Bronkodilatörler
KOAH'ı
Ne Kadar Tedavi Ediyor?

Esra Uzaslan

Saat	Konu	Eğitimci
14.45-15.00	Açılış, Tanışma ve Beklentiler	Prof. Dr. Akın KAYA, Prof. Dr. Tevfik ÖZLÜ
1. OTURUM **Oturum Başkanları: Prof. Dr. Akın KAYA, Prof. Dr. Erdoğan ÇETİNKAYA**		
15.00-15.20	GOLD Kılavuzunda Taşlar Yerine Oturdu Mu?	Doç. Dr. Esra ERTAN YAZAR
15.20-15.40	KOAH'da Fenotipler ve ACO Bilmecesi	Prof. Dr. Tevfik ÖZLÜ
15.40-16.00	KOAH'da İmmünizasyon İşe Yarıyor Mu?	Yrd. Doç. Dr. Özlem ERÇEN DİKEN
16.00-16.20	Tartışma	
16.20-17.00	Çay ve Kahve Arası	
2. OTURUM **Oturum Başkanları: Prof. Dr. Mehmet KARADAĞ, Uzm. Dr. Murat KIYIK**		
17.00-17.20	Bronkodilatörler KOAH'ı Ne Kadar Tedavi Ediyor?	Prof. Dr. Esra KUNT UZASLAN
17.20-17.40	KOAH'da IKS'nin Pabucu Dama Atıldı Mı?	Prof. Dr. Arzu MİRİCİ
17.40-18.00	KOAH'da Cerrahi: Volüm Azaltıcı Cerrahi ve Transplantasyon	Doç. Dr. Ali YEĞİNSU
18.00-18.20	KOAH'da Komorbidite ve Komplikasyonların Yönetimi	Doç. Dr. Sevinç SARIÇ ULAŞLI
18.20-18.45	Tartışma	
19.00-21.00	Akşam Yemeği	

KOAH Değerlendirmesindeki Tarihsel Süreç

GOLD 2010[1]

Bronkodilatör sonrası FEV_1'e göre KOAH şiddetinin spirometrik sınıflandırması

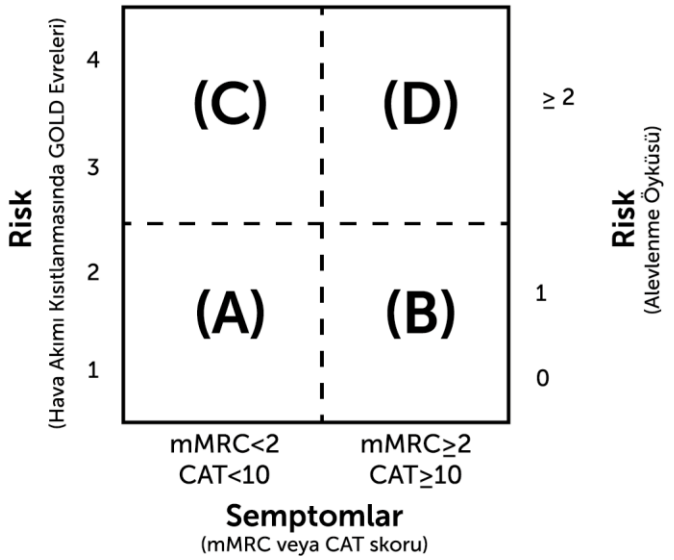
Evre I: Hafif	$FEV_1/FVC<0.70$ $FEV_1 \geq$ %80 beklenen
Evre II: Orta	$FEV_1/FVC<0.70$ %50 $\leq FEV_1 <$ %80 beklenen
Evre III: Ağır	$FEV_1/FVC<0.70$ %30 $\leq FEV_1 <$ %50 beklenen
Evre IV: Çok Ağır	$FEV_1/FVC<0.70$ $FEV_1 <$ %30 beklenen veya $FEV_1 <$ %50 beklenen ve kronik solunum yetmezliği

- FEV_1'e göre evreleme ve evrelere göre tedavi
- Heterojen bir hastalık olduğunun farkına varılıyor
- Sadece FEV_1 artık yeterli değil

TEK BOYUTLU DEĞERLENDİRME

GOLD 2011[2]

Semptomlar, spirometrik sınıflandırma ve alevlenme riski arasındaki ilişki

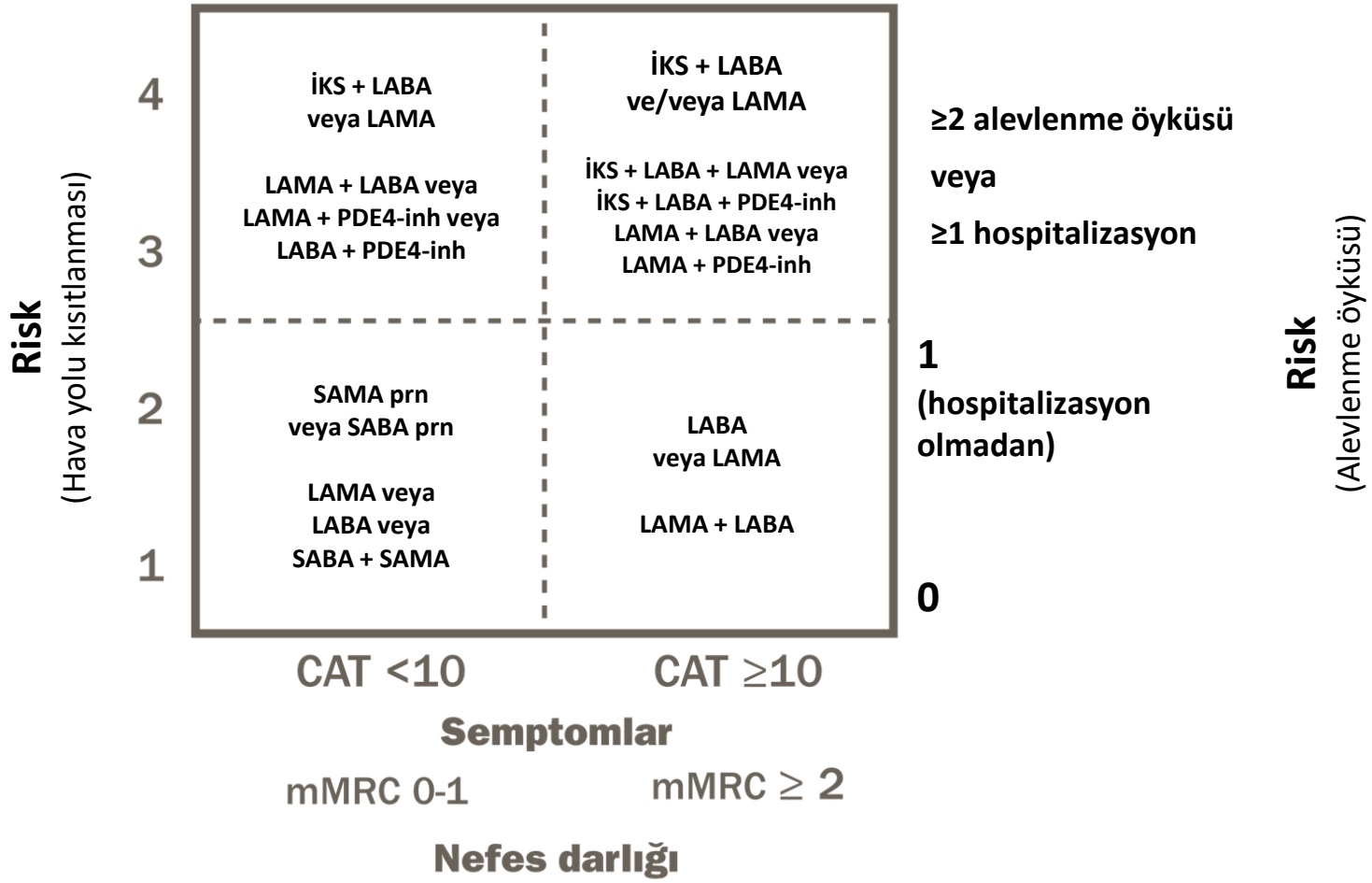


- Sadece havayolu obstrüksiyonu değil, semptomlar ve alevlenmeler de önemli
- Ampirik bir kategorizasyon sistemi, halen kanıt çok az

