

KOAH'ta steroidlerin pabucu dama mı atıldı?

PROF.DR.ARZU MIRICI-2018 İSTANBUL

KOAH'ın patofizyolojik özellikleri

- ▶ Mukus hipersekresyonu
- ▶ Mukosilyer transportta azalma
- ▶ Mukozal hasar

- ▶ Enflamatuvar hücre sayısında/aktivasyonunda artma:
 - ▶ CD8⁺ T-lenfositleri
 - ▶ monositler/makrofajlar
 - ▶ nötrofiller
 - ▶ mast hücreleri
- ▶ Enflamatuvar mediyatör artışı: IL-8, TNF- α , LTB-4 ve oksidanlar
- ▶ Proteaz/antiproteaz dengesizliği

IL = interlökin
LTB-4 = lökotrien B4
TNF- α = tümör nekroz faktör- α



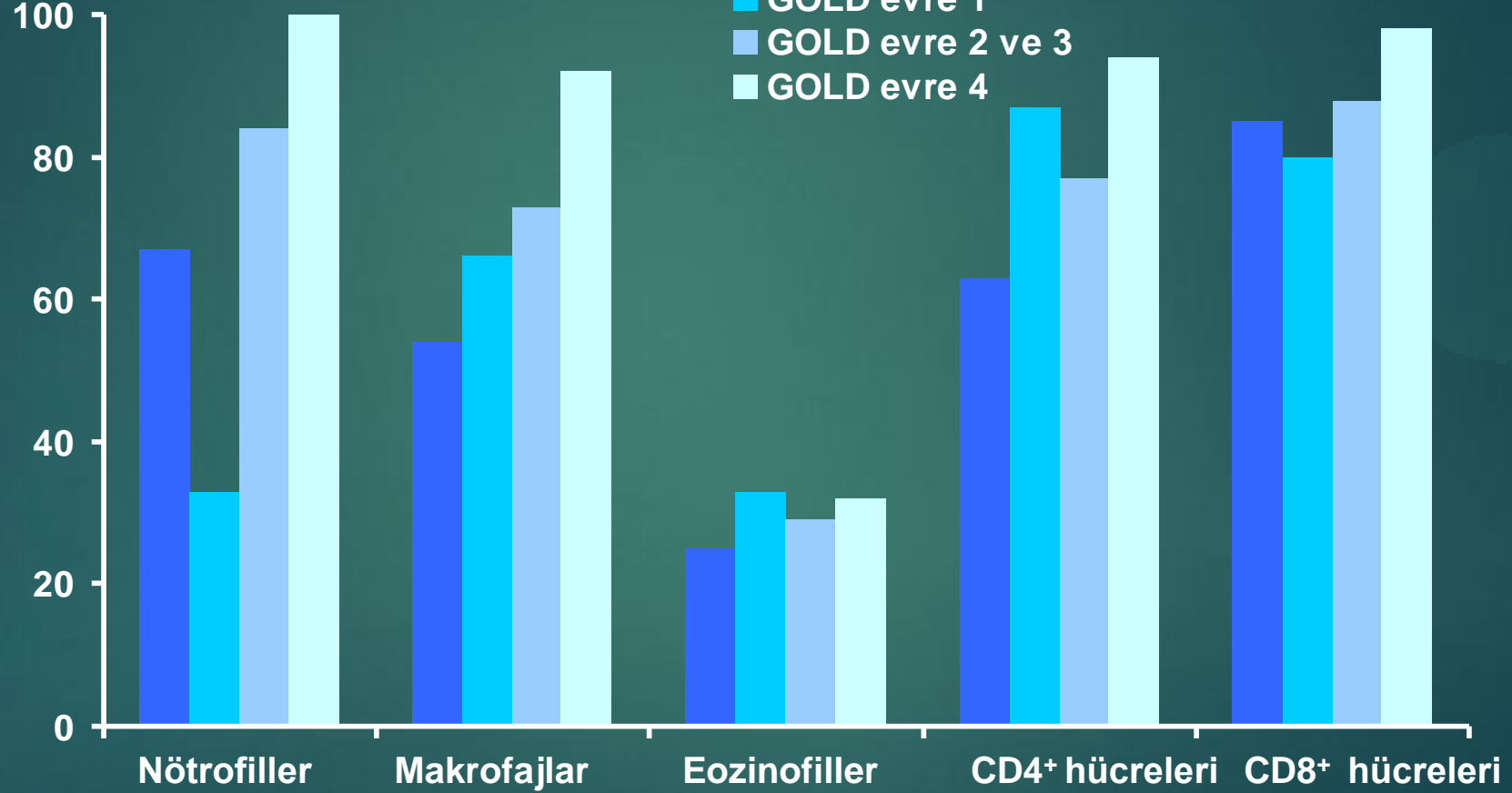
- ▶ Goblet hücre hiperplazisi/metaplazisi
- ▶ Mukus bezi hipertrofisi
- ▶ Düz kas kitlesinde artış
- ▶ Hava yolu fibrozu
- ▶ Alveol yıkımı

- ▶ Kötu beslenme
- ▶ BKİ azalması
- ▶ İskelet kası hasarı
 - ▶ halsizlik
 - ▶ zayıflama

- ▶ Elastik geri çekilmenin kaybı
- ▶ Düz kas kontraksiyonunda artış
- ▶ Alveol bağlantılarının kaybı

KOAH'ın erken evrelerinde bile enflamasyon vardır

Hava yollarında ölçülen hücreler (%)



Hogg et al. N Engl J Med 2004

KOAH tedavisinin amacı nedir?

- ▶ Semptomlar
- ▶ FEV1 düşme hızı
- ▶ Alevlenmeler
- ▶ Mortalite
- ▶ Sağlık harcamaları



- ▶ Yaşam kalitesi
- ▶ Egzersiz kapasitesi
- ▶ Solunum Fonksiyonu



KOAH ta inhaler steroidlerin etkisi

- ▶ **Hava yolu inflamasyonu**
- ▶ Alevlenme sıklığı
- ▶ FEV1 azalması
- ▶ Yaşam Kalitesi
- ▶ Ölüm
- ▶ Yan etkiler

