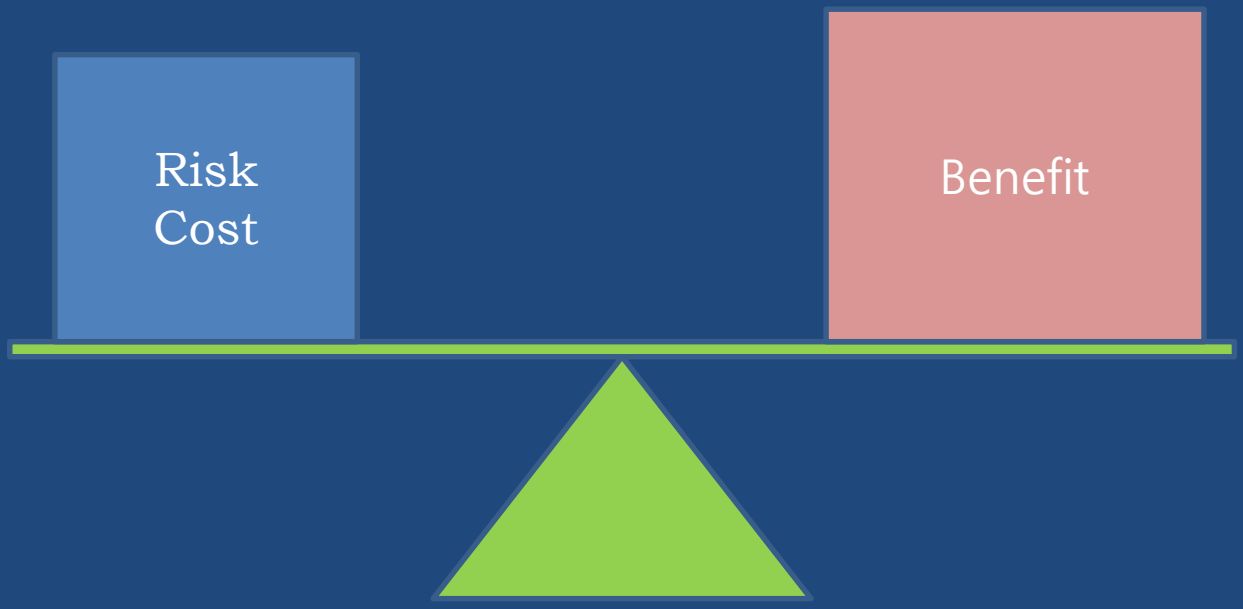


Group	First Choice	Alternatives
A	prn SAMA or prn SABA	LAMA or LABA or SABA/SAMA
B	LAMA or LABA	LAMA/LABA
C	ICS/LABA or LAMA	LAMA/LABA or LAMA/PDE4I or LABA/PDE4I
D	ICS/LABA and/or LAMA	ICS/LABA and LAMA or ICS/LABA and PDE4I or LAMA/LABA or LAMA/PDE4I

: Triple Therapy

From the *Global Strategy for the Diagnosis, Management and Prevention of COPD,* Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016. Available from: http://www.goldcopd.org/.

Risk and Benefit

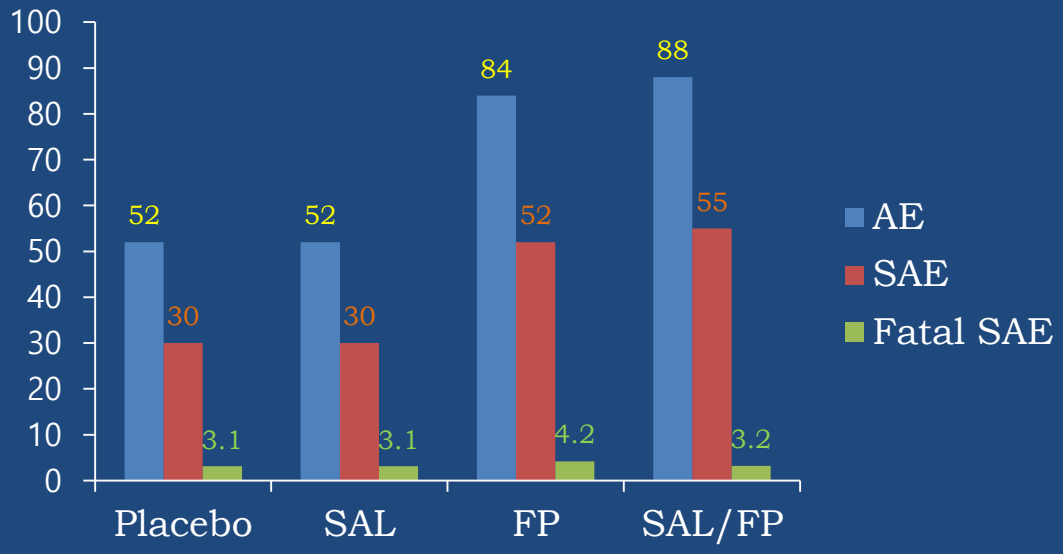


Contents

- Risk of ICS
- Benefit of ICS
- Withdrawal of ICS
- Cost

ICS and Risks

- Pneumonia



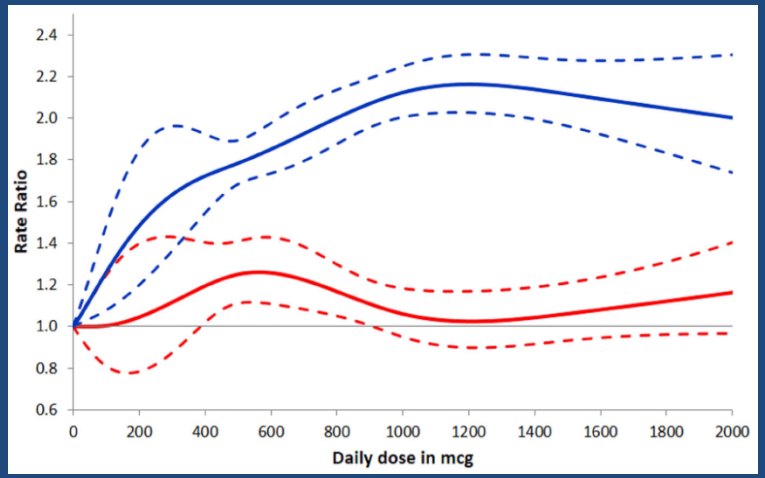
From TORCH, Event rate per 1000 Tx-yrs

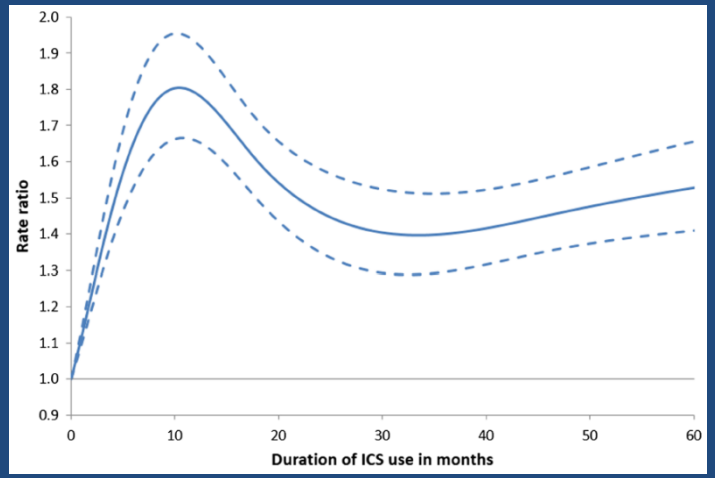
Eur Respir J 2009;34(3):641-647

ICS and Risks

- Pneumonia: population based nested case-control study
- 163,514 patients (Quebec health insurance database)

ICS exposure	Cases	Controls	Crude rate ratio	Adjusted* rate ratio	95% CI
Prior COPD hospitalisation					
Number of subjects	2975	8249			
No use, %†	23.03	30.56	1.00	1.00	Reference
Fluticasone current use, %‡	39.36	27.48	1.96	1.75	1.56 to 1.97
Budesonide current use, %‡	5.71	5.32	1.39	1.19	0.97 to 1.47
No prior COPD hospitalisation					
Number of subjects	17 369	189 456			
No use, %†	50.48	62.48	1.00	1.00	Reference
Fluticasone current use, %‡	21.99	11.58	2.47	2.01	1.92 to 2.10
Budesonide current use, %‡	5.07	4.80	1.34	1.14	1.06 to 1.23





Thorax 2013;68(11):1029-1036

ICS and Risks

- Pneumonia: Discontinuation of ICS and Risk
- 103,386 patients (Quebec health insurance database)