ÇOK BOYUTLU DEĞERLENDİRME

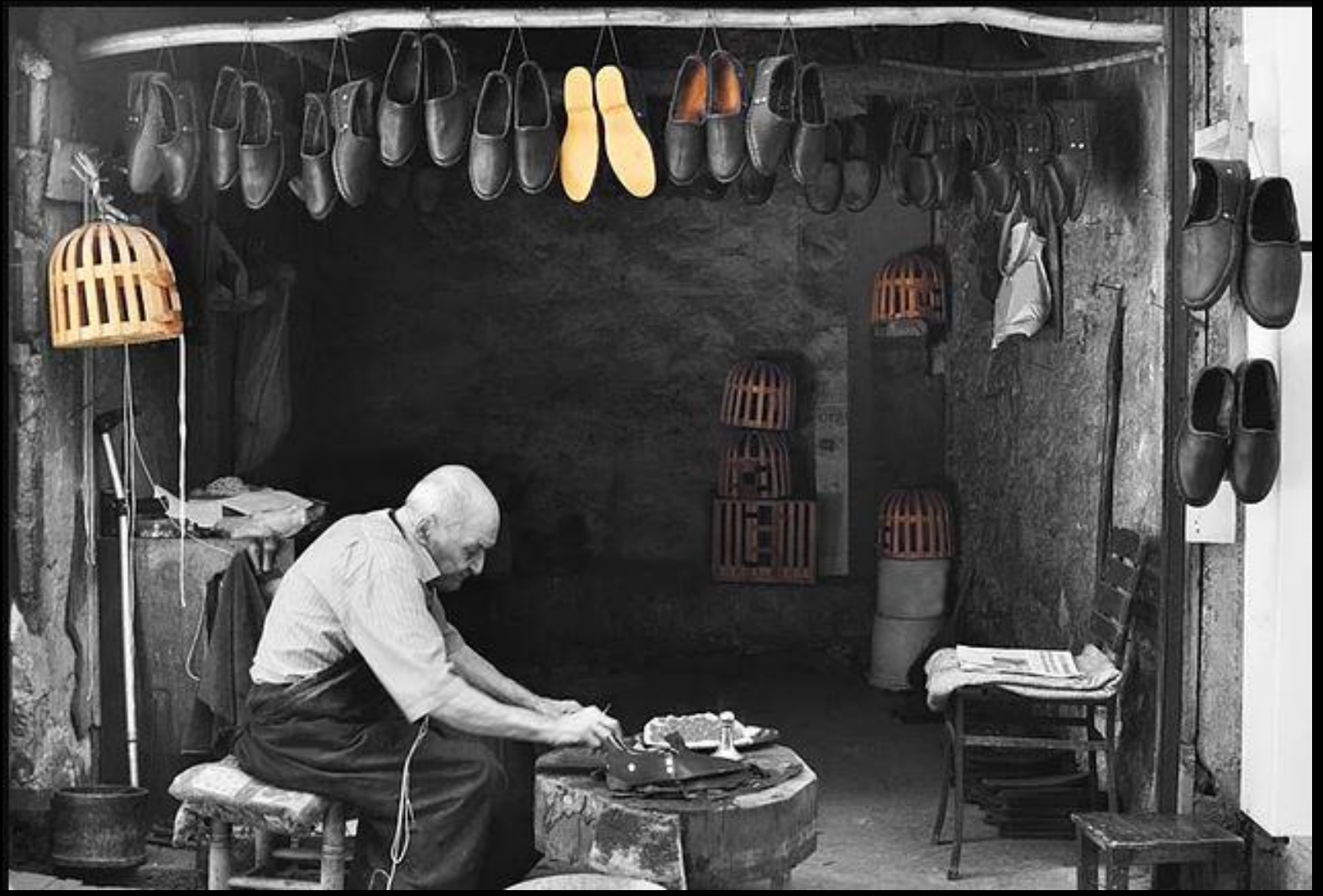
1. GOLD Updated 2010. **2.** GOLD Revised 2011

GOLD 2011
KOAH'ın Farmakolojik Tedavisi



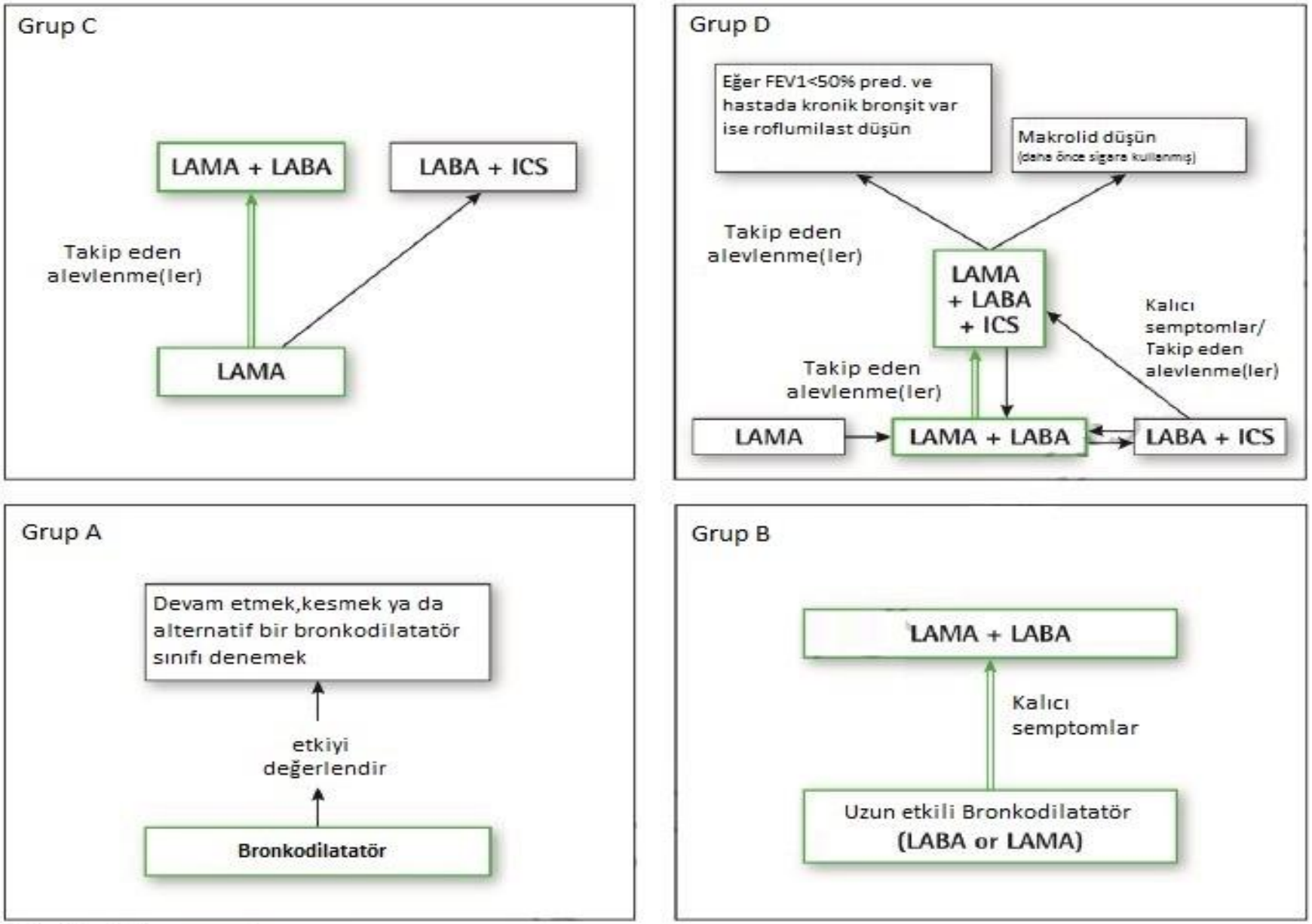
Global Initiative for Chronic Obstructive Lung Disease (GOLD) Global Strategy for the Diagnosis Management and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2011. Available at www.goldcopd.org