İnhaler steroidlerin hava yolu inflamasyonuna etkisi

- ▶ doz ve süre
 - ▶ Total hücre sayısı
 - ▶ Nötrofil
 - ▶ Lenfosit

BMC Pulmonary Medicine

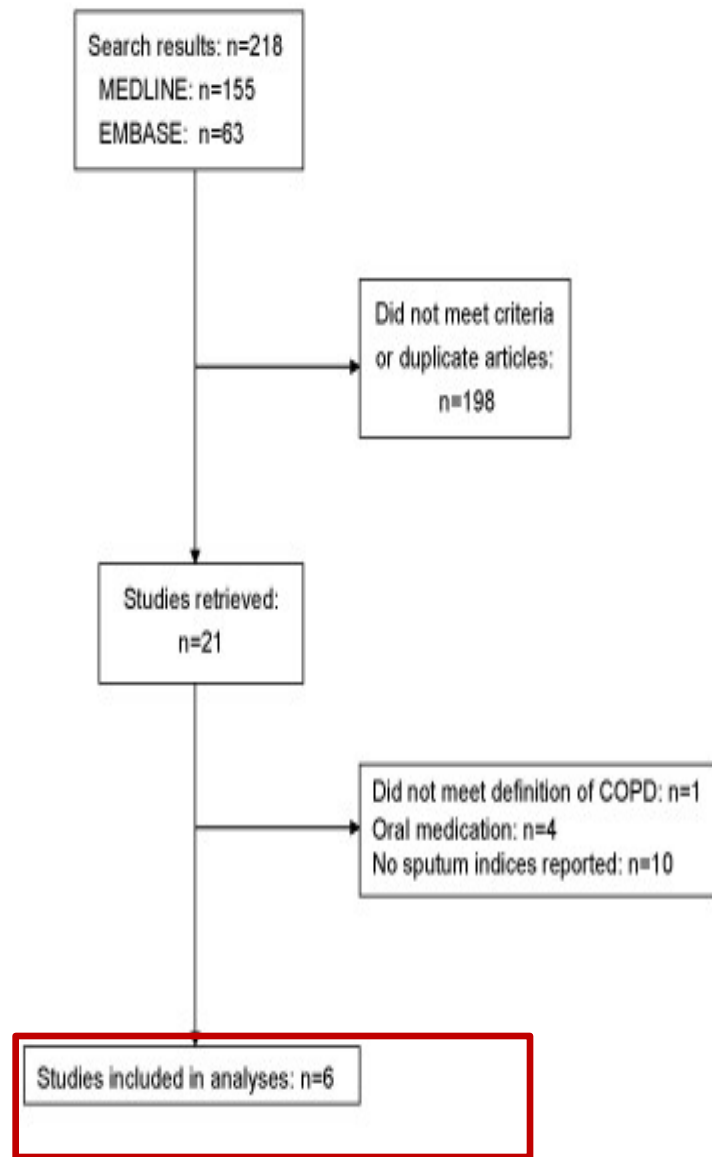


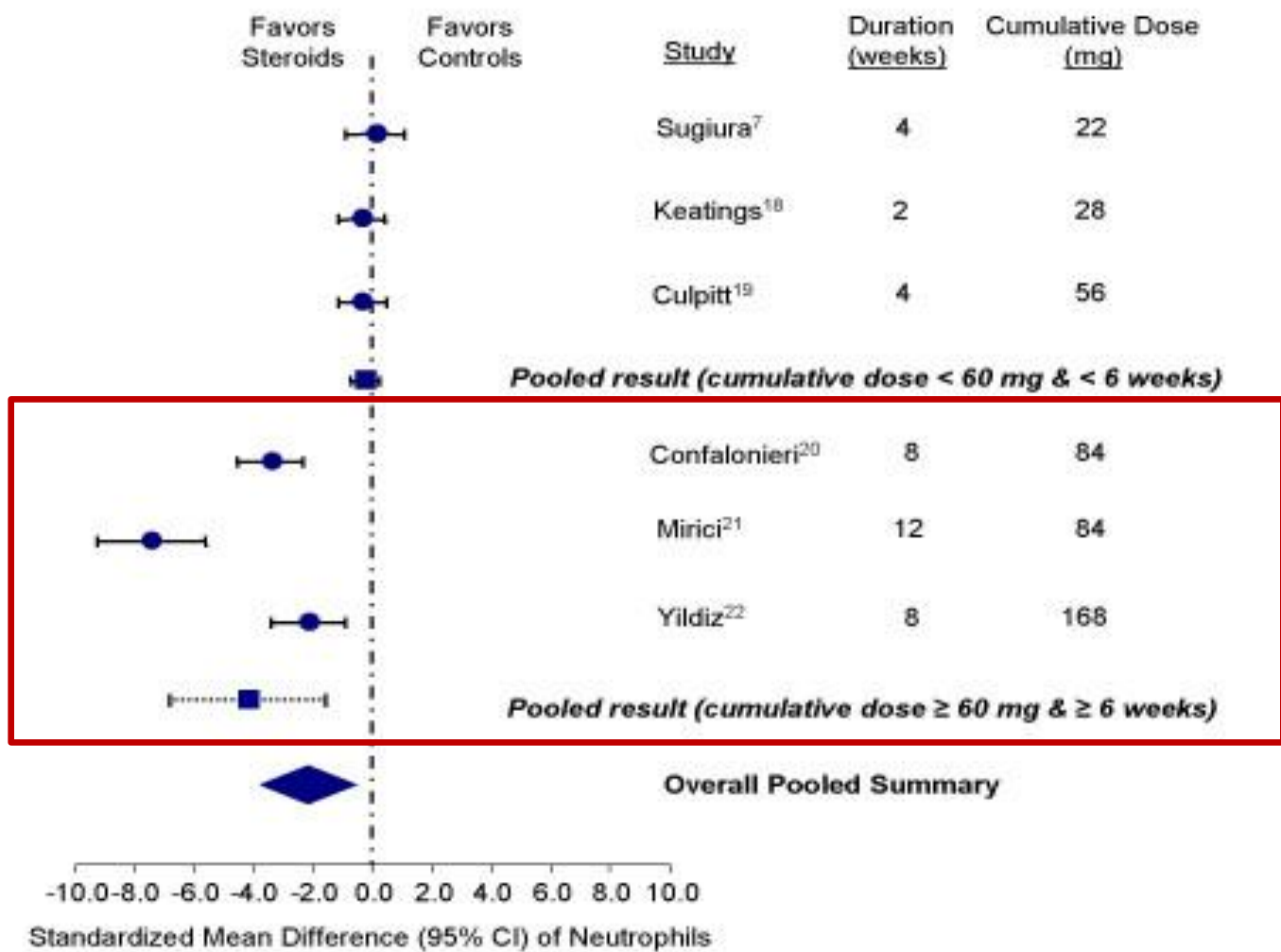
Research article

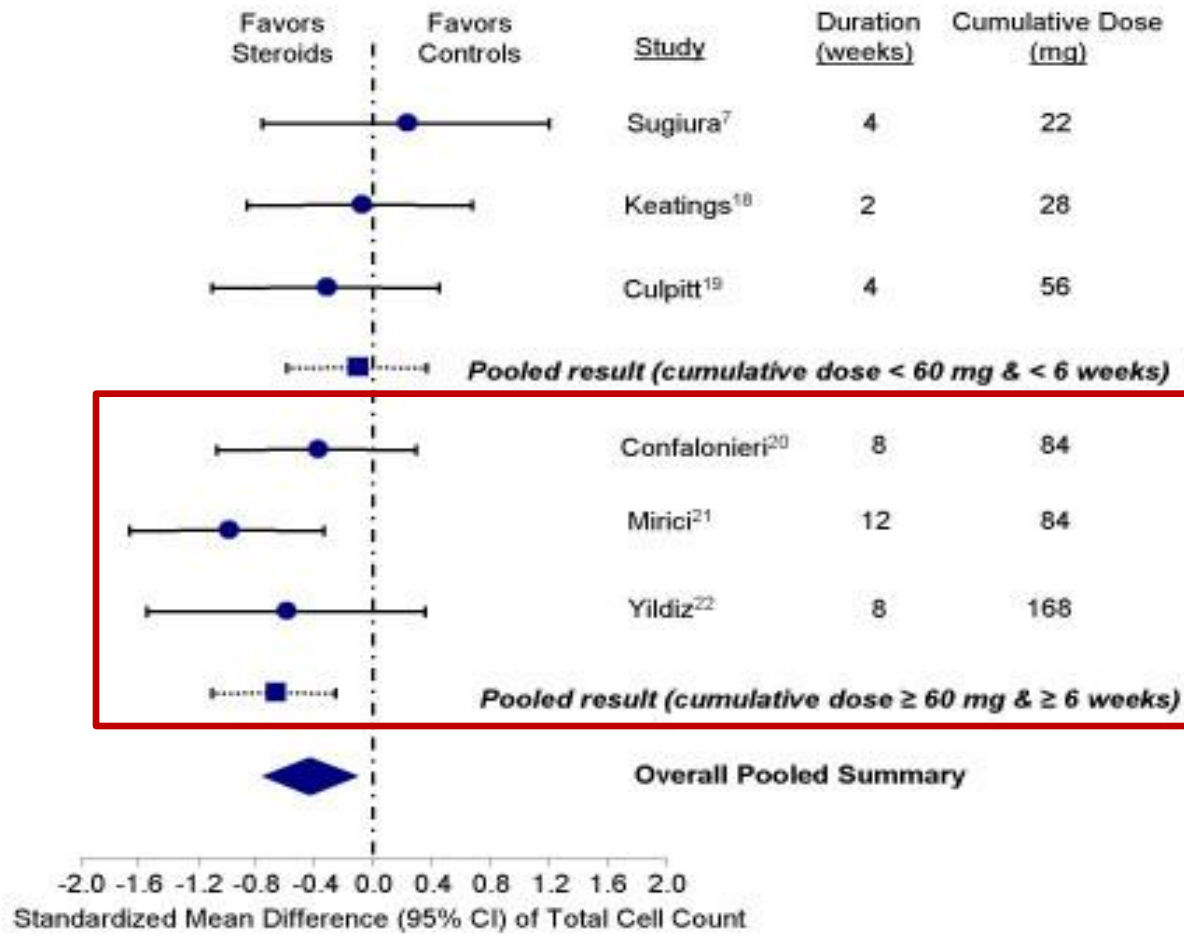
Open Access

Effects of inhaled corticosteroids on sputum cell counts in stable chronic obstructive pulmonary disease: a systematic review and a meta-analysis