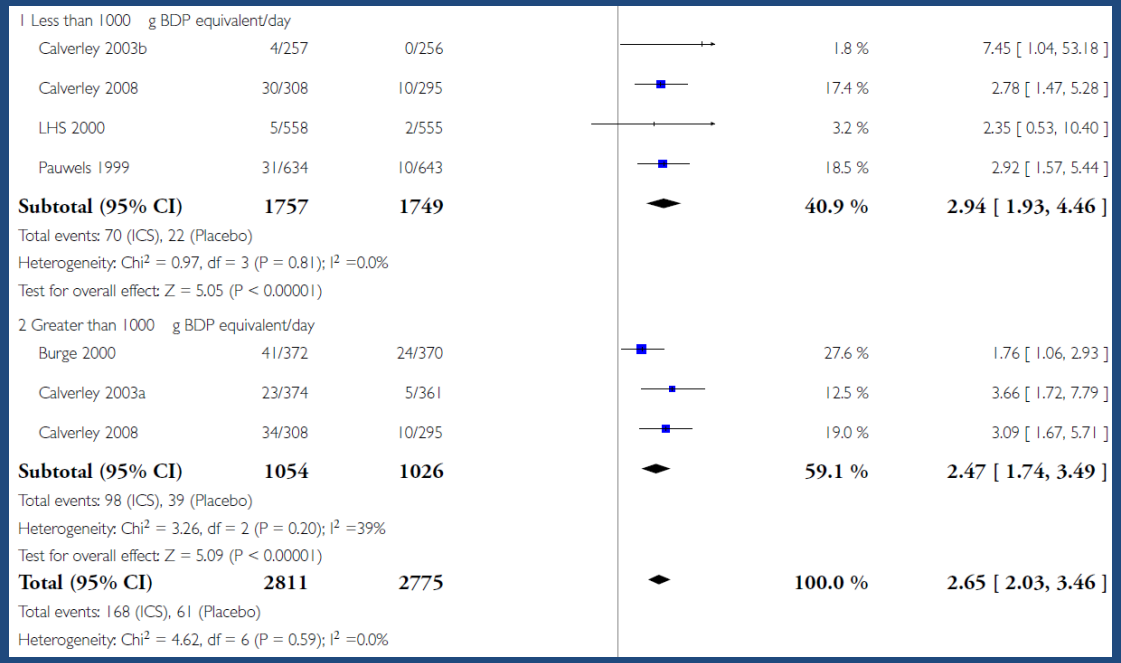
Variable	Pneumonia Case Subjects	Control Subjects	Crude RR	Adjusted[a] RR	95% CI
No. of subjects	14,020	132,697	...	...	...
Any inhaled corticosteroid					
Current use[b]	45.6	30.3	1.00	1.00	Reference
Discontinued use	54.4	69.7	0.48	0.63	0.60-0.66
Fluticasone					
Current use	31.0	17.0	1.00	1.00	Reference
Discontinued use	30.8	34.0	0.48	0.58	0.54-0.61
Budesonide					
Current use	5.6	6.6	1.00	1.00	Reference
Discontinued use	9.3	16.5	0.65	0.87	0.78-0.97
Other ICS[c]					
Current use	9.0	6.7	1.00	1.00	Reference
Discontinued use	14.3	19.2	0.52	0.75	0.68-0.82

-37%

Chest 2015;148(5):1177-1183

ICS and Risks

- Candidiasis



1 Less than 1000 g BDP equivalent/day				
Calverley 2003b	4/257	0/256	1.8 %	7.45 [1.04, 53.18]
Calverley 2008	30/308	10/295	17.4 %	2.78 [1.47, 5.28]
LHS 2000	5/558	2/555	3.2 %	2.35 [0.53, 10.40]
Pauwels 1999	31/634	10/643	18.5 %	2.92 [1.57, 5.44]
Subtotal (95% CI)	**1757**	**1749**	**40.9 %**	**2.94 [1.93, 4.46]**
Total events: 70 (ICS), 22 (Placebo)				
Heterogeneity: Chi^2 = 0.97, df = 3 (P = 0.81); I^2 =0.0%				
Test for overall effect: Z = 5.05 (P < 0.00001)				
2 Greater than 1000 g BDP equivalent/day				
Burge 2000	41/372	24/370	27.6 %	1.76 [1.06, 2.93]
Calverley 2003a	23/374	5/361	12.5 %	3.66 [1.72, 7.79]
Calverley 2008	34/308	10/295	19.0 %	3.09 [1.67, 5.71]
Subtotal (95% CI)	**1054**	**1026**	**59.1 %**	**2.47 [1.74, 3.49]**
Total events: 98 (ICS), 39 (Placebo)				
Heterogeneity: Chi^2 = 3.26, df = 2 (P = 0.20); I^2 =39%				
Test for overall effect: Z = 5.09 (P < 0.00001)				
Total (95% CI)	**2811**	**2775**	**100.0 %**	**2.65 [2.03, 3.46]**
Total events: 168 (ICS), 61 (Placebo)				
Heterogeneity: Chi^2 = 4.62, df = 6 (P = 0.59); I^2 =0.0%				

Cochrane Database Syst Rev 2012;7:CD002991

ICS and Risks

- Tuberculosis

Chest 2013;143(4):1018-1024
Am J Respir Crit Care Med 2011;183(5):675-678

- Cataracts

N Engl J Med 1997;337(1):8-14
Eur Respir J 2006;27(6):1168-1174

- Osteoporosis and fracture

Thorax 2011;66(8):699-708

- Glaucoma / Diabetes mellitus / Adrenal insufficiency

Am J Med 2010;123(11):1001-1006
Endocrinol Diabetes Metab Case Rep 2014;2014:130080
Eur Respir J 2015;45(2):525-537

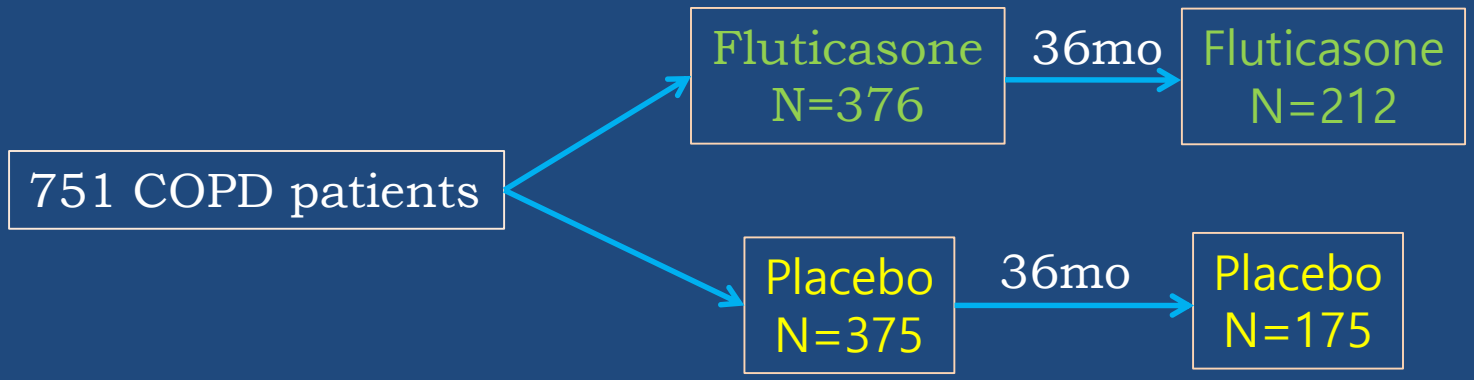
CHA 의과학대학교
CHA 차병원

Contents

- Risk of ICS
- Benefit of ICS
- Withdrawal of ICS
- Cost

The ISOLDE Study

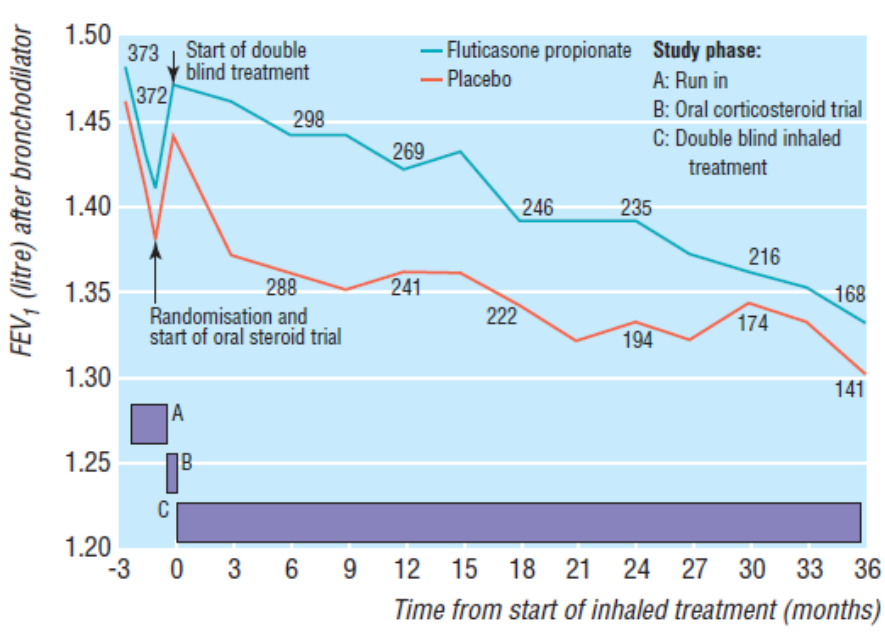
- Fluticasone propionate (500)