Saat	Konu	Eğitimci
14.45-15.00	Açılış, Tanışma ve Beklentiler	Prof. Dr. Akın KAYA, Prof. Dr. Tevfik ÖZLÜ
1. OTURUM Oturum Başkanları: Prof. Dr. Akın KAYA, Prof. Dr. Erdoğan ÇETİNKAYA		
15.00-15.20	GOLD Kılavuzunda Taşlar Yerine Oturdu Mu?	Doç. Dr. Esra ERTAN YAZAR
15.20-15.40	KOAH'da Fenotipler ve ACO Bilmecesi	Prof. Dr. Tevfik ÖZLÜ
15.40-16.00	KOAH'da İmmünizasyon İşe Yarıyor Mu?	Yrd. Doç. Dr. Özlem ERÇEN DİKEN
16.00-16.20	Tartışma	
16.20-17.00	Çay ve Kahve Arası	
2. OTURUM Oturum Başkanları: Prof. Dr. Mehmet KARADAĞ, Uzm. Dr. Murat KIYIK		
17.00-17.20	Bronkodilatörler KOAH'ı Ne Kadar Tedavi Ediyor?	Prof. Dr. Esra KUNT UZASLAN
17.20-17.40	KOAH'da IKS'nin Pabucu Dama Atıldı Mı?	Prof. Dr. Arzu MİRİCİ
17.40-18.00	KOAH'da Cerrahi: Volüm Azaltıcı Cerrahi ve Transplantasyon	Doç. Dr. Ali YEĞİNSU
18.00-18.20	KOAH'da Komorbidite ve Komplikasyonların Yönetimi	Doç. Dr. Sevinç SARIÇ ULAŞLI
18.20-18.45	Tartışma	
19.00-21.00	Akşam Yemeği	



GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE™

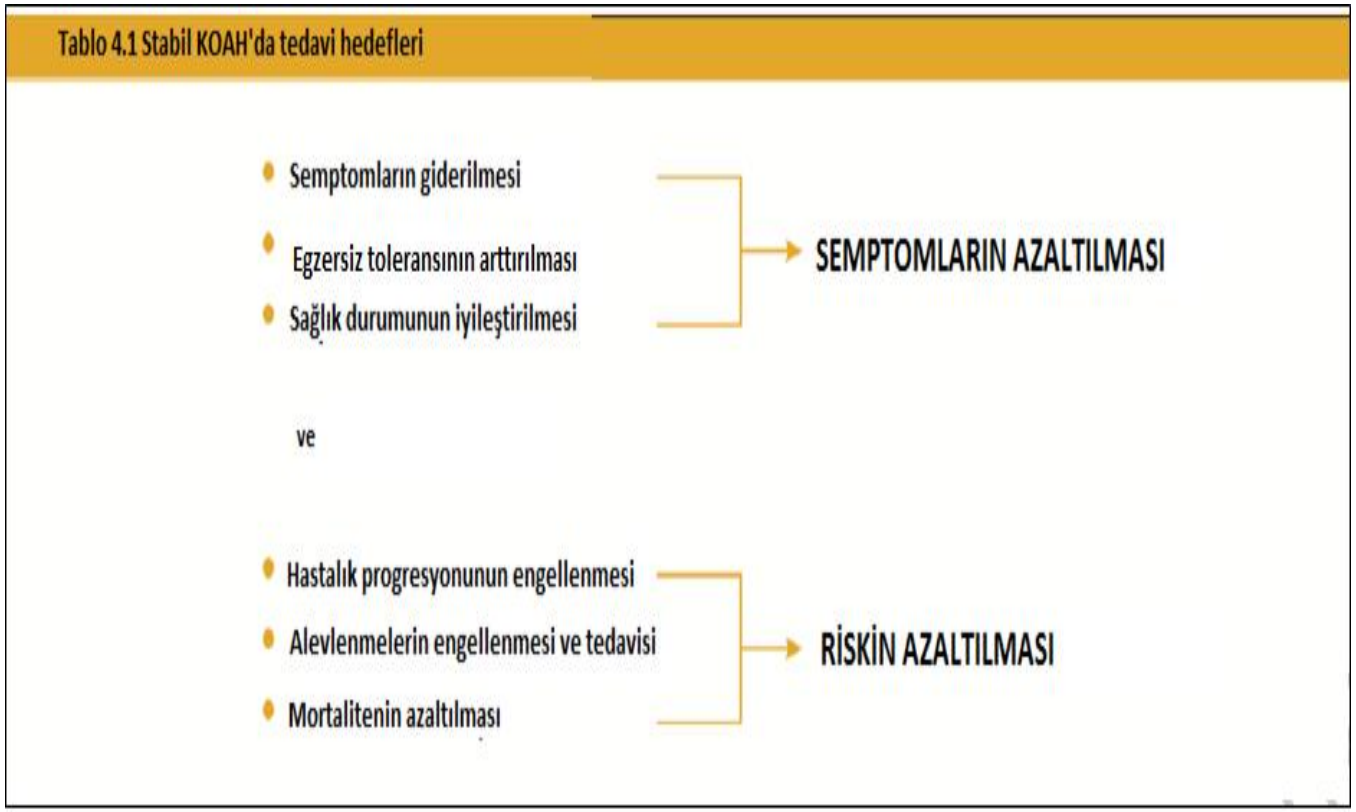
Bronkodilatörler
KOAH' ı Ne Kadar Tedavi Ediyor?



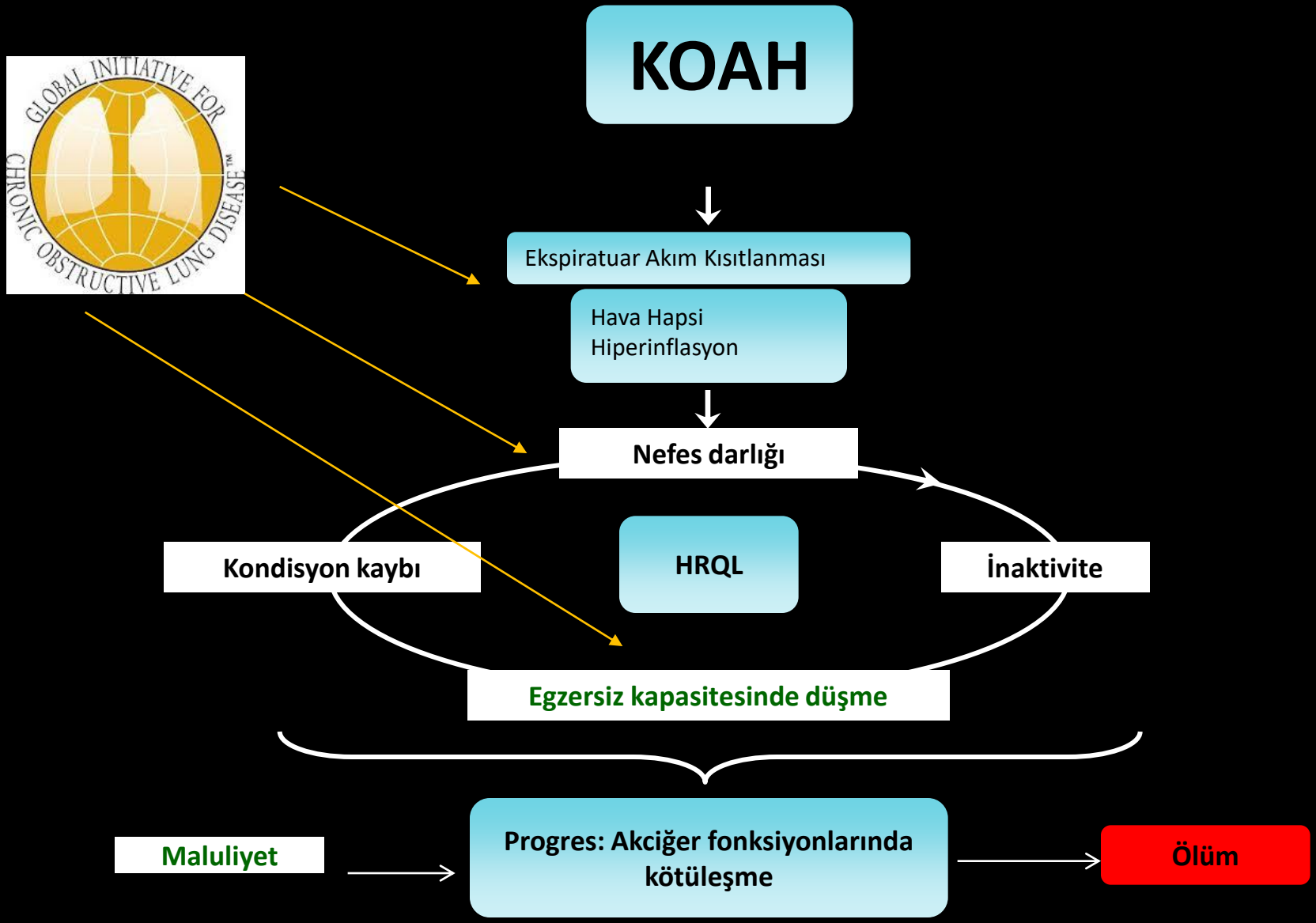
Ref: GOLD 2017 son rapor – 16 Kasım 2016' da yayınlanmıştır.