Wen Qi Gan[†], SF Paul Man and Don D Sin^{*†}







KOAH ta inhaler steroidlerin etkisi

- ▶ Hava yolu inflamasyonu
- ▶ **Alevlenme sıklığı**
- ▶ FEV1 azalması
- ▶ Yaşam Kalitesi
- ▶ Ölüm
- ▶ Yan etkiler

İnhaler steroidlerin alevlenmelerin önlenmesine etkisi

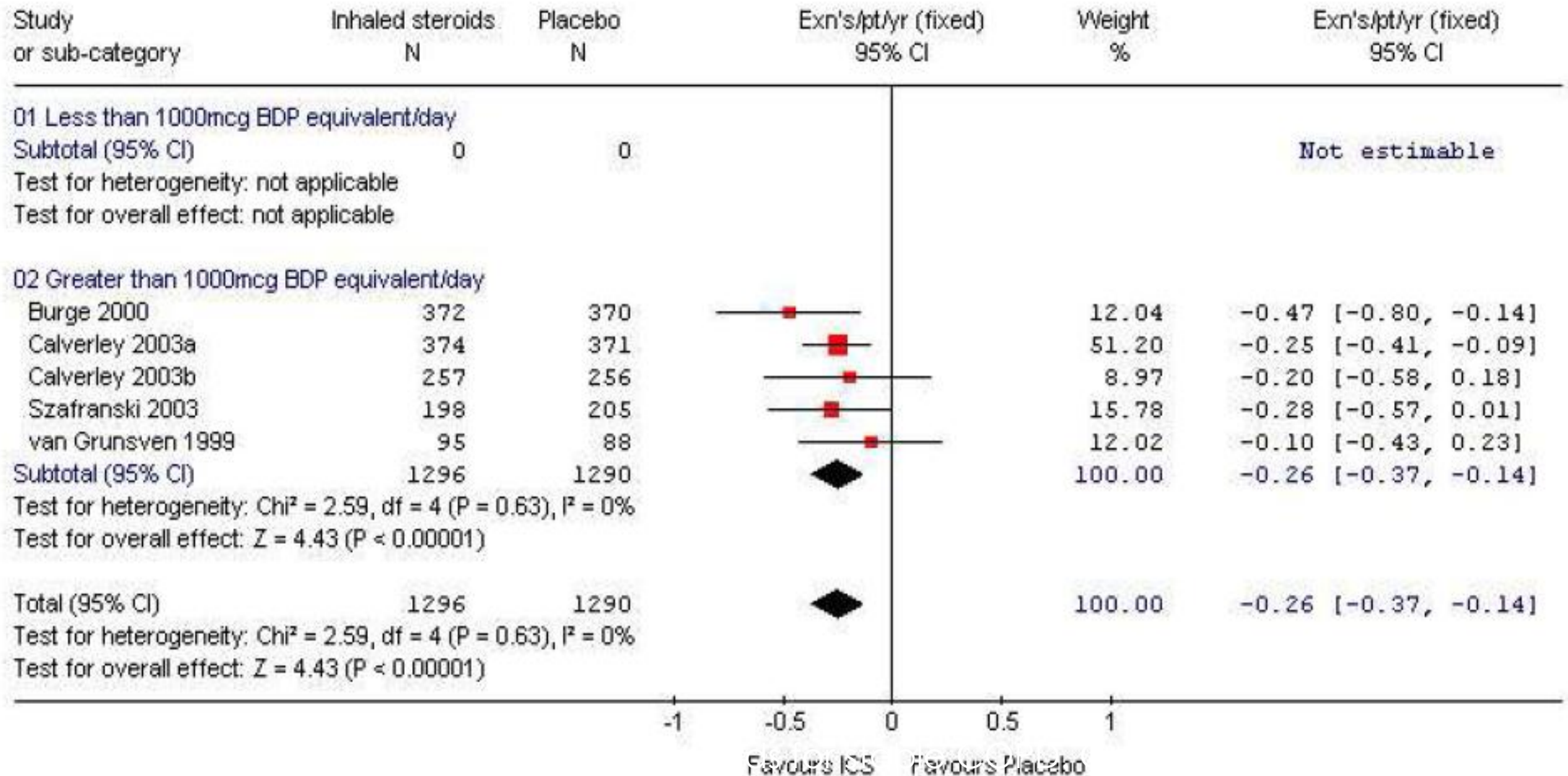
- ▶ Sıklık
- ▶ Süre
- ▶ Yatış süresi
- ▶ Sistemik steroid kullanımı
- ▶ Antibiyotik gerektiren
- ▶ İlk alevlenmeye kadar geçen süre
- ▶ NTT-number need to treat-tedavi gerektiren hasta
- ▶ Intend to treat (ITT)

Alevlenme tanımı

Study	Definition of COPD Exacerbation
Vestbo [89]	An exacerbation was defined as an affirmative answer to the question, "Have you since your last visit experienced more cough and phlegm than usual?"
Weir [90]	No definition provided
Senderovitz [91]	No definition provided
ISOLDE [95]	Worsening of respiratory symptoms that required treatment with oral corticosteroids or antibiotics, or both
LHS [97]	Events that required hospitalization, emergency department visits or non-routine visits to a physician
Mahler [115]	Exacerbations defined according to treatment
COPE [109]	Worsening of respiratory symptoms that required treatment with a short course of oral corticosteroids or antibiotics
Szafranski [100]	Severe exacerbations (use of oral steroids and/or antibiotics and/or hospitalization due to respiratory symptoms)
TRISTAN [102]	Worsening of COPD symptoms that required treatment with antibiotics, oral corticosteroids, or both
Hanania [116]	Defined by treatment, with moderate exacerbations requiring treatment with antibiotics and/or corticosteroids, and severe exacerbations requiring hospitalization
Calverley [101]	Exacerbations requiring medical intervention (oral antibiotics and/or corticosteroids or hospitalization)
COSMIC [110]	Mild exacerbation required use of SABA >3 times/day above patient specific reference rescue value. Moderate exacerbations required the use of CS p.o. while severe exacerbations required hospitalization.
Kardos [105]	Moderate/severe exacerbations were defined as worsening symptoms of COPD requiring antibiotics, oral corticosteroids, mycolytics, theophylline and/or hospitalization
OPTIMAL [103]	Physician-directed, short-term use of oral or intravenous steroids, oral or IV antibiotics or both
TORCH [104]	Symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids or hospitalization
INSPIRE [117]	Exacerbations that required treatment with oral corticosteroids and/or antibiotics or required hospitalization.
WISP [111]	a) An unreported exacerbation fulfilled symptom criteria on diary cards for a COPD exacerbation but was not managed with antibiotics or oral steroids. b) A moderate exacerbation was defined as a COPD exacerbation treated with a course of antibiotics or oral steroids. c) A severe exacerbation was defined as a COPD exacerbation treated with a course of antibiotics or oral steroids and resulting in hospital admission.
Ferguson [156]	Moderate to severe exacerbations were defined as worsening symptoms of COPD requiring treatment with oral corticosteroids, antibiotics, or hospitalization
Calverley [237]	Exacerbations requiring treatment with antibiotics or oral corticosteroids
COOPT [118]	One or more subsequent unscheduled contacts with either a GP or a chest physician due to worsening of respiratory symptoms (<u>mild</u> : no change in treatment, <u>moderate</u> : treated with prednisolone and/or antibiotics, <u>severe</u> : emergency room visit or hospitalization)
Shaker [119]	Defined as a combination of 2 of the 3 following criteria: increased dyspnea, increased sputum production and change in sputum color
Anzueto [106]	Moderate/severe exacerbations were defined as worsening symptoms of COPD requiring antibiotics, oral corticosteroids and/or hospitalization
Sharafkhaneh [107]	An exacerbation was defined as worsening of symptoms requiring oral corticosteroids and/or hospitalization