BMJ 2000;320:1297-1303

The ISOLDE Study

Efficacy parameter	Placebo	Fluticasone propionate	Treatment difference between drug and placebo (95% CI)	P value
FEV_1 after bronchodilator:				
No of patients	325*	339*		
Mean change in FEV_1 ml/year (SE)	–59 (4.4)	–50 (4.1)	9 (6.0) (–3 to 20)	0.161
Predicted FEV_1 at 3 months	1.37	1.44	0.076 (0.056 to 0.097)	<0.001
Predicted FEV_1 at 3 years	1.20	1.30	0.100 (0.064 to 0.135)	<0.001
Health status:				
No of patients	291*	309*		
Mean change in questionnaire score (SE) (units/year)	3.17 (0.31)	2.00 (0.29)	–1.17 (0.40) (–1.95 to –0.39)	0.004
Annual exacerbation rate:				
No of patients	370	372		
Mean (SD) rates	1.90 (2.63)	1.43 (1.93)		
Median (range) rates	1.32 (0 to 30)	0.99 (0 to 26)	–0.3 (–0.4 to 0.0)†	0.026



BMJ 2000;320:1297-1303

The TORCH Study

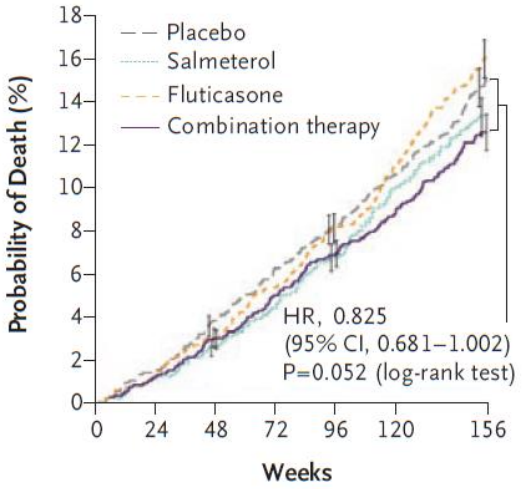
- 6184 COPD patients: Placebo, SAL, FP, SAL/FP

Efficacy analysis for exacerbation						Rate Ratio (95% CI)	
Annual rate							
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

N Engl J Med 2007;356:775-789

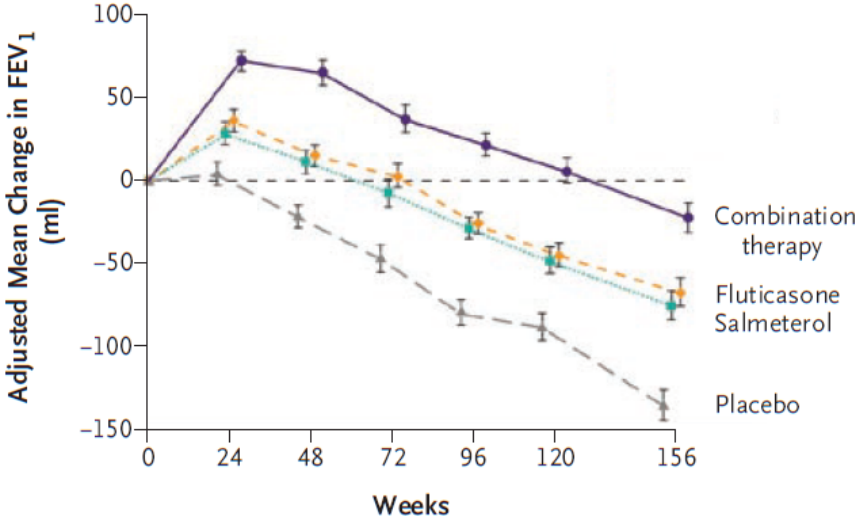
The TORCH Study

B Death from Any Cause



No. of Patients							
Placebo	1524	1500	1464	1428	1399	1361	1293
Salmeterol	1521	1502	1481	1451	1417	1368	1316
Fluticasone	1534	1512	1487	1450	1409	1363	1288
Combination therapy	1533	1514	1487	1456	1426	1393	1339

E FEV_1



No. of Patients							
Placebo	1524	1248	1128	1049	979	906	819
Salmeterol	1521	1317	1218	1127	1054	1012	934
Fluticasone	1534	1346	1230	1157	1078	1006	908
Combination therapy	1533	1375	1281	1180	1139	1073	975

N Engl J Med 2007;356:775-789

Benefit of ICS

- Reduce Exacerbations
- Improve Symptoms and QOL
- No sufficient evidence: mortality benefit, lung function decline

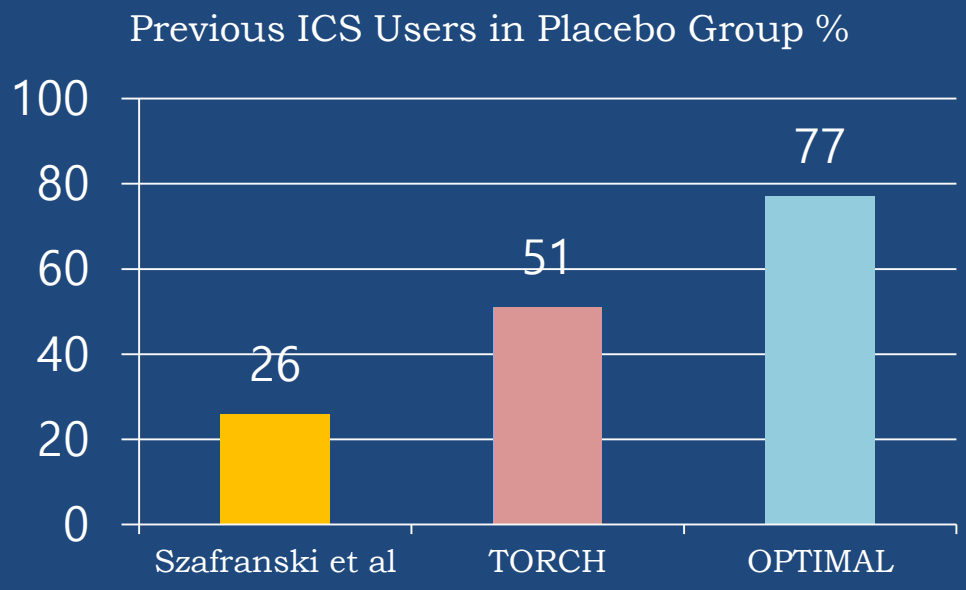
Methodological Issues

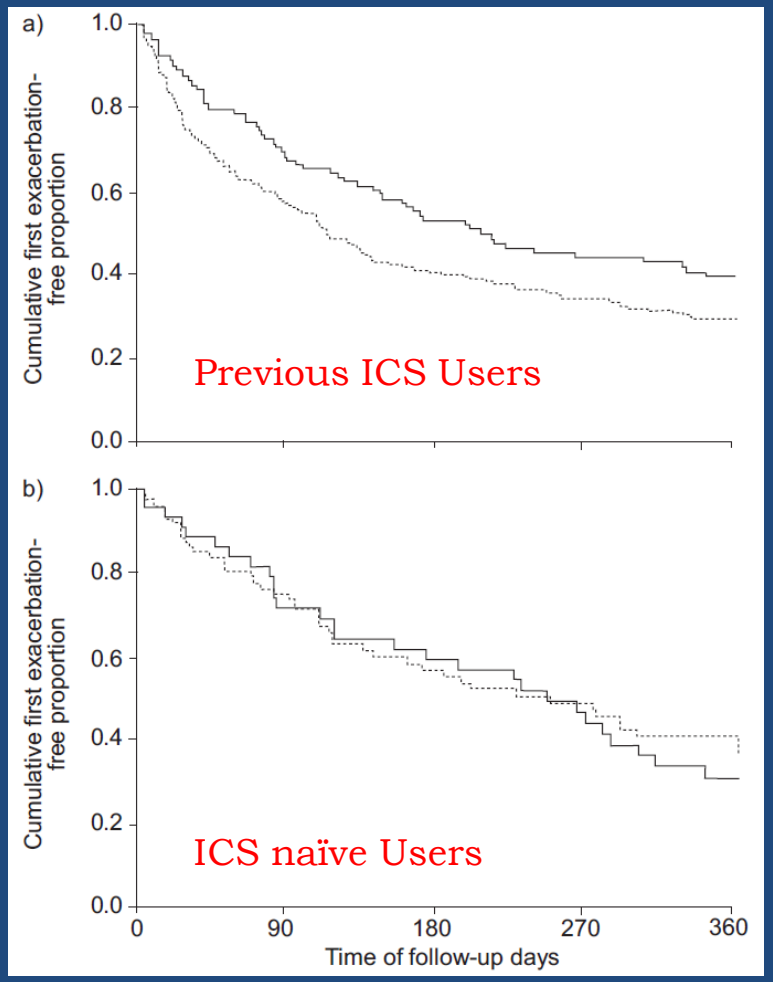
- Methodological Issues including TORCH

- Many patients were already receiving ICS before randomization
- Analyses did not look beyond the first exacerbation
- Stopped following the patients who discontinued the drugs
- Did not fully exploit the data