Neden Bronkodilatörler ?

Tedavinin Amaçları



GOLD 2011-2018



HRQL = Sağlıkla İlişkili Yaşam Kalitesinde Bozulma

Ferro T. Clinical Pulmonary Medicine 2005; Decramer M. Eur Respir Rev 2006

GOLD 2018 - Yeni ABCD Değerlendirmesi

Spirometrik olarak konmuş tanı

Post-bronkodilator $FEV_1/FVC < 0.7$

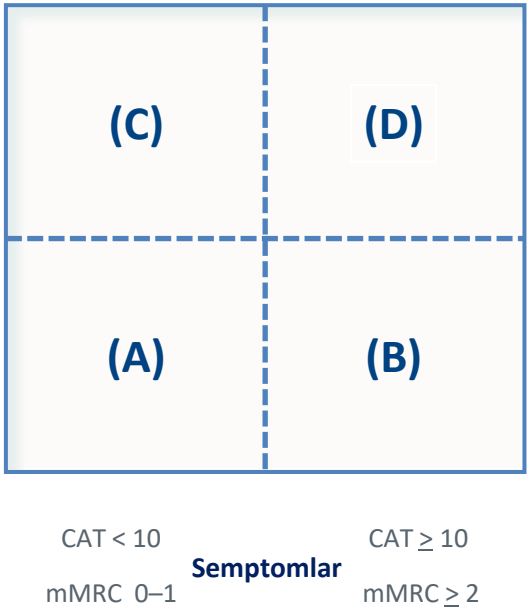
Havayolu obstrüksiyonunun değerlendirmesi

FEV_1 (% beklenenin)	
GOLD 1	≥ 80
GOLD 2	50-79
GOLD 3	30-49
GOLD 4	< 30

Orta ve Ağır Alevlenme öyküsü

- ≥ 2, yada ≥ 1 hastaneye yatış gerektiren
- 0 veya 1 (hastaneye yatış olmadan)

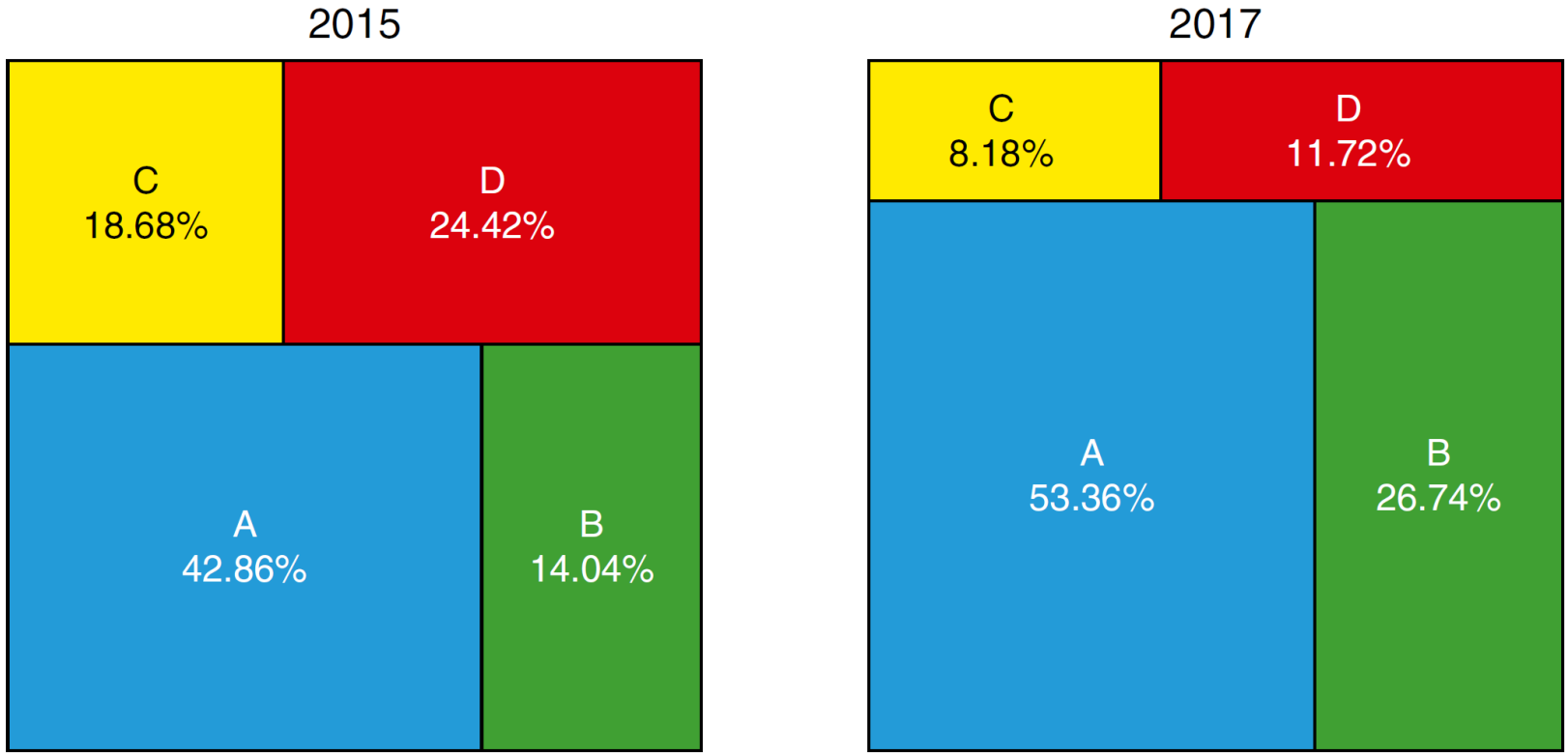
Semptomlar yada alevlenme riskinin değerlendirmesi



Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports

Impact on Grouping and Outcomes

Carlos Cabrera López[1], Ciro Casanova Macario[2], José María Marín Trigo[3], Juan P. de-Torres[4], Rebeca Sicilia Torres[1], Jesús María González[5], Francesca Polverino[6], Miguel Divo[6], Víctor Pinto Plata[7], Javier J. Zulueta[4], and Bartolomé Celli[6]



Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports

Impact on Grouping and Outcomes

Carlos Cabrera López[1], Ciro Casanova Macario[2], José María Marín Trigo[3], Juan P. de-Torres[4], Rebeca Sicilia Torres[1], Jesús María González[5], Francesca Polverino[6], Miguel Divo[6], Víctor Pinto Plata[7], Javier J. Zulueta[4], and Bartolomé Celli[6]