İnhale kortikosteroidlerin Alevlenme sıklığına etkisi

Figure 03. Forest plot showing impact of steroids on the rates of exacerbations



KOAH ta inhaler steroidlerin etkisi

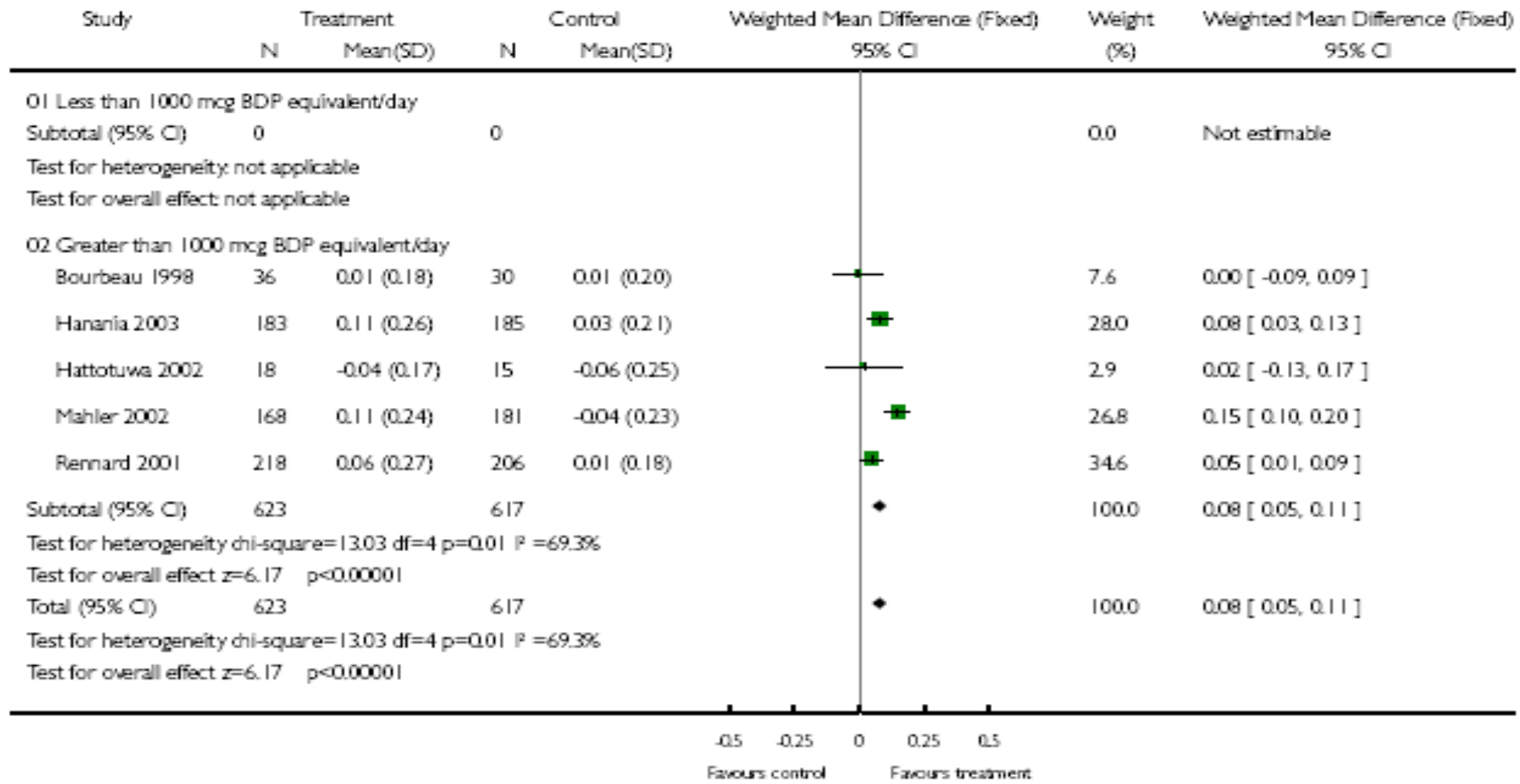
- ▶ Hava yolu inflamasyonu
- ▶ Alevlenme sıklığı
- ▶ **FEV1 azalması**
- ▶ Yaşam Kalitesi
- ▶ Ölüm
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Inhale kortikosteroidlerin FEV1 düzeyine etkisi

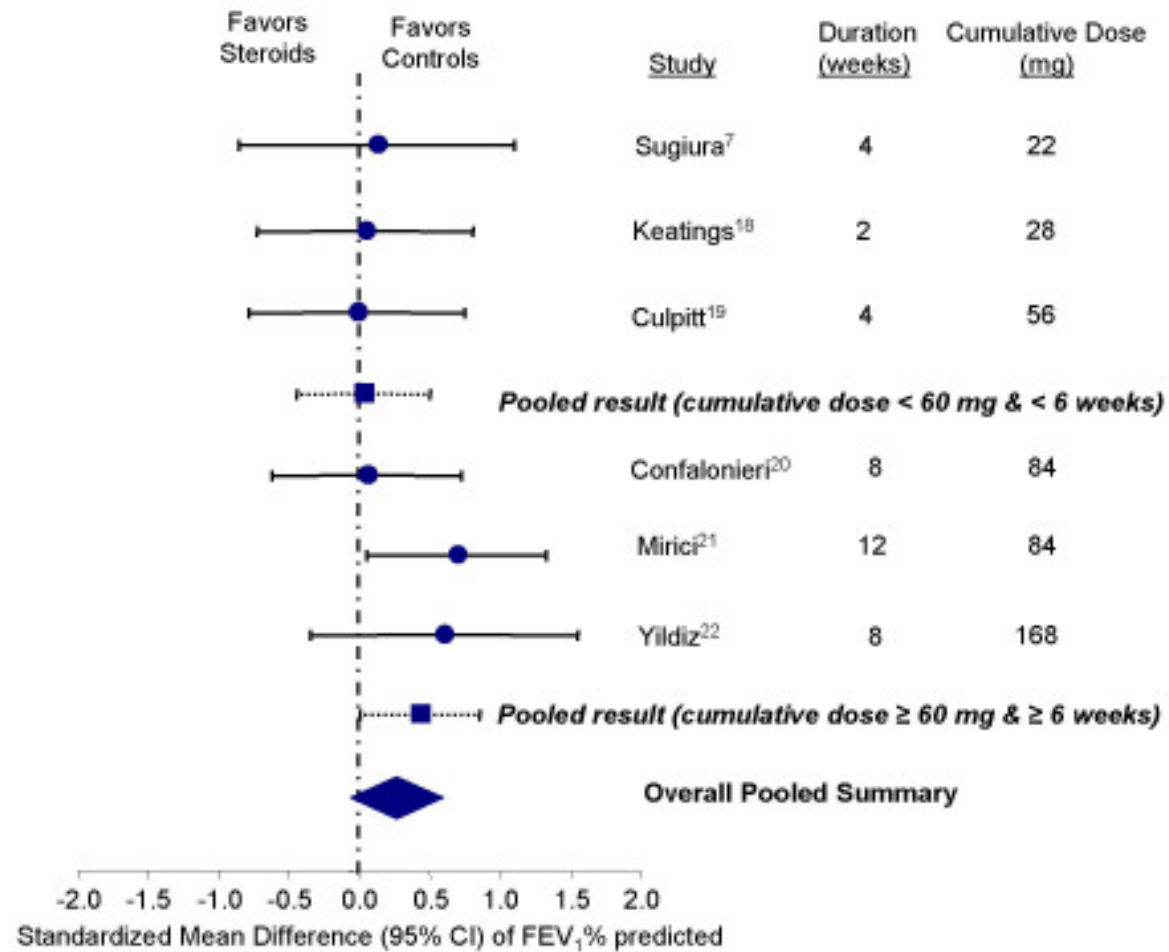
Review: Inhaled corticosteroids for stable chronic obstructive pulmonary disease

Comparison: 02 ICS versus placebo, parallel group studies, greater than 2 months to 6 months, (all doses)