Eur Respir J 2008;31:927-933

Methodological Issues



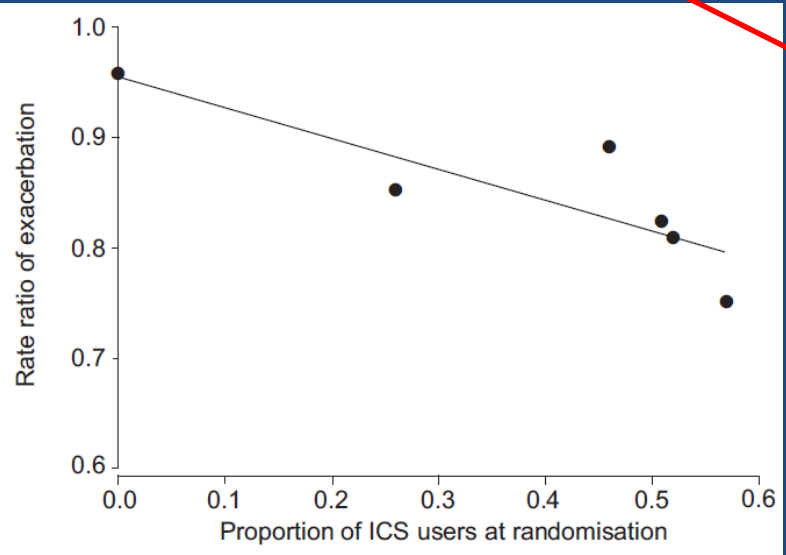


Eur Respir J 2008;31:927-933

Methodological Issues

TABLE 2 Randomised controlled trials comparing an inhaled corticosteroid (ICS; alone) to placebo that include data on the rate ratio of exacerbation and previous use of ICSs prior to randomisation

First author [Ref.]	ICS		Placebo			Rate ratio of exacerbation	p-value
	Subjects n	Withdrawal %	Subjects n	Withdrawal %	Prior ICS use %		
VESTBO [18]	145	25	145	35	0	0.96	0.736#
BURGE [19]	372	43	370	53	57	0.75	0.026
SZAFRANSKI [6]	198	31	205	44	26	0.85	0.224
CALVERLEY [20]	374	29	361	39	52	0.81	0.003
CALVERLEY [7]	257	40	256	41	46	0.89	0.308
CALVERLEY [1]	1534	38	1524	44	51	0.82	0.001



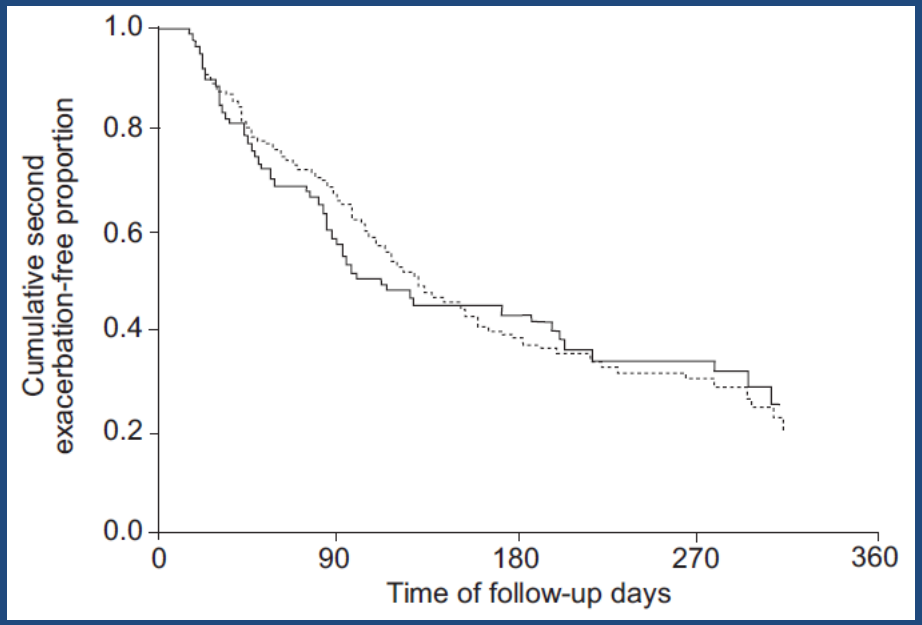
Possible bias

Eur Respir J 2008;31:927-933

Methodological Issues

TABLE 3 Analyses of the effect of inhaled corticosteroid (ICS) use compared with bronchodilators on the rate of exacerbation over different follow-up periods using the Canadian Optimal Therapy of COPD Trial data

	Subjects n	Rate of exacerbation yr^{-1}		Rate ratio (95% CI)
		ICS	Bronchodilators	
Follow-up period				
Entire observation period	449	1.39	1.67	0.83 (0.66–1.04)
Until discontinuation only	449	1.30	1.69	0.78 (0.61–0.99)
After discontinuation	137	2.02	1.64	1.23 (0.78–1.95)



Eur Respir J 2008;31:927-933

Methodological Issues

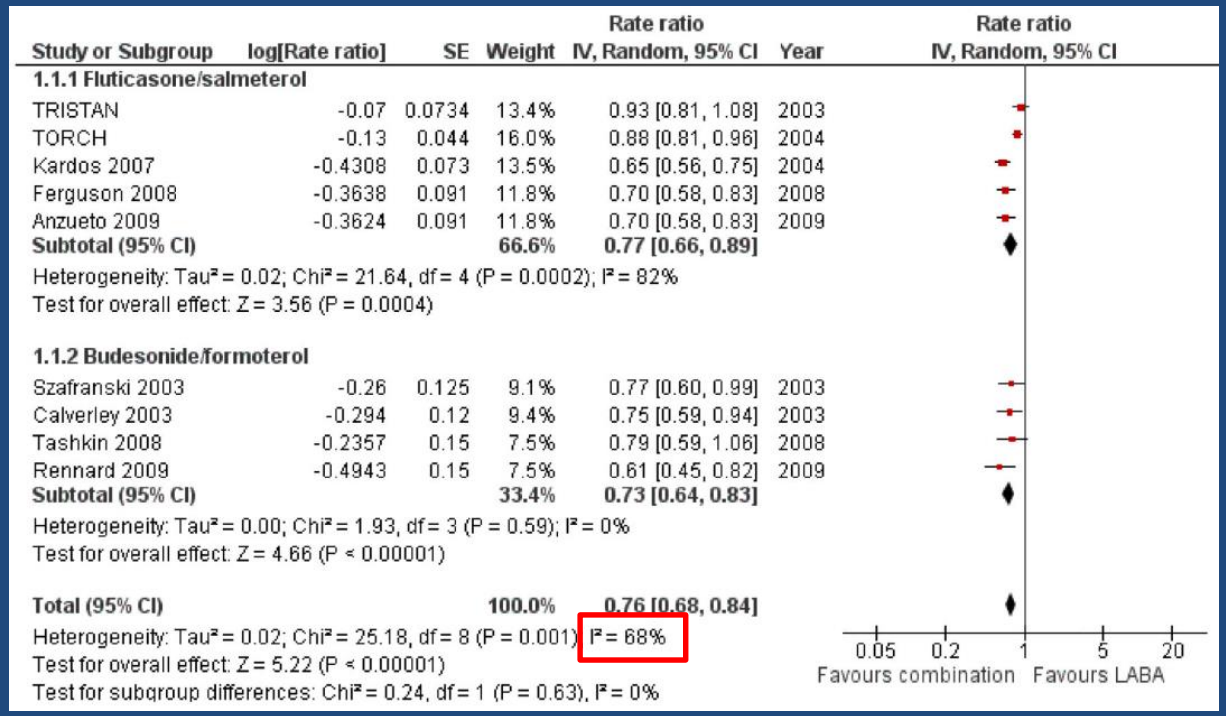
TABLE 4 Factorial analysis of Towards a Revolution in COPD Health (TORCH) data of the independent effects of fluticasone and salmeterol on the 3-yr incidence of all-cause mortality

	Medication allocated		Crude RR	Adjusted RR (95% CI)
	Yes deaths/total n	No deaths/total n		
Medication				
Fluticasone	439/3067	436/3045	1.00	1.00 (0.89–1.13)
Salmeterol	398/3054	477/3058	0.83	0.83 (0.74–0.95)

RR: relative rate ratio; CI: confidence interval.

Eur Respir J 2008;31:927-933

Methodological Issues



Cochrane Database Syst Rev 2012;9:CD006829

Contents

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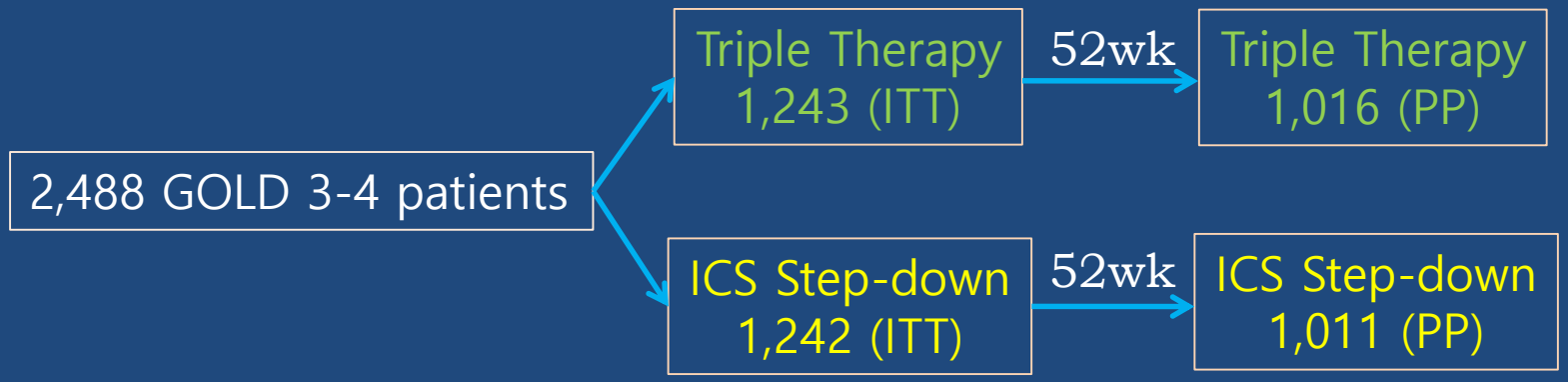
The WISDOM Study