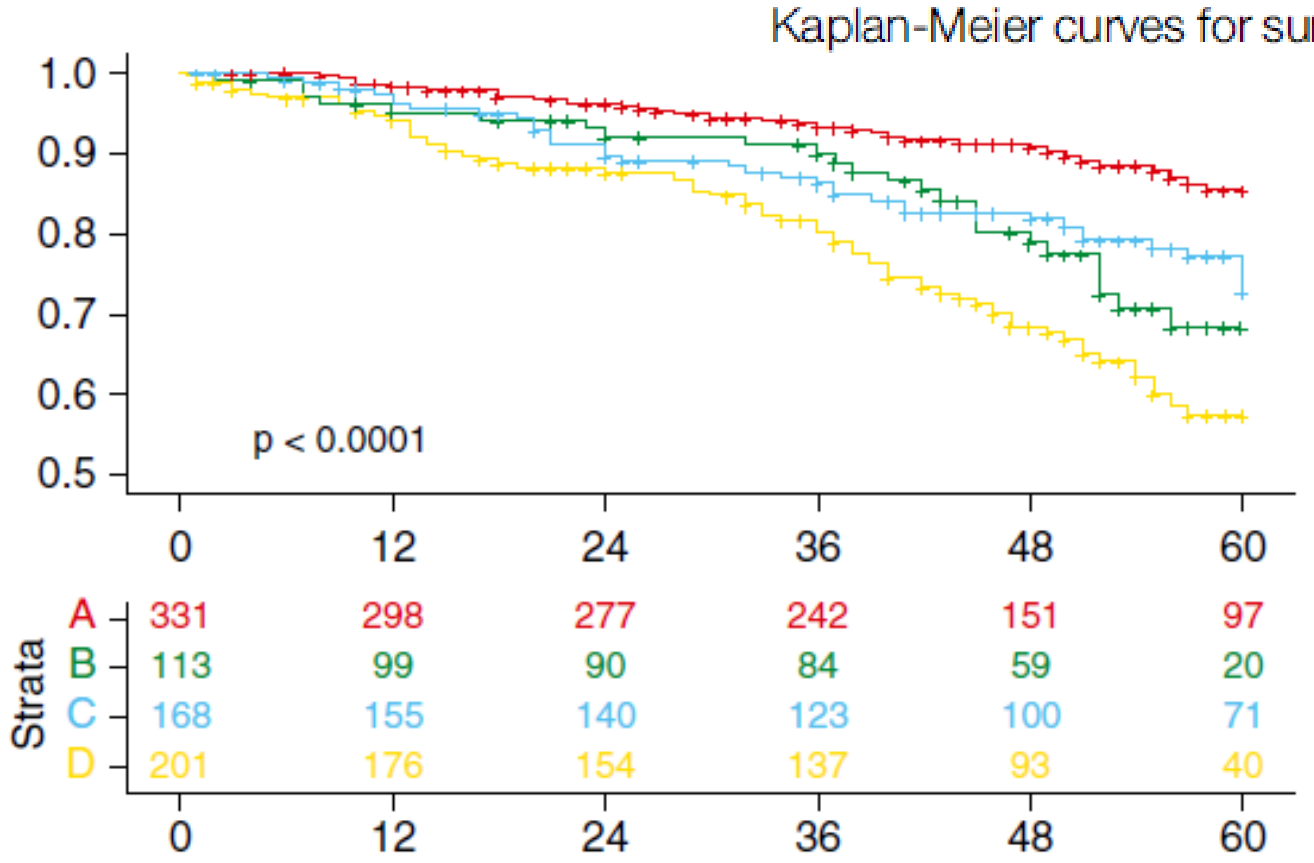
Group	Obstruction	*n* (%)
A	GOLD 1	104 (27)
	GOLD 2	217 (55)
	GOLD 3	65 (16)
	GOLD 4	6 (2)
B	GOLD 1	19 (10)
	GOLD 2	85 (44)
	GOLD 3	72 (37)
	GOLD 4	17 (9)
C	GOLD 1	10 (11)
	GOLD 2	46 (50)
	GOLD 3	28 (30)
	GOLD 4	8 (9)
D	GOLD 1	7 (7)
	GOLD 2	38 (36)
	GOLD 3	41 (39)
	GOLD 4	20 (18)

Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports

Impact on Grouping and Outcomes

Carlos Cabrera López[1], Ciro Casanova Macario[2], José María Marín Trigo[3], Juan P. de-Torres[4], Rebeca Sicilia Torres[1], Jesús María González[5], Francesca Polverino[6], Miguel Divo[6], Víctor Pinto Plata[7], Javier J. Zulueta[4], and Bartolomé Celli[6]