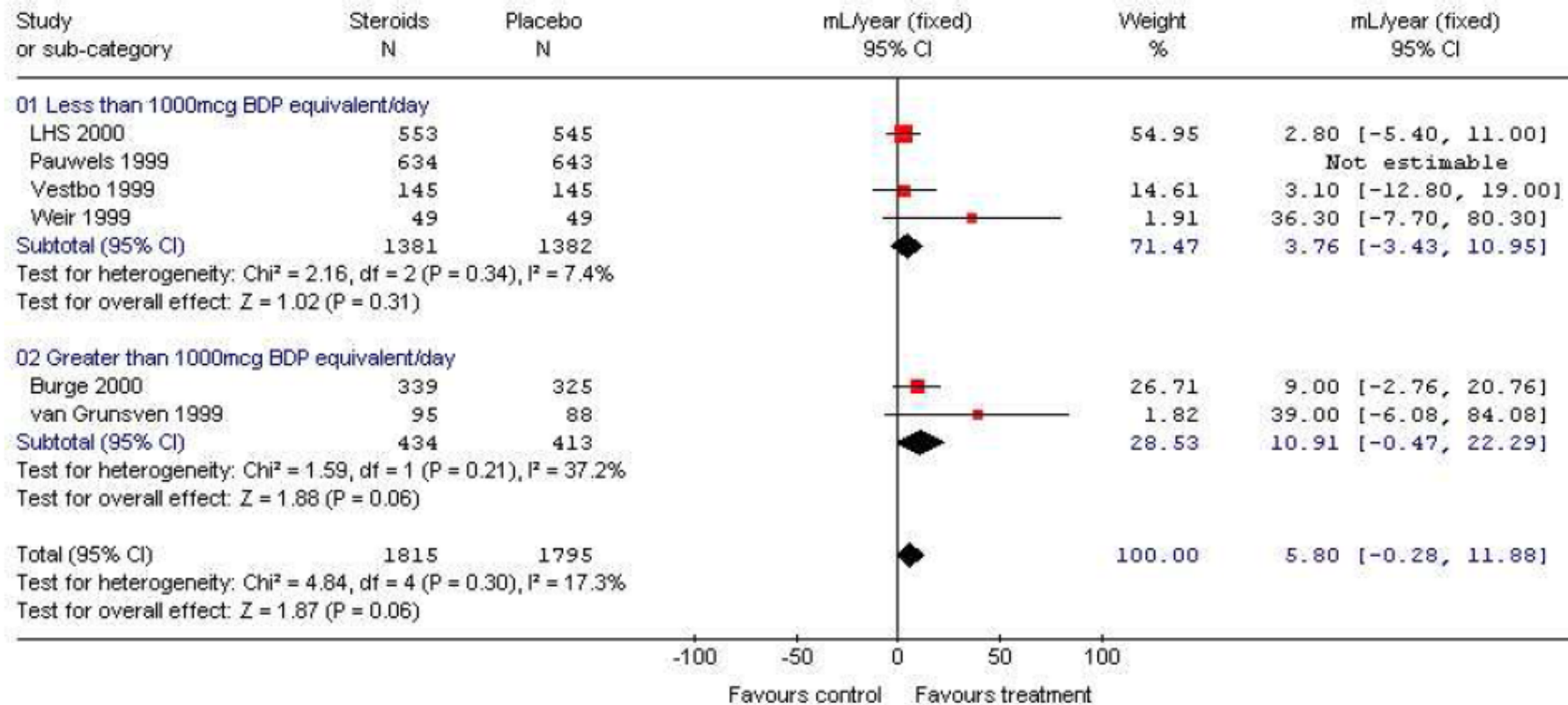
Outcome: 01 Change in pre-bronchodilator FEV1 compared with baseline



Young IA. Inhaled corticosteroids for stable COPD. Cochrane Database of Systematic Reviews 2007, Issue 2. Art No: CD002991

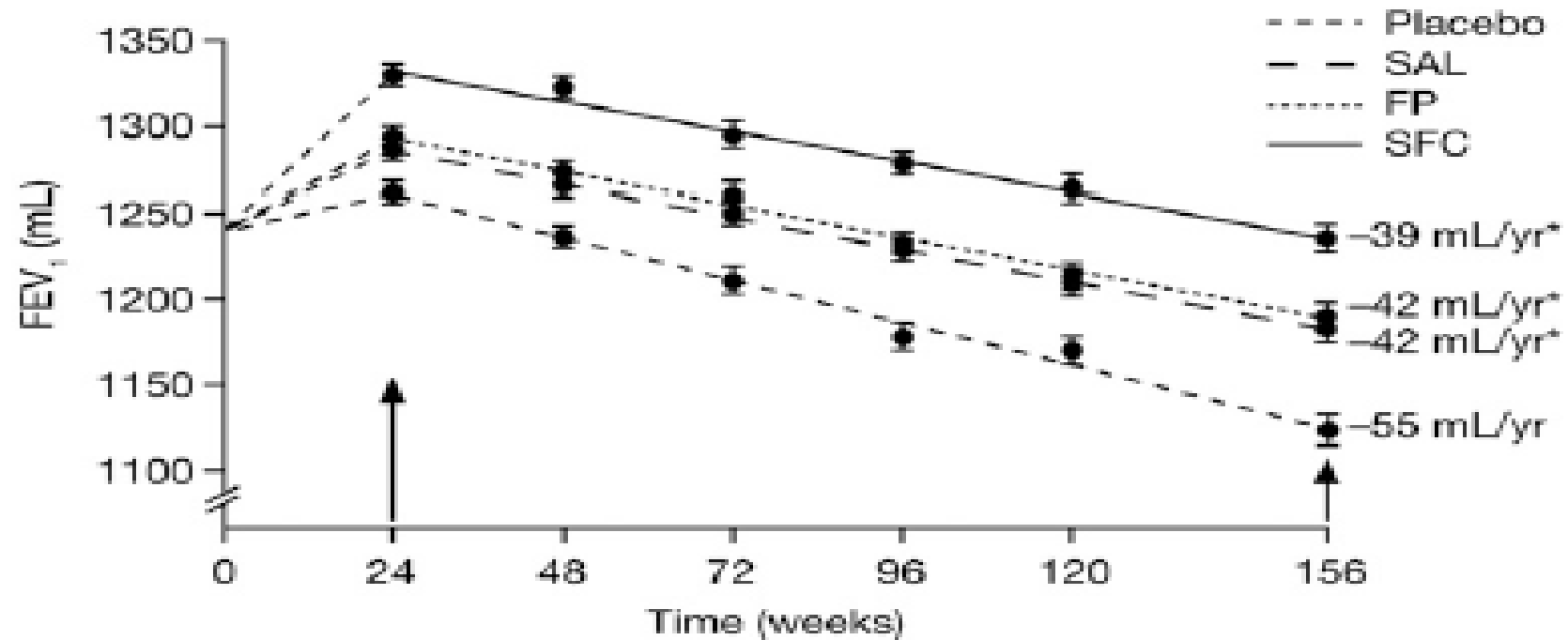


İnhale kortikosteroidlerin Yıllık FEV₁ azalmasına etkisi



Effect of Pharmacotherapy on Rate of Decline of Lung Function in Chronic Obstructive Pulmonary Disease