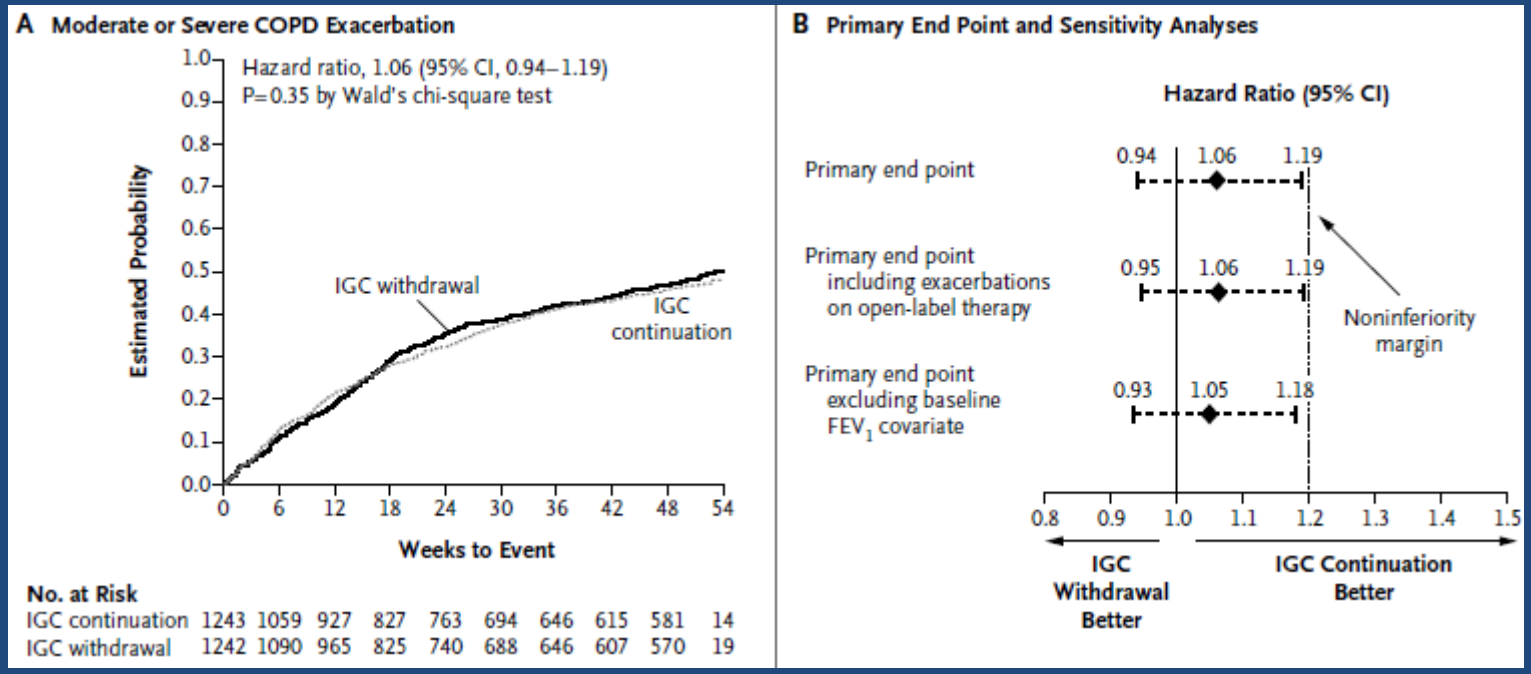
- Triple Therapy vs ICS Step-Down: Non-inferiority design



N Engl J Med 2014;371(14):1285-1294

The WISDOM Study

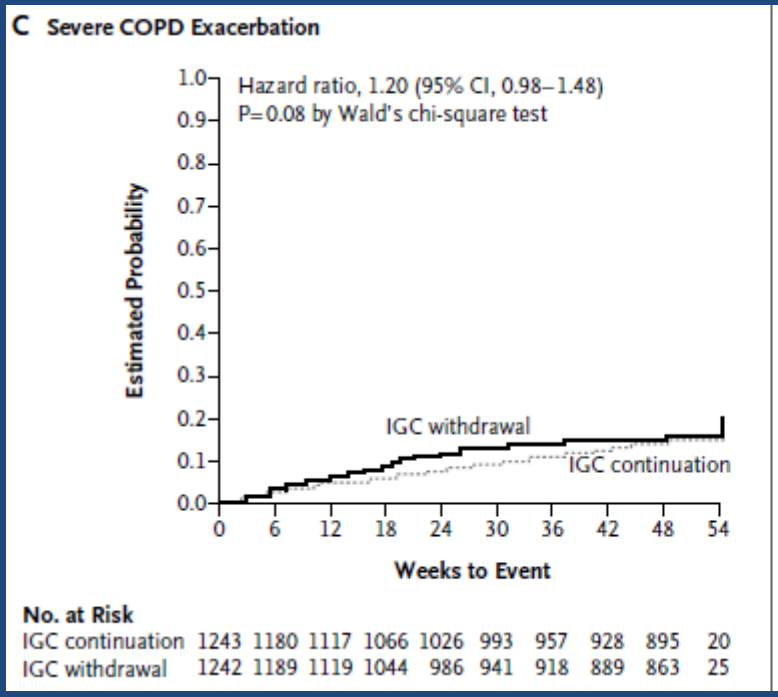
- Primary end-point: Moderate to severe exacerbation

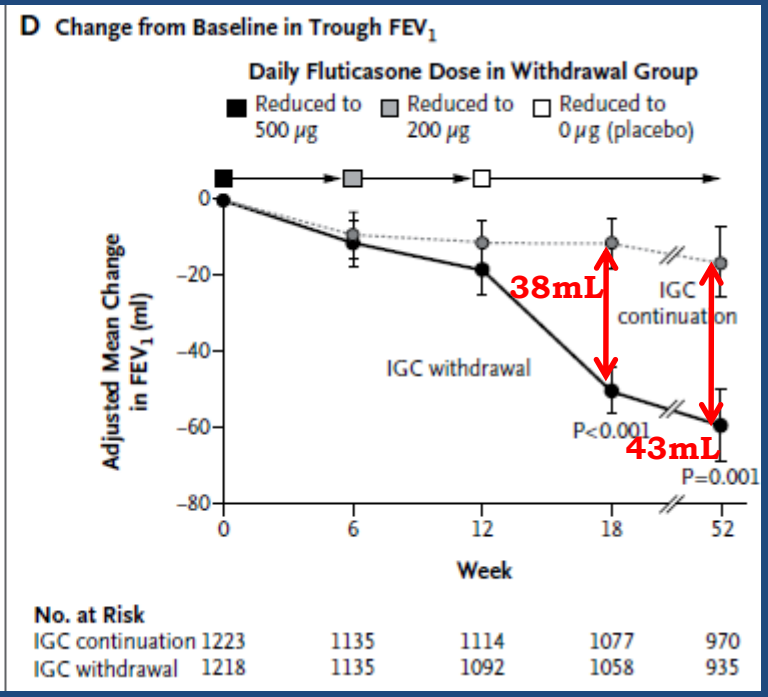


N Engl J Med 2014;371(14):1285-1294

The WISDOM Study

- Severe exacerbation / FEV_1 change





N Engl J Med 2014;371(14):1285-1294

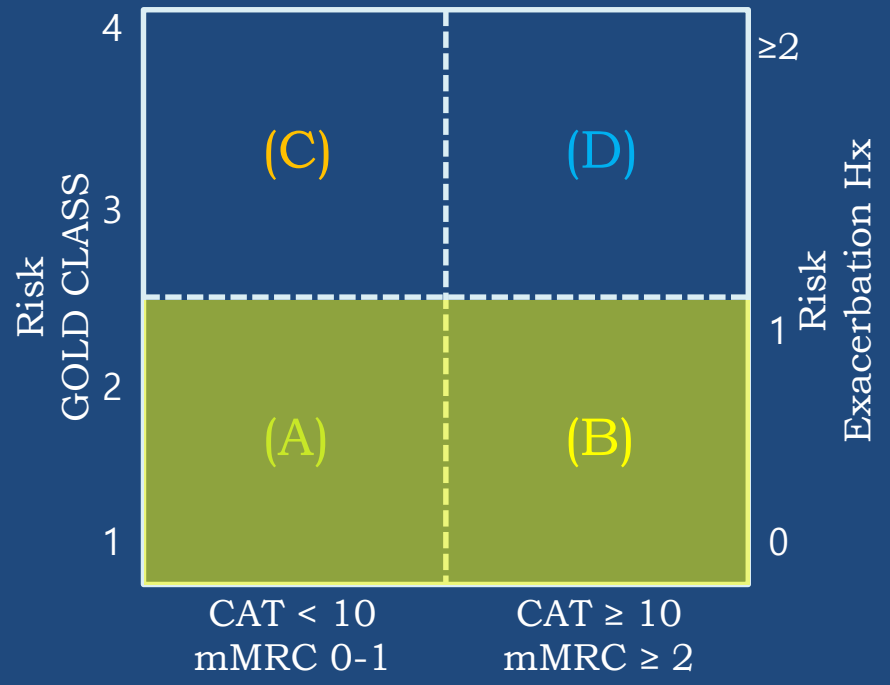
The WISDOM Study

- Limitations

- RCT: not a real-life study
- Discrepancies between recommendation and real-life practice
- Some patients newly started triple therapy (6 week run-in)
- Relatively short f-up duration (52 weeks)