Sağkalım



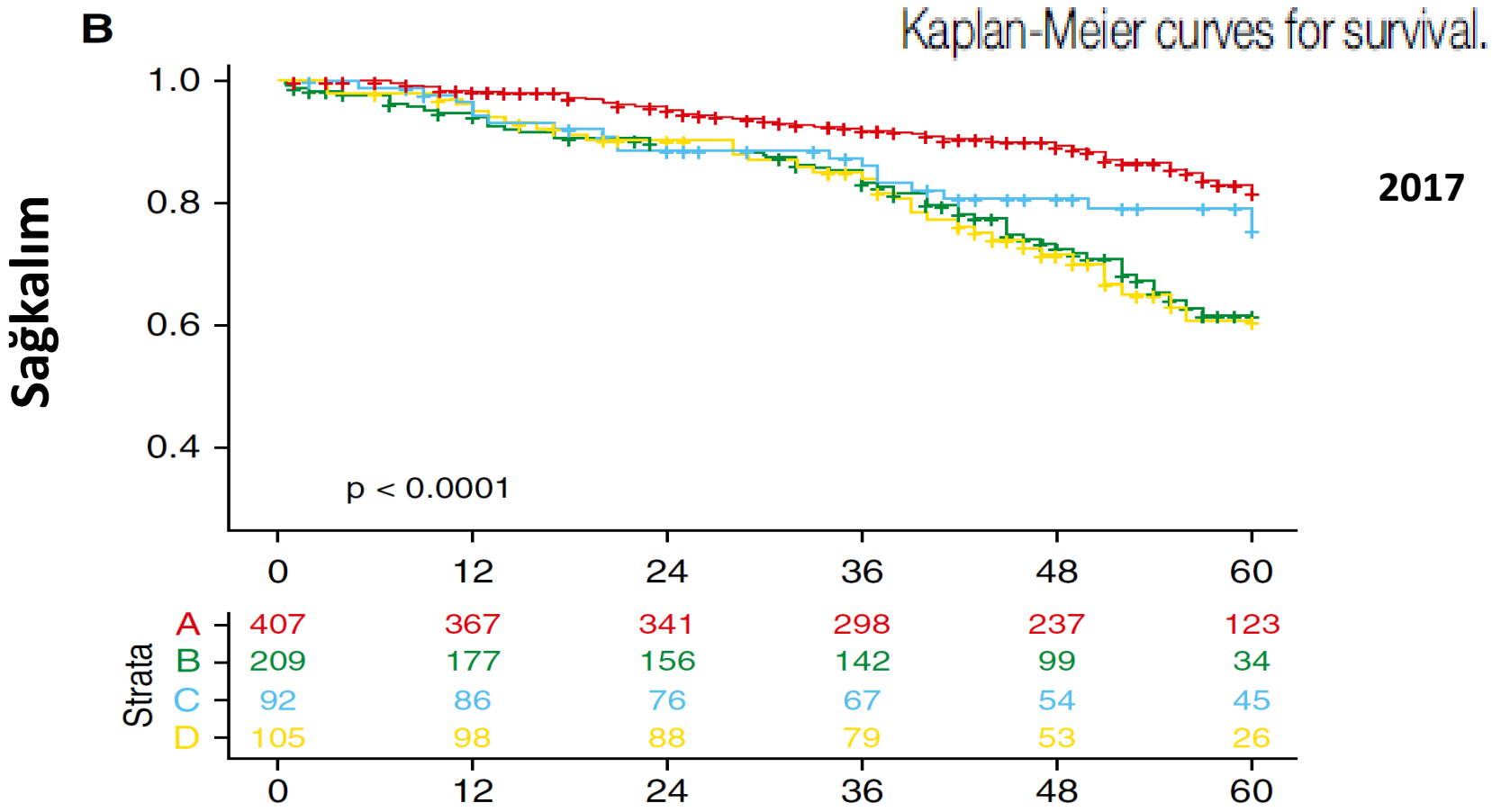
2015

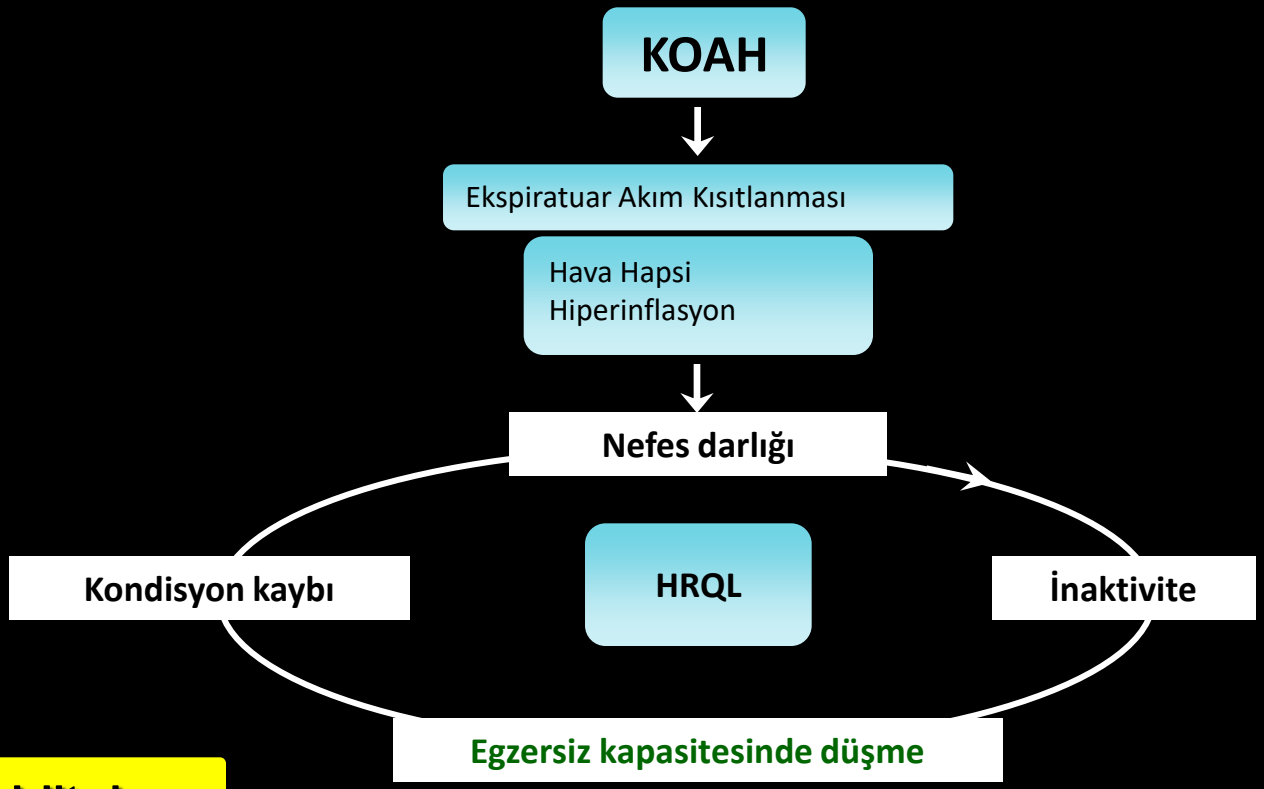
American Journal of Respiratory and Critical Care Medicine Volume 197 Number 4 | February 15 2018

Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports

Impact on Grouping and Outcomes

Carlos Cabrera López[1], Ciro Casanova Macario[2], José María Marín Trigo[3], Juan P. de-Torres[4], Rebeca Sicilia Torres[1], Jesús María González[5], Francesca Polverino[6], Miguel Divo[6], Víctor Pinto Plata[7], Javier J. Zulueta[4], and Bartolomé Celli[6]





HRQL = Sağlıkla İlişkili Yaşam Kalitesinde Bozulma

Ferro T. Clinical Pulmonary Medicine 2005; Decramer M. Eur Respir Rev 2006

Komorbideteler

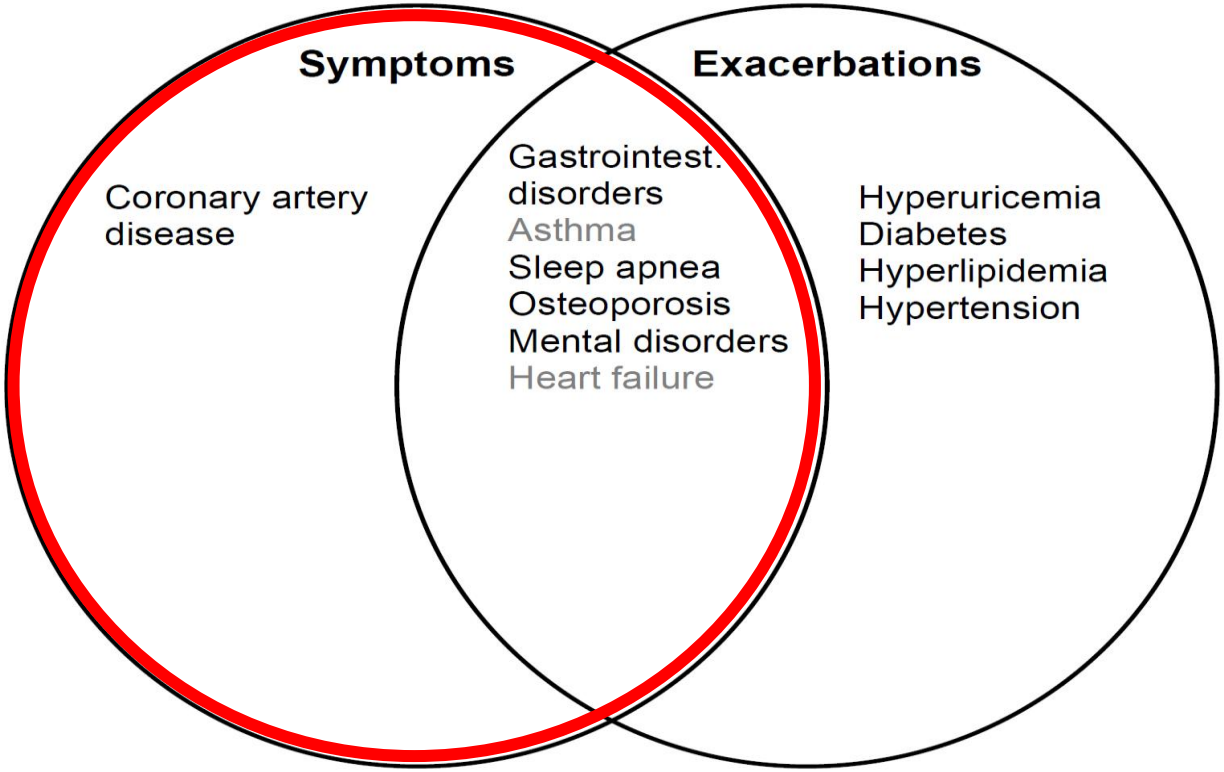
KOAH olgularınında komorbidite sıklığı:

- % 50’ sinde 1 - 2
- % 15.8’ inde 3 - 4
- % 6.8’ inde 5 ve üstü
- % 6’ sın da yok

- Genel populasyonda komorbidite 1.8 ise KOAH’da 3.7

The revised GOLD 2017 COPD categorization in relation to comorbidities

Kathrin Kahnert[a,*], Peter Alter[b], David Young[c], Tanja Lucke[d], Joachim Heinrich[d], Rudolf M. Huber[a], Jürgen Behr[a], Margarethe Wacker[e], Frank Biertz[f], Henrik Watz[g], Robert Bals[h], Tobias Welte[i], Hubert Wirtz[j], Felix Herth[k], Jørgen Vestbo[l], Emiel F. Wouters[m], Claus F. Vogelmeier[b], Rudolf A. Jörres[d]