Results from the TORCH Study



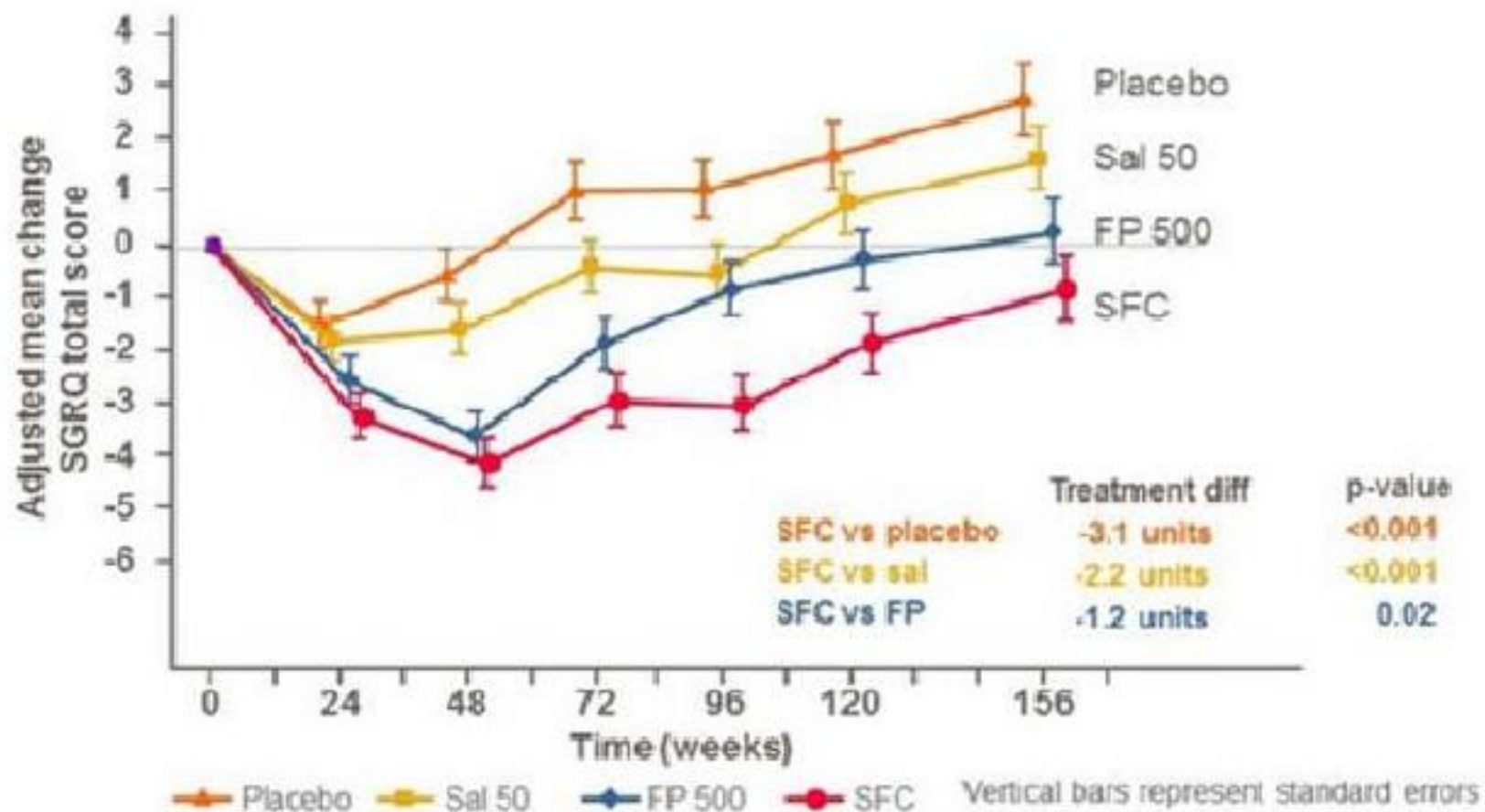
No. of patients

Placebo	1261	1248	1128	1049	979	906	819
SAL	1334	1317	1218	1127	1054	1012	934
FP	1356	1346	1230	1157	1078	1006	908
SFC	1392	1375	1281	1180	1139	1073	975

KOAH ta inhaler steroidlerin etkisi

- ▶ Hava yolu inflamasyonu
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- ▶ FEV1 azalması
- ▶ **Yaşam Kalitesi**
- ▶ Ölüm
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ICS/LABA significantly improves QoL (TORCH)

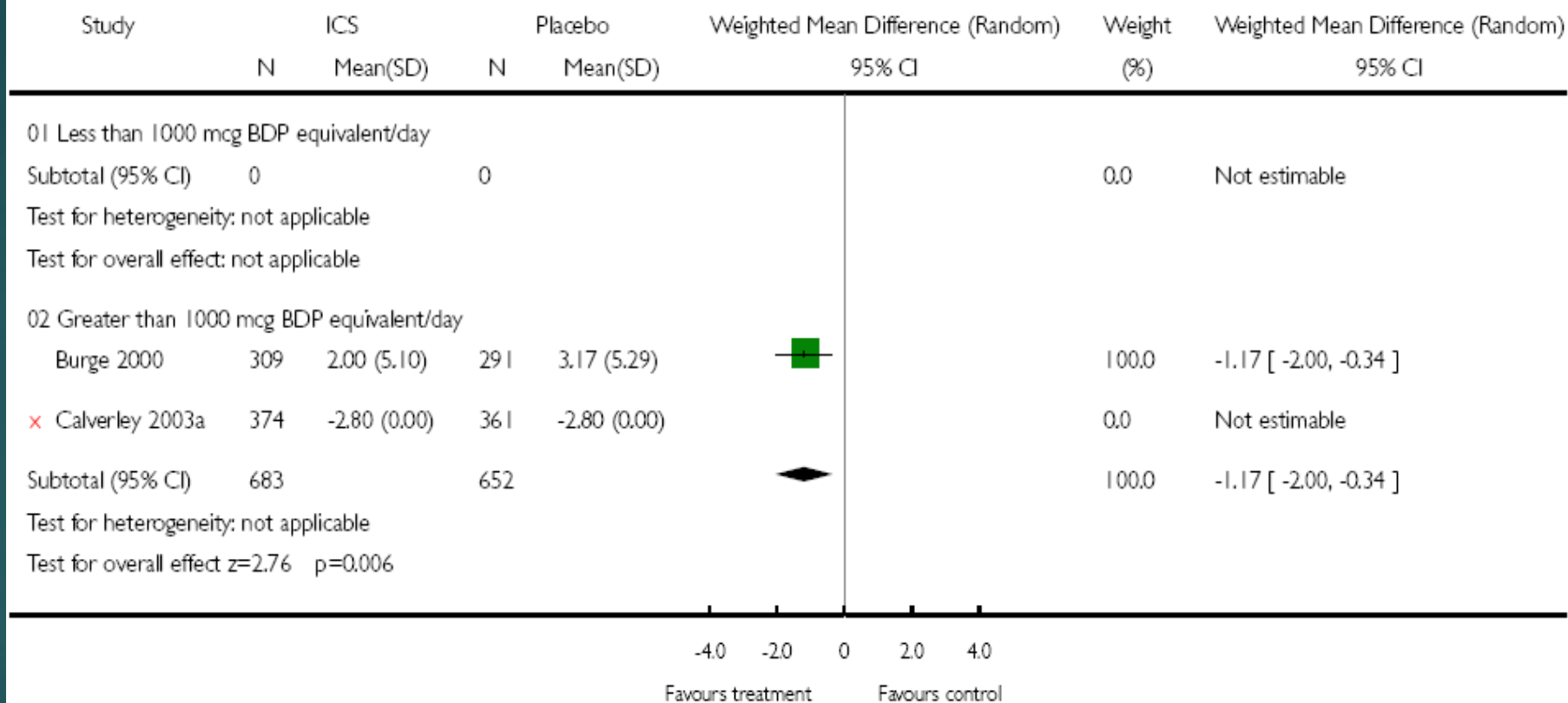


İnhale kortikosteroidlerin Yaşam kalitesine (SGRQ skoruna) etkisi

Review: Inhaled corticosteroids for stable chronic obstructive pulmonary disease

Comparison: 01 ICS versus placebo, parallel group studies, greater than 6 months (all doses)

Outcome: 09 Change in SGRQ total score (units/yr)



Young IA. Inhaled corticosteroids for stable COPD. Cochrane Database of Systematic Reviews 2007, Issue 2. Art No: CD002991

Zervas et al 2013

Study	Drug	N=	months	PLC B	LABA	ICS	ICS+LABA
ISOLDE	FP,PLCB	751	36	+3.17		+2.00	
Calverley	BF,BUD,For,PLCB	1022	12		-4.10	-3.00	-7.50
Szafranski	BF,BUD, FOR, PLCB	812	12	-0.03	-3.60	-1.90	-3.90
TRISTAN	SFP, SAL, FP, PLCB	1465	12	-2.30	-3.40	-3.10	-4.50
Sharafkhaneh	BF,FOR	1219	12		-5.9		-5.5(160/9) -7.2(320/9)

KOAH ta inhaler steroidlerin etkisi

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- ▶ **Ölüm**
- ▶ Yan etkiler

İnhaler steroidlerin KOAH'ta mortaliteye etkisi

Farklı popülasyonlarda;