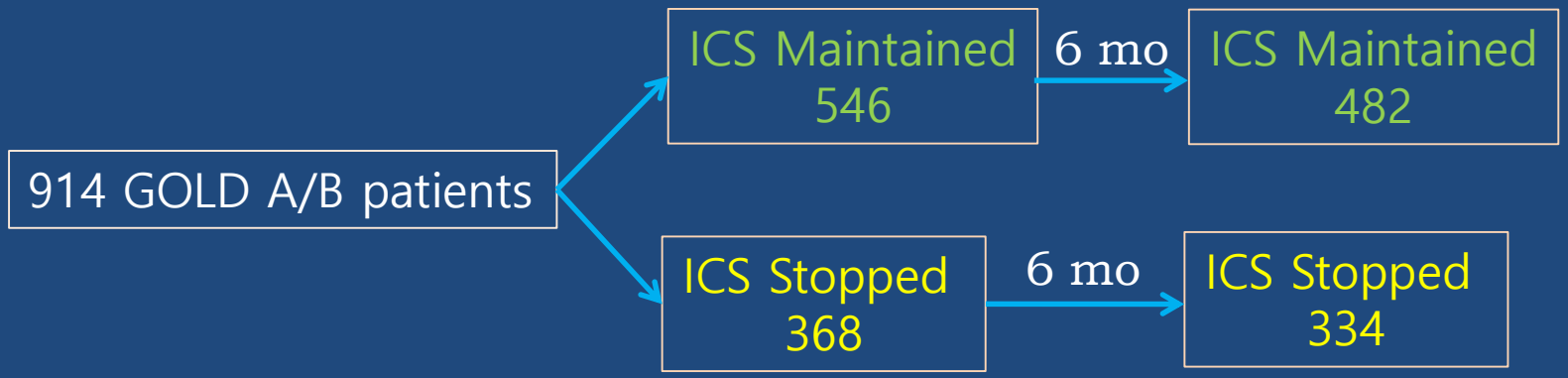
The OPTIMO Study

- Prospective, real-life study (Not a RCT)
- Low-risk patient (GOLD A/B)
- Only some received triple therapy