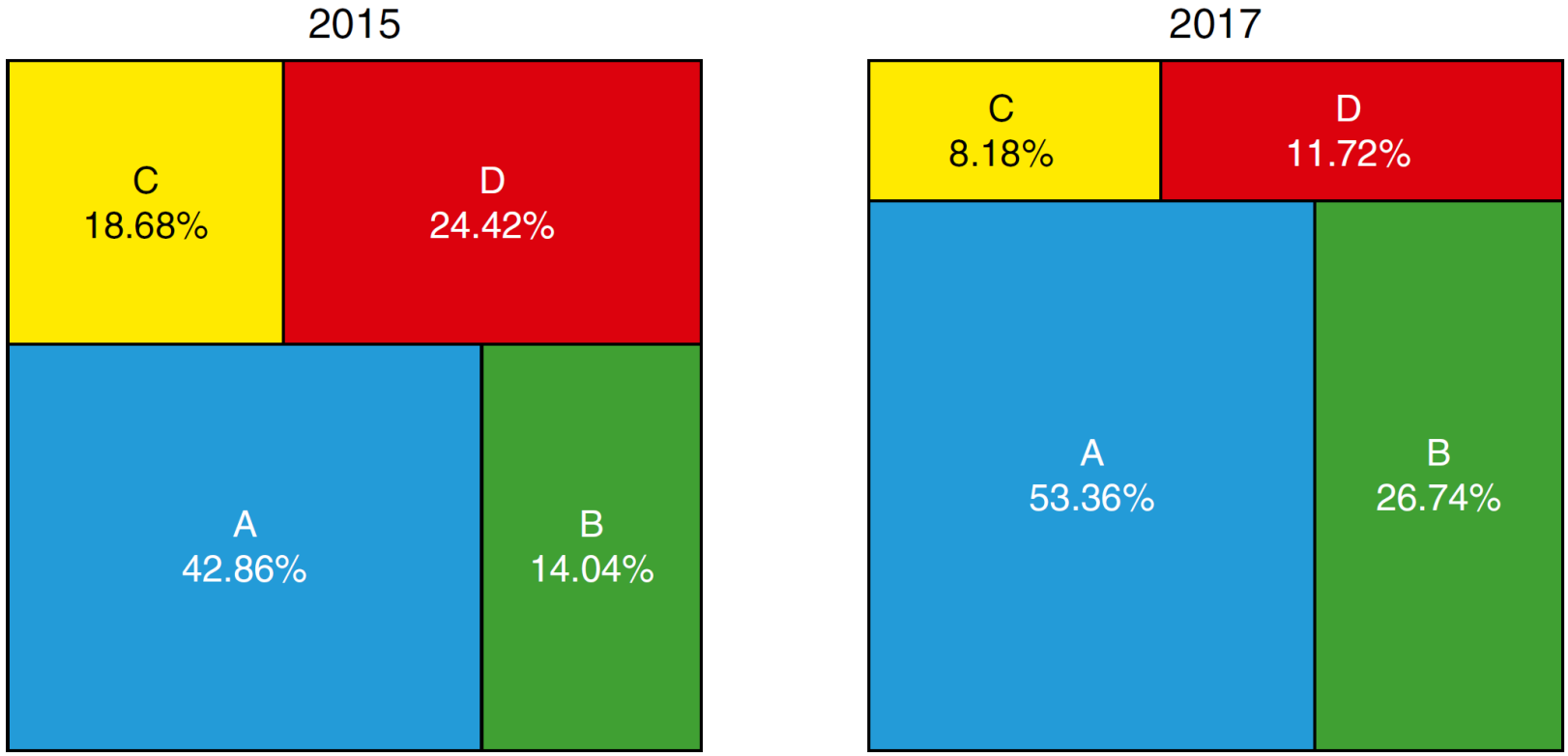


Respiratory Medicine 134 (2018) 79–85

Comparison of the 2017 and 2015 Global Initiative for Chronic Obstructive Lung Disease Reports

Impact on Grouping and Outcomes

Carlos Cabrera López[1], Ciro Casanova Macario[2], José María Marín Trigo[3], Juan P. de-Torres[4], Rebeca Sicilia Torres[1], Jesús María González[5], Francesca Polverino[6], Miguel Divo[6], Víctor Pinto Plata[7], Javier J. Zulueta[4], and Bartolomé Celli[6]



The revised GOLD 2017 COPD categorization in relation to comorbidities

Comorbidities	GOLD 2017 grouping according to CAT		GOLD 2017 grouping according to mMRC		Overall prevalence %
	BD vs. AC (symptoms)	CD vs. AB (exacerbations)	BD vs. AC (symptoms)	CD vs. AB (exacerbations)	
Hyperlipidemia	1.231 [0.930; 1.629]	**1.275*** [1.051; 1.548]	0.981 [0.803; 1.199]	**1.304**** [1.074; 1.584]	42.8
Heart failure	**3.228*** [1.144; 9.111]	**1.840**** [1.203; 2.813]	1.591 [0.995; 2.543]	**1.852**** [1.205; 2.845]	9.9
Hypertension	1.132 [0.853; 1.502]	**1.234*** [1.018; 1.518]	0.965 [0.786; 1.185]	**1.265*** [1.035; 1.546]	56.6
Coronary artery disease	**2.020**** [1.306; 3.127]	1.256 [0.976; 1.616]	**1.902***** [1.452; 2.493]	1.220 [0.947; 1.573]	17.1
Diabetes	0.742 [0.492; 1.118]	**1.424*** [1.066; 1.901]	1.197 [0.883; 1.623]	**1.344*** [1.007; 1.793]	13.0
Mental disorder	**2.839***** [1.852; 4.351]	**1.303*** [1.046; 1.625]	**1.585***** [1.253; 2.007]	**1.304*** [1.044; 1.629]	24.2

*p < 0.05, **p < 0.01, ***p ≤ 0.001. F

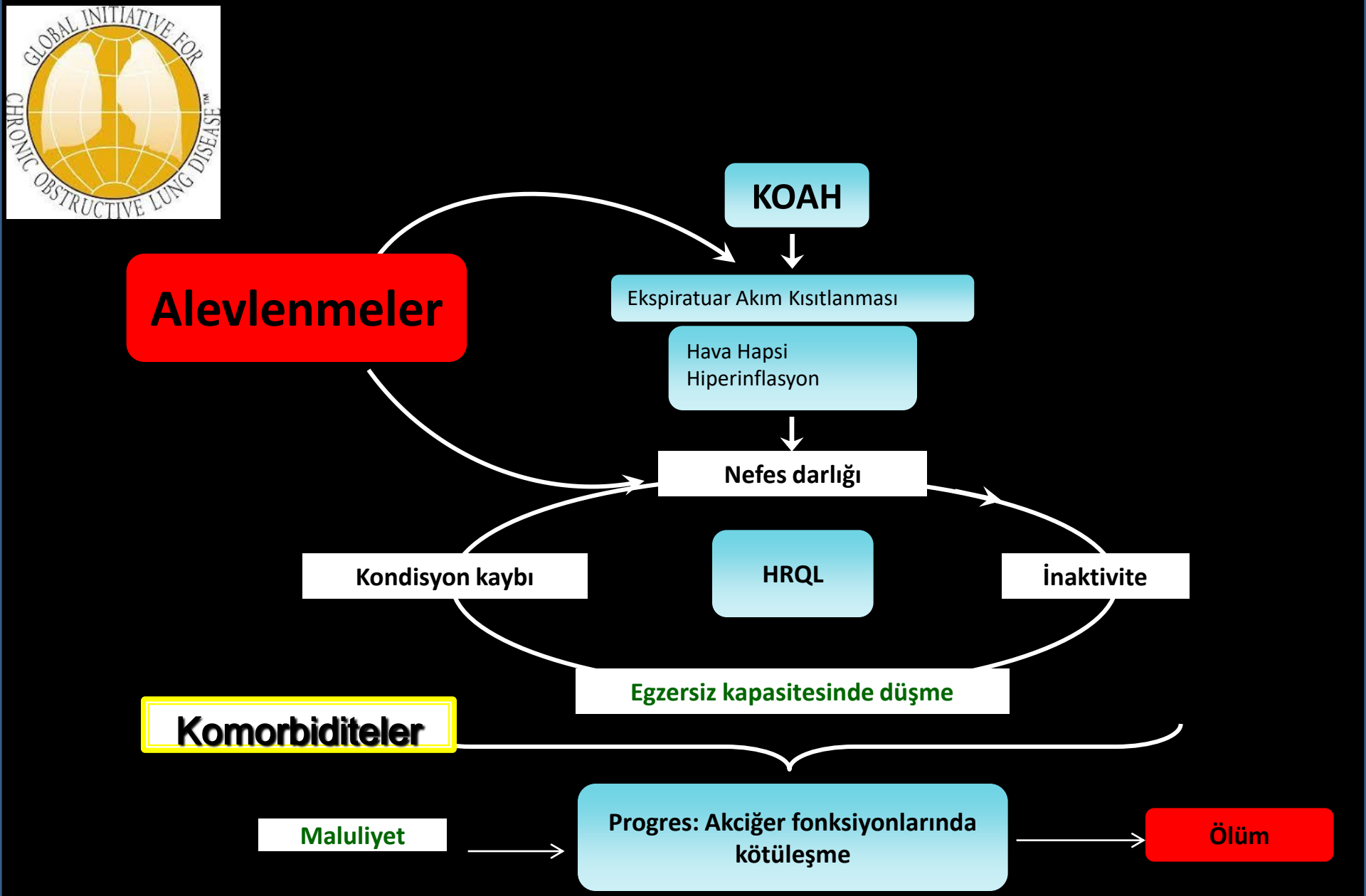
The revised GOLD 2017 COPD categorization in relation to comorbidities