- ▶ TORCH %14.3
- ▶ **UPLIFT %15.4**
- ▶ PATHOS %10.9

KOAH ta inhaler steroidlerin etkisi

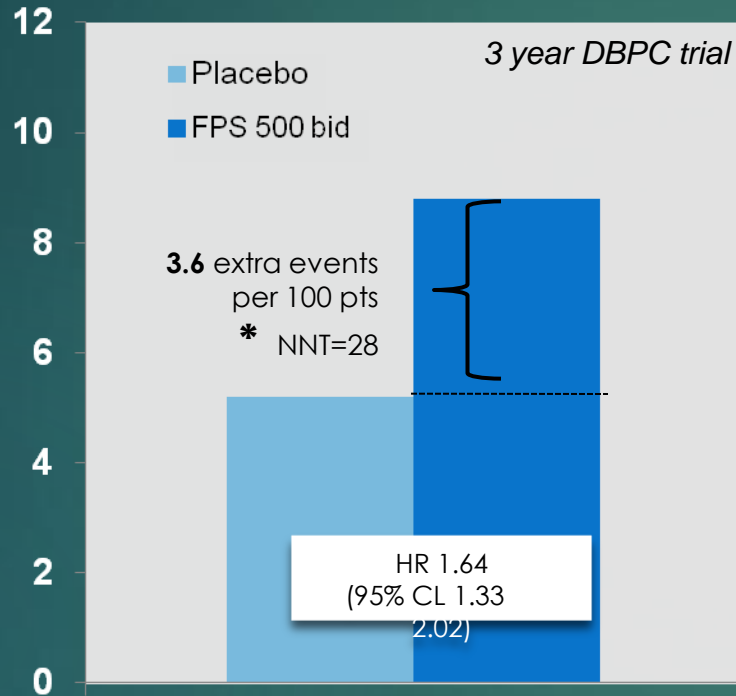
- ▶ Hava yolu inflamasyonu
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- ▶ Ölüm
- ▶ **Yan etkiler**

İnhaler steroidlerin yan etkileri

- ▶ Artmış Pnömoni riski
- ▶ Osteoporoz ve artmış kırık riski
- ▶ Katarakt ya da glokom
- ▶ Diabetes mellitus

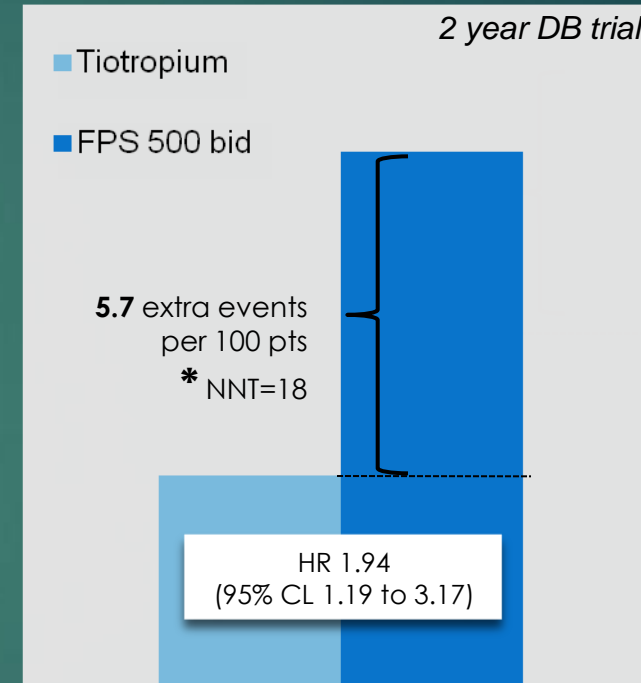
Uzun dönem çalışmalarda ;

Pneumonia rate per 100pt-yrs



TORCH Trial

Crim et al Eur Respir J 2009, 34: 641

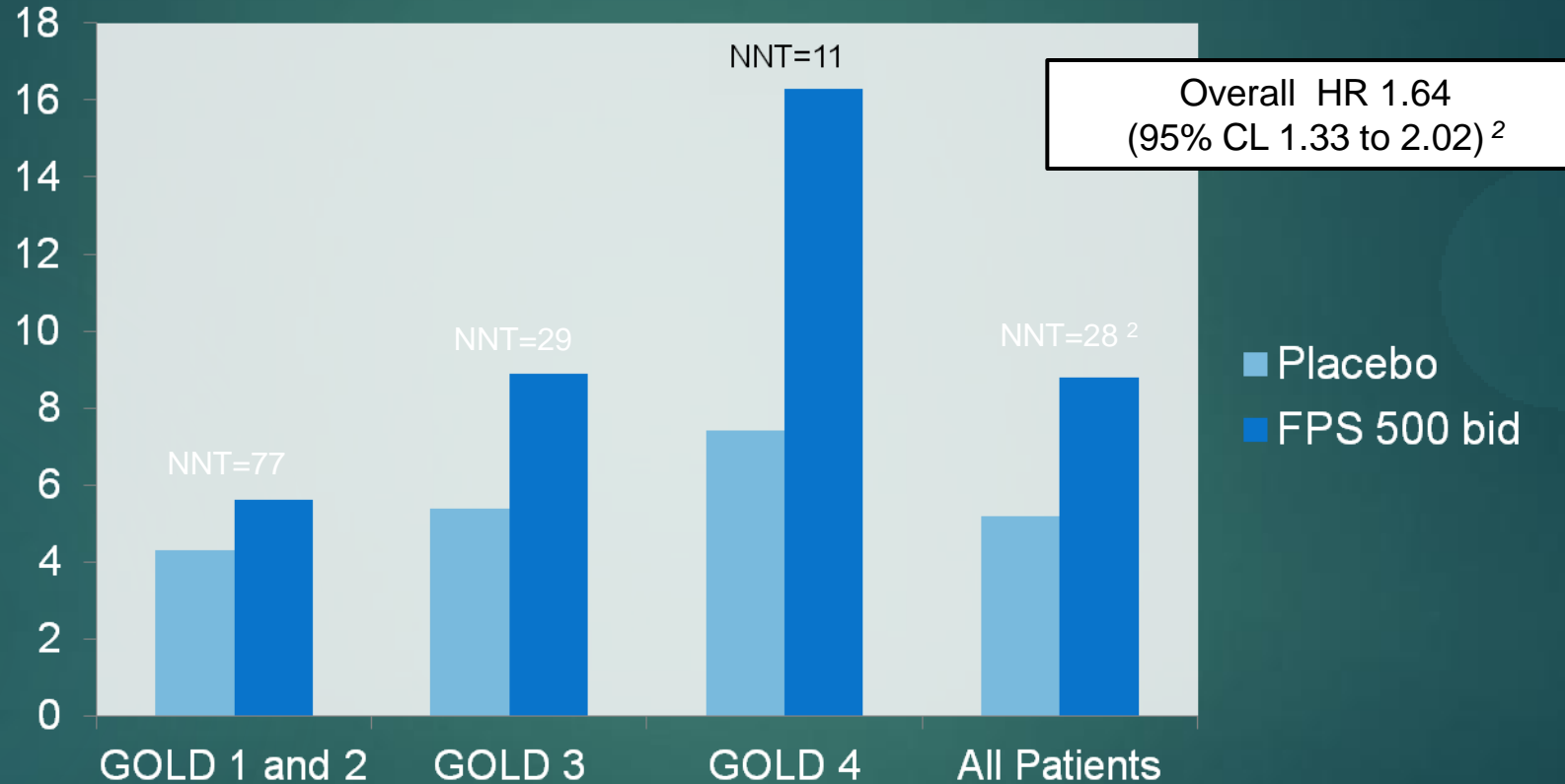


INSPIRE Trial

Calverley et al. Chest 2011;139:505

TORCH study: KOAH'ta pnomoni sıklığı hastalığın evresi ile ilişkilidir.

Pneumonia rate per 100pt-yrs in TORCH



1. Jenkins et al Respiratory Research 2009,10: 59.

2. Crim et al Eur Respir J 2009, 34: 641

Üç yıldan fazla inhaler steroid kullanan KOAH'lı olgularda pnömoni sıklığı

Corticosteroid type (No. of studies)	ICS containing regimen n/N (%)	Non ICS control n/N (%)	Adjusted Pneumonia Odd Ratio (95% CI)
Fluticasone (16)*	612 / 7,919 (7.7)	364 / 7,705 (4.7)	1.67 (1.47, 1.89) **
Budesonide (7)*	140 / 3,801 (3.7)	94 / 2,760 (3.4)	1.19 (0.92, 1.53) [ns]
Mometasone (1)	25 / 616 (4.1)	6 / 295 (2.0)	2.00 (0.83, 4.81) [ns]

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Inhale kortikosteroidler neden sorun?

- ▶ Aşırı kullanılıyor
- ▶ Pnömoni riski önemli
- ▶ Bazı olgular yanıtız
- ▶ Steroid fobisi

GOLD-2017

Global Initiative for Chronic Obstructive Lung Disease

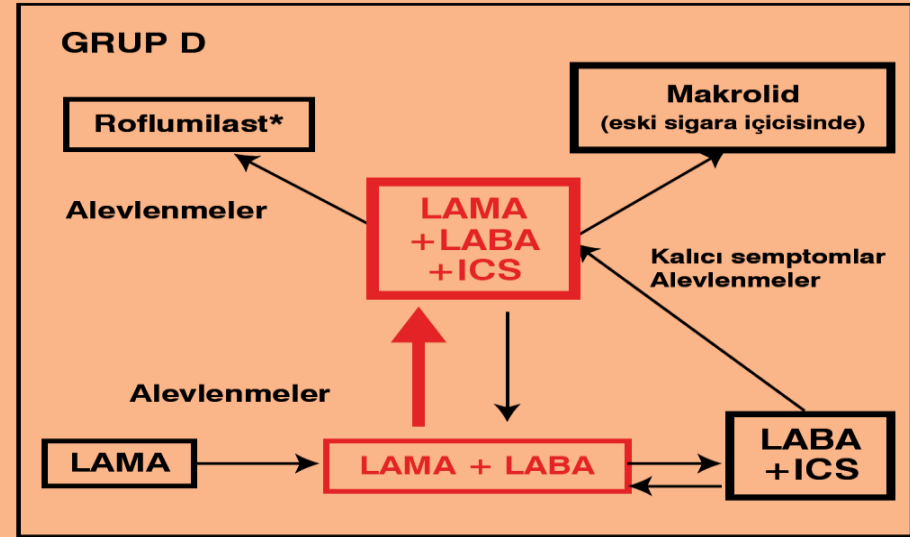
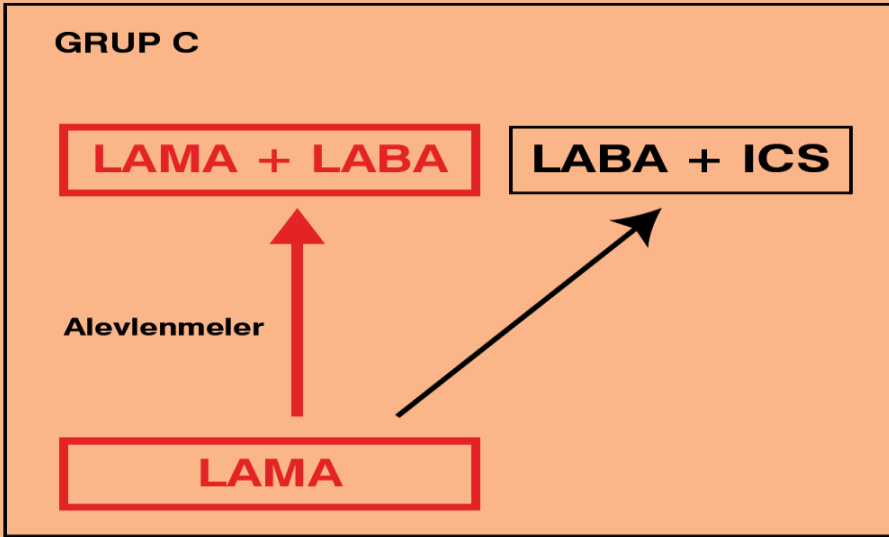


GLOBAL STRATEGY FOR THE DIAGNOSIS,
MANAGEMENT, AND PREVENTION OF
CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2017 REPORT

- ▶ Tanımdan inflamasyon çıkarıldı
- ▶ Evrelemeden Solunum fonksiyonu çıkarıldı
- ▶ Kalıcı semptomlar ve alevlenme önemsendi
- ▶ Tedavide bronkodilatörlere öncelik verildi
- ▶ LAMA'ların 3 çalışma ile öne çıkması
- ▶ (POET, INVIGORATE, SPARK)
- ▶ LANTERN ve FLAME (LABA/LAMA vs LABA/IKS)



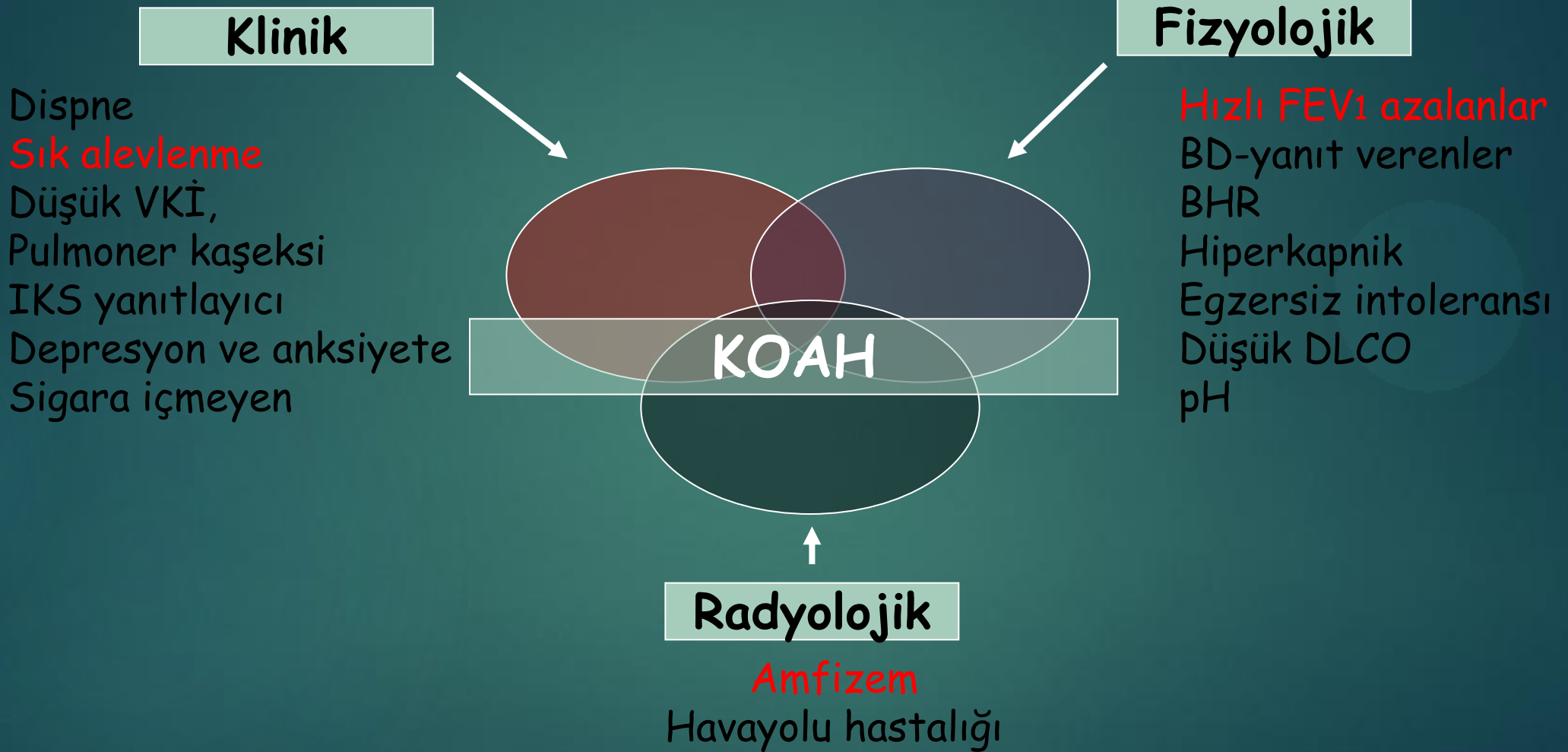
Şekil 2: GOLD 2017'e Göre Stabil KOAH'da Farmakolojik Tedavi Önerileri



İlk tercih tedavi:

*FEV₁ < %50 beklenenin ve kronik bronşit fenotini

KOAH Fenotipleri



Astım KOAH overlap-AKOS-AKO %20

- Birçok rehber LABA+IKS ilk tercih olarak önerir
- WISDOM-IKS çekilince alevlenme riski arttı
- Eosinofili-%2-İlk tercih LABA+IKS

Hiperinflasyon/Amfizem fenotipi

- Semptomlar ön planda
- Alevlenme riski düşük
- Hızlı FEV1 kaybı