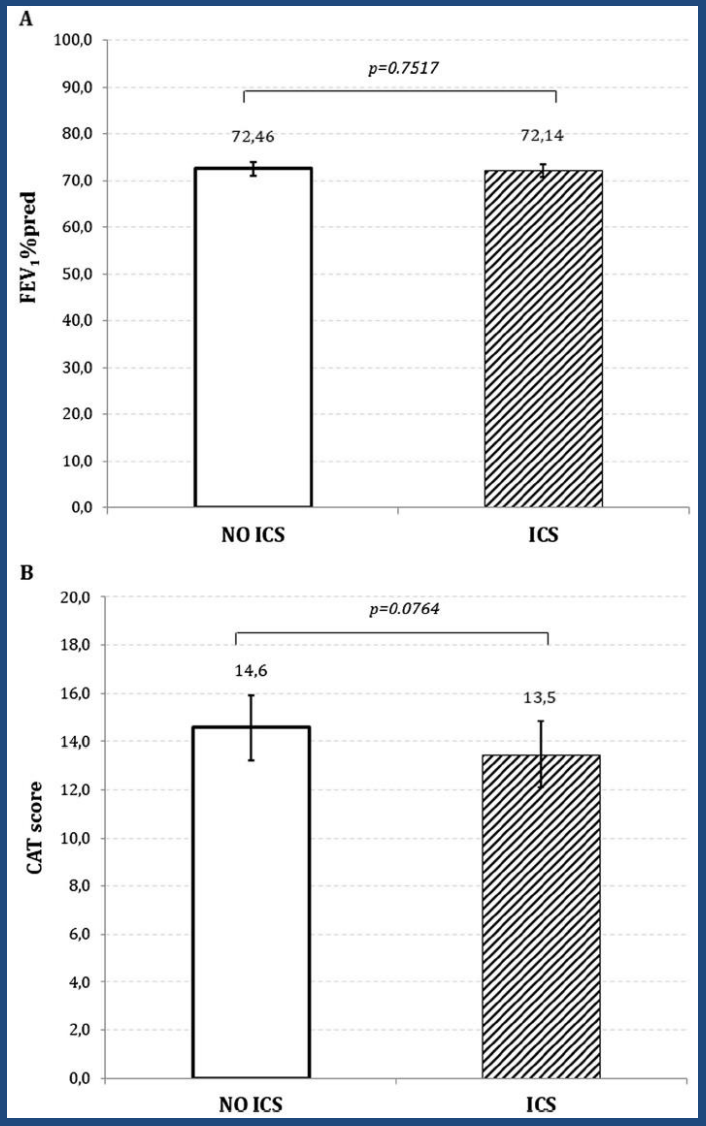
Respir Res 2014;15:77

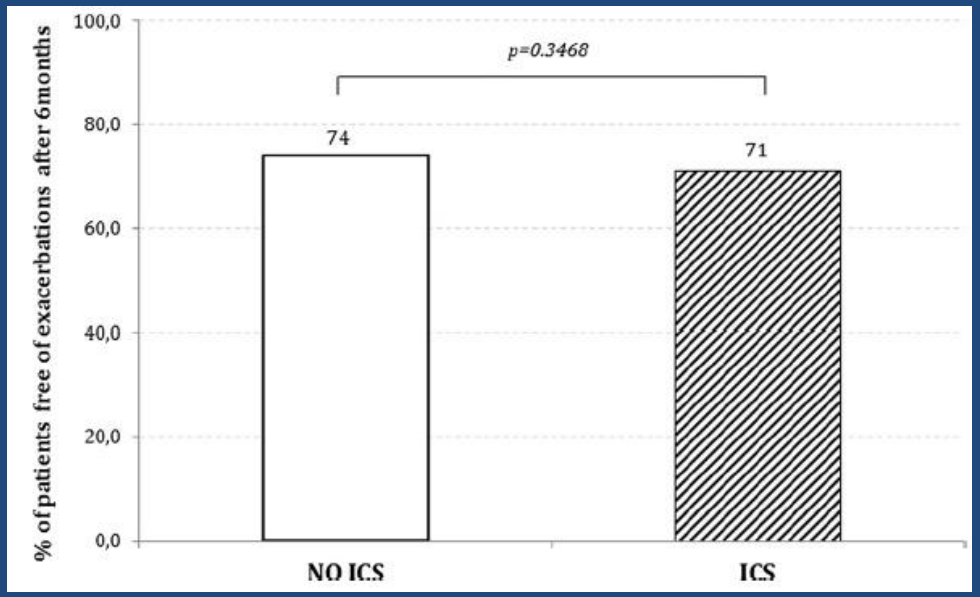
The OPTIMO Study



Respir Res 2014;15:77

The OPTIMO Study





Respir Res 2014;15:77

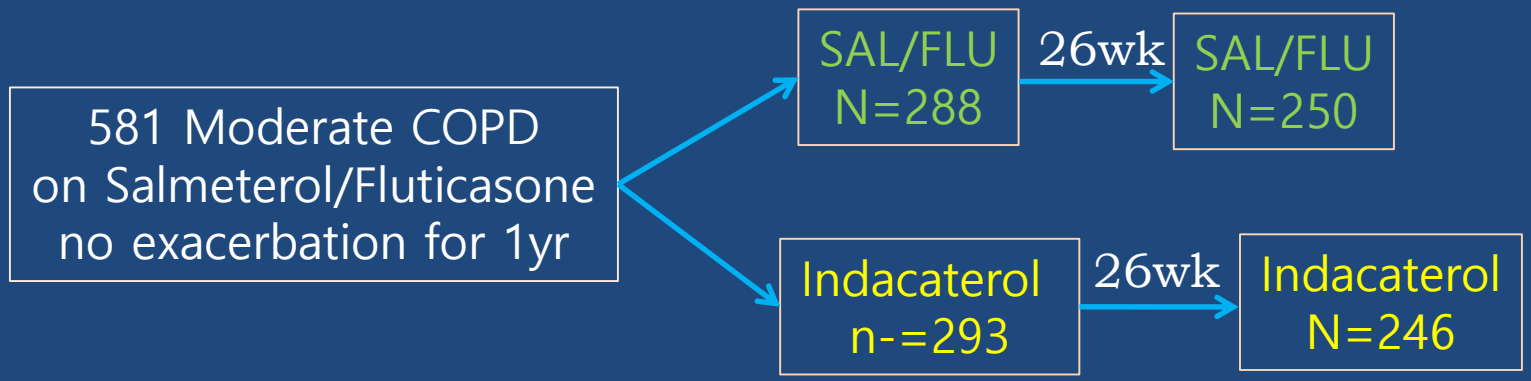
The OPTIMO Study

- Limitations

- Not de-escalation of triple therapy
- Short f-up duration
- GOLD A/B

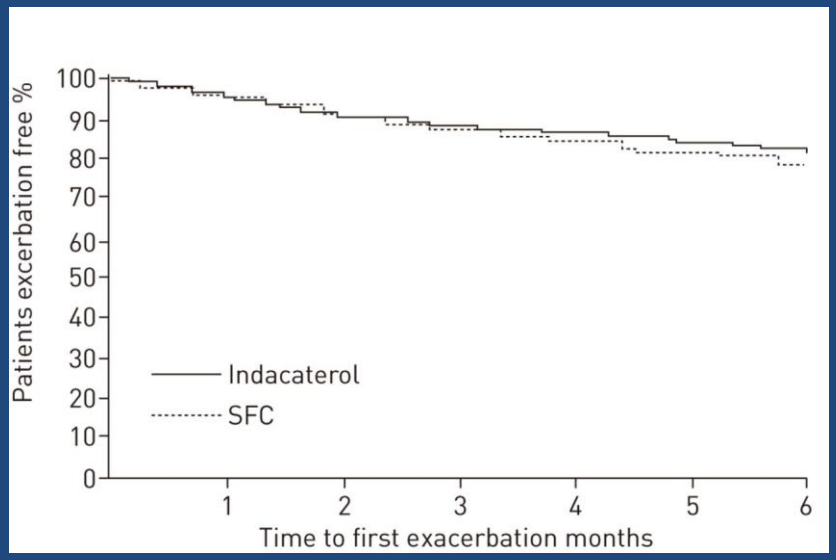
The INSTEAD Study

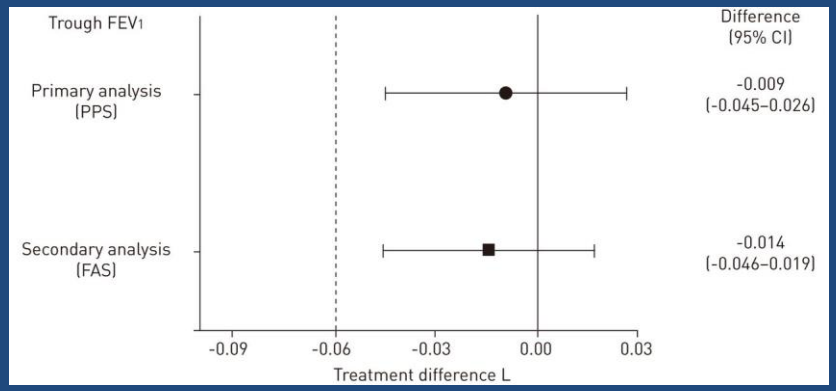
- Moderate COPD, a parallel group RCT
- Randomized switch trial of indacaterol vs Sal/flu

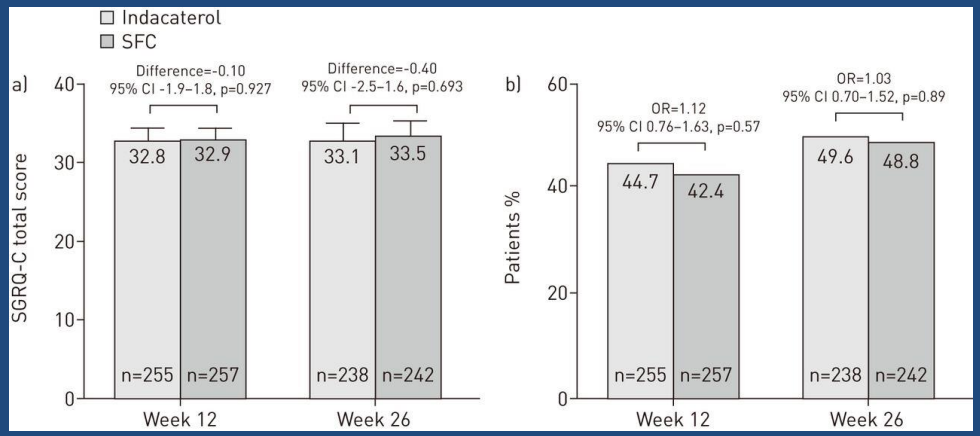


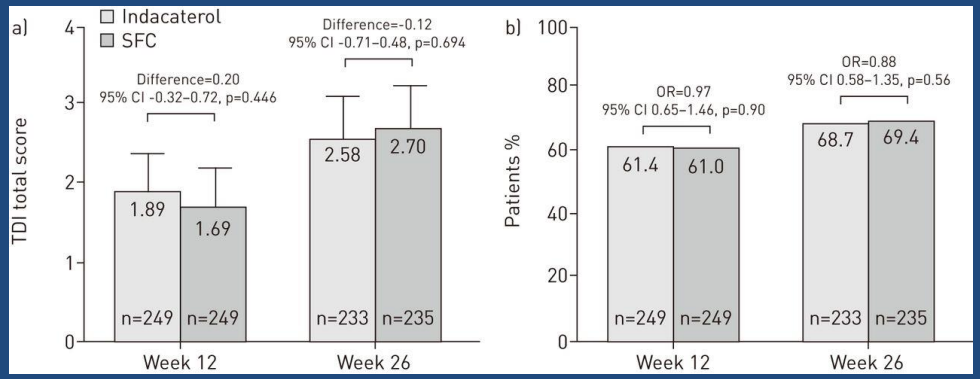
Eur Respir J 2014;44(6):1548-1556

The INSTEAD Study









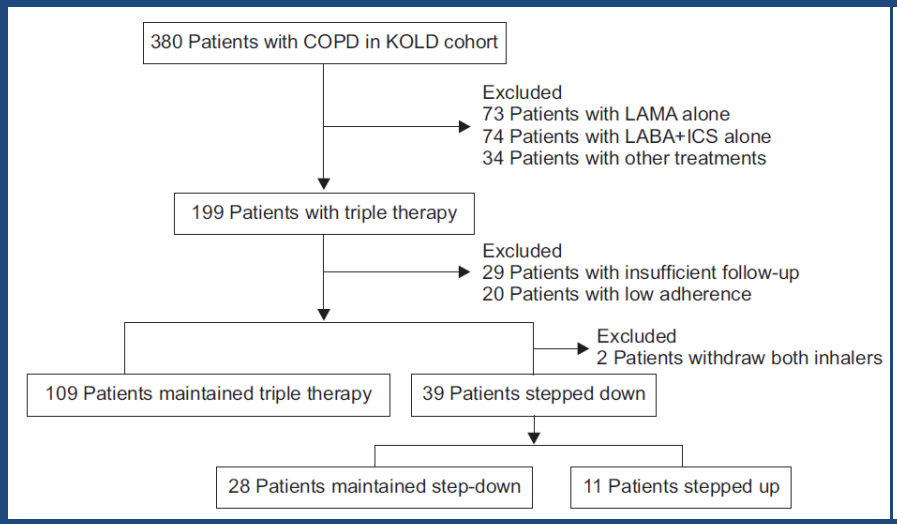
Eur Respir J 2014;44(6):1548-1556

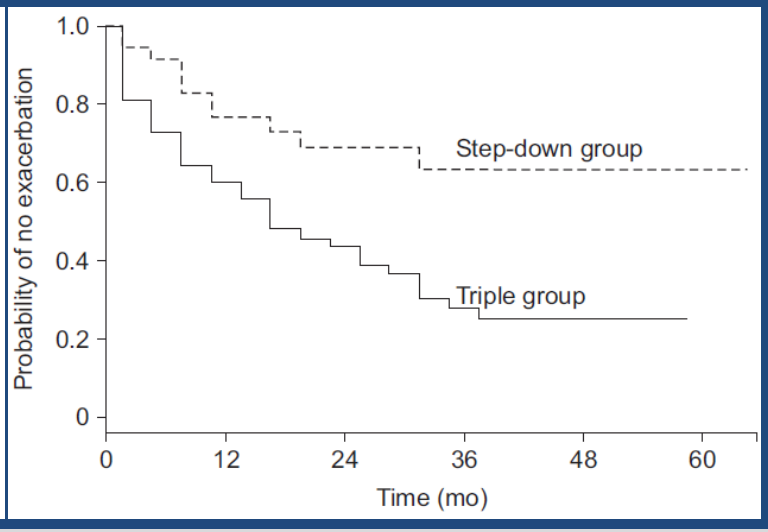
The INSTEAD Study

- Limitations

- Not triple therapy de-escalation
- Moderate COPD
- Relatively short f/up duration