Kathrin Kahnert[a,*], Peter Alter[b], David Young[c], Tanja Lucke[d], Joachim Heinrich[d], Rudolf M. Huber[a], Jürgen Behr[a], Margarethe Wacker[e], Frank Biertz[f], Henrik Watz[g], Robert Bals[h], Tobias Welte[i], Hubert Wirtz[j], Felix Herth[k], Jørgen Vestbo[l], Emiel F. Wouters[m], Claus F. Vogelmeier[b], Rudolf A. Jörres[d]

Respiratory Medicine 134 (2018) 79–85

Comorbidities	GOLD 2017 grouping according to CAT		GOLD 2017 grouping according to mMRC		Overall prevalence %
	BD vs. AC (symptoms)	CD vs. AB (exacerbations)	BD vs. AC (symptoms)	CD vs. AB (exacerbations)	
Gastrointestinal disorders	**1.548**** [1.167; 2.053]	**1.801***** [1.489; 2.179]	**1.607***** [1.317; 1.961]	**1.750***** [1.445; 2.119]	46.3
Asthma	**3.314***** [1.973; 5.568]	**1.641***** [1.287; 2.093]	1.079 [0.831; 1.400]	**1.762***** [1.380; 2.151]	17.7
Hyperuricemia	1.275 [0.866; 1.877]	**1.439**** [1.119; 1.851]	1.092 [0.839; 1.421]	**1.454**** [1.130; 1.871]	18.1
Osteoporosis	**1.700*** [1.062; 2.720]	**1.465**** [1.126; 1.905]	**1.592***** [1.197; 2.117]	**1.421**** [1.090; 1.852]	15.8
Sleep apnea	**2.747****	**1.463***	**1.441***	**1.485***	10.4

*p < 0.05, **p < 0.01, ***p ≤ 0.001. F



HRQL = Sağlıkla İlişkili Yaşam Kalitesinde Bozulma

Ferro T. Clinical Pulmonary Medicine 2005; Decramer M. Eur Respir Rev 2006

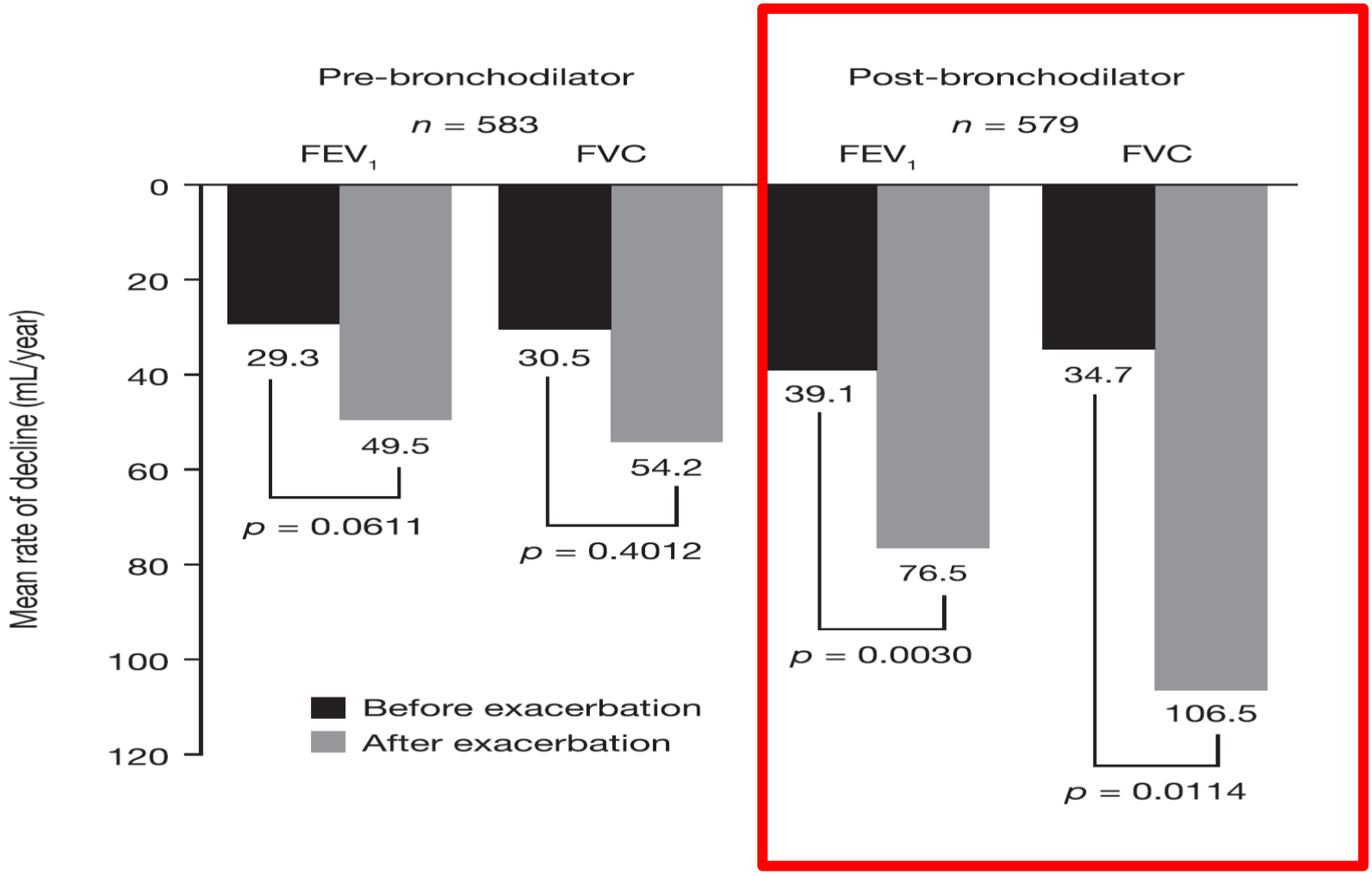
FEV1 Kaybı ve Alevlenme İlişkisi

- 1 tane orta veya alevlenmeyi takiben
- Postbronkodilatör FEV1 de ortalama düşüş alevlenme öncesi dönemdeki düşüşe göre artmış
- Post BD FEV1 kaybı
  - Alevlenme öncesi 39.1 ml/yıl
  - Alevlenme sonrası 76.5 ml/yıl ($p < 0.003$)
- Post BD FVC kaybı
  - Alevlenme öncesi 34.7 ml/yıl
  - Alevlenme sonrası 106.5ml/yıl ($p < 0.011$)

Respiratory Medicine 128 (2017) 85–91

Effect of a single exacerbation on decline in lung function in COPD