The KOLD Cohort Study





Variable	Triple (n=109)		Step-down (n=39)		p-value for the change after the IT
	Just before the IT*	Just after the IT*	Just before the IT*	Just after the IT*	
Pre-bronchodilator FEV_1, L	1.31±0.44	1.28±0.46	1.49±0.38	1.48±0.36	0.752
Pre-bronchodilator FEV_1, % predicted	44.75±13.67	44.53±14.45	49.40±11.80	49.33±11.01	0.485
IC, % predicted	77.51±22.15	76.05±24.19	76.56±21.33	75.60±21.28	0.470
RV/TLC, % predicted	48.66±11.51	49.60±11.38	42.23±11.89	43.83±12.12	0.983
MMRC	1.86±1.14	1.94±1.09	1.87±1.11	1.72±1.05	0.146
6MWD, m	422.45±86.04	413.07±99.16	432.27±101.86	403.85±105.52	0.019
SGRQ total score	36.21±17.53	36.91±19.22	30.81±15.26	35.25±17.10	0.037
Exacerbation frequency/yr	0.78±0.99	0.72±1.00	0.36±0.58	0.28±0.65	0.266

Tuberc Respir Dis 2016;79:22-30

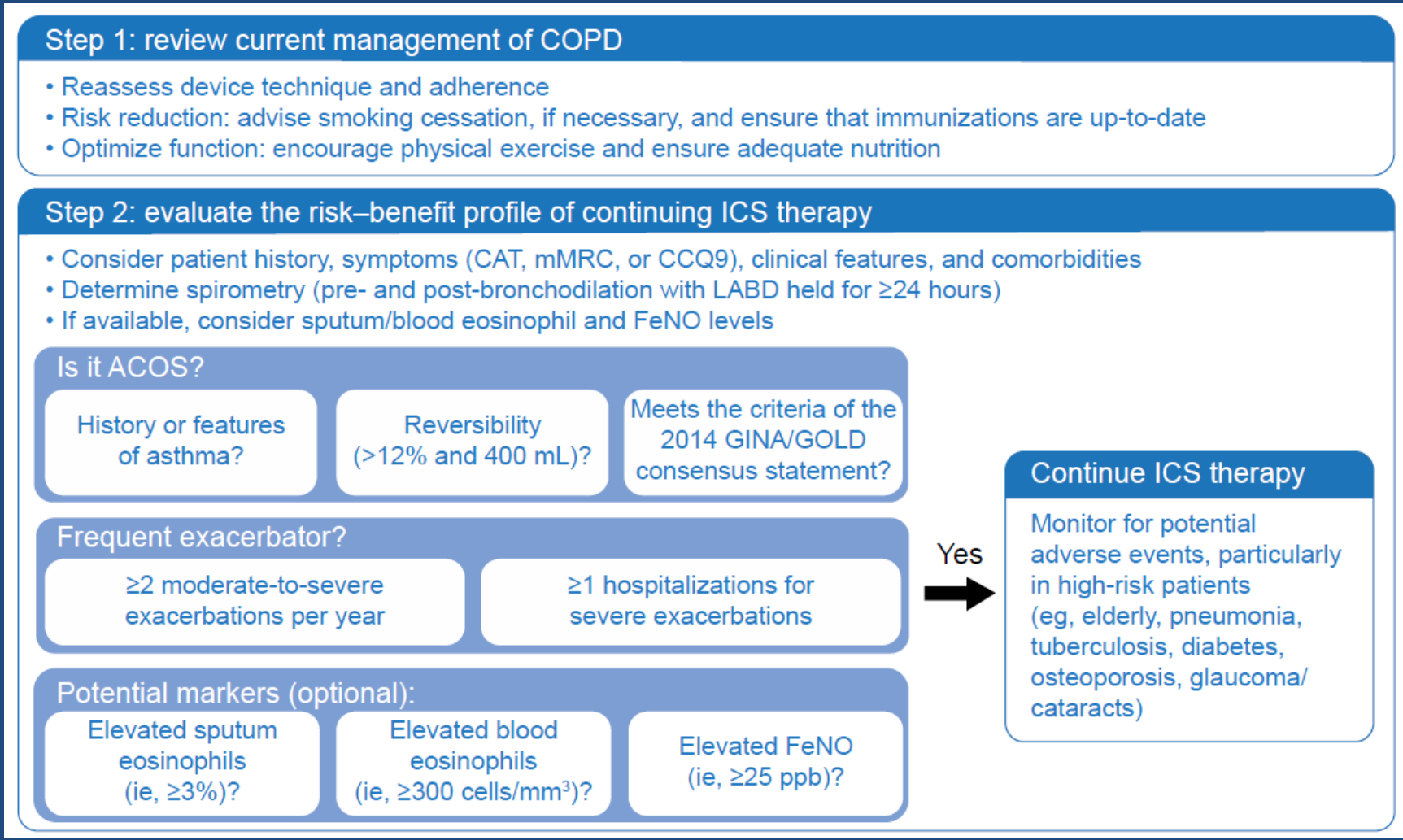
Contents

- Risk of ICS
- Benefit of ICS
- Withdrawal of ICS
- Cost

Example

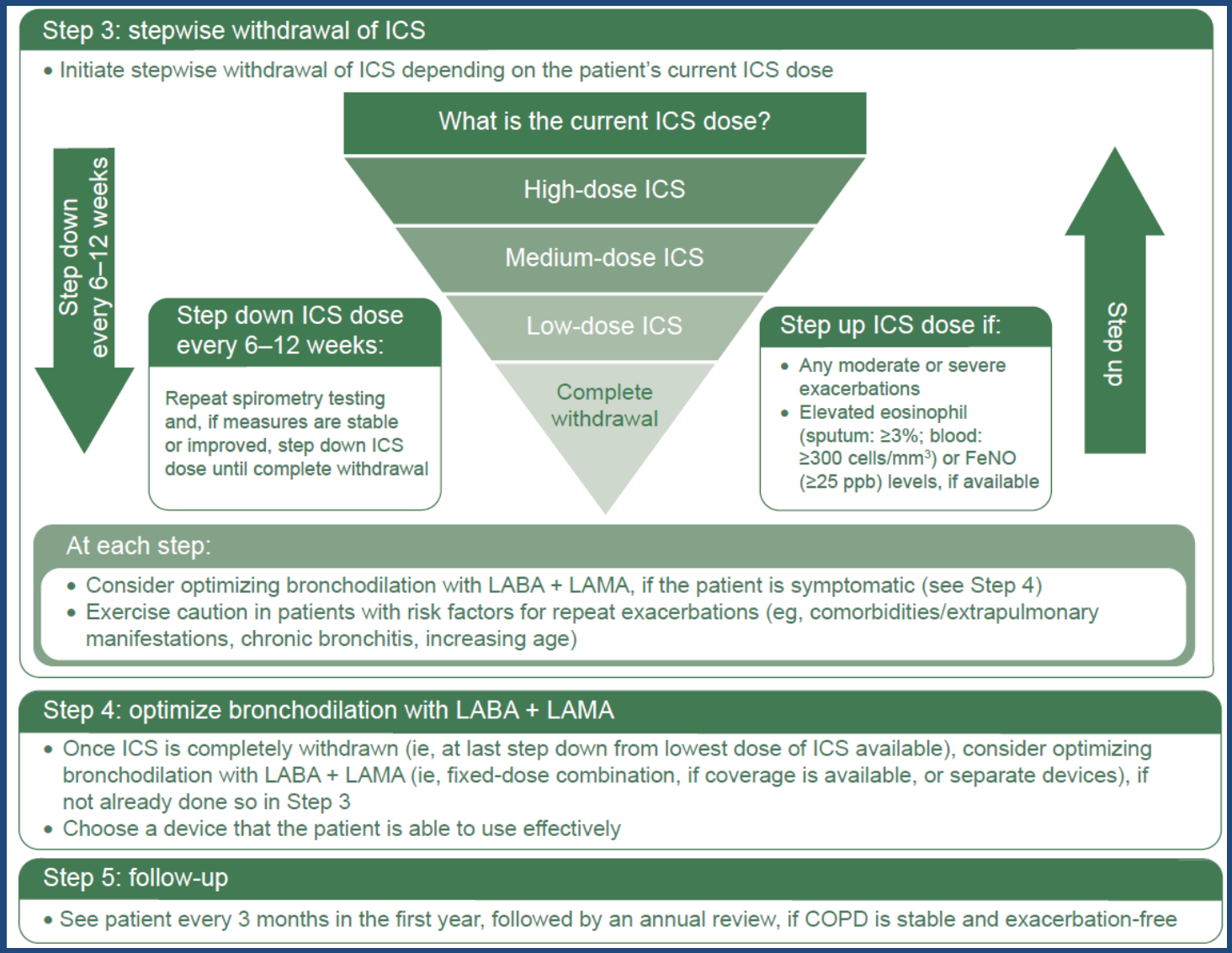
- Bud/Fo (320/9) + Tiotropium = 51,455 + 44,880 = 96,335/mo
- SAL/FP (500/50) + Tiotropium = 38,898 + 44,880 = 83,778/mo
- SAL/FP (250/50) + Aclidinium = 30,596 + 39,235 = 69,831/mo
- Indacaterol + Aclidinium = 38,300 + 39,235 = 77,535/mo
- Vilanterol + Umeclidinium = 45,657/mo
- Indacaterol + Glycopyrronium = 42,980/mo

A Proposal



Int J Chron Obstruct Pulmon Dis 2015;10:2535-2548

A Proposal



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Conclusion: De-escalation

Less Risk of
- Pneumonia
- Candidiasis
- Cataracts
- Tuberculosis
- Osteoporosis, etc..

Less Cost
Less Compliance Issue

Doubtful role of ICS in COPD

Recent studies showed safety: WISDOM / OPTIMO / INSTEAD / ILLUMINATE, etc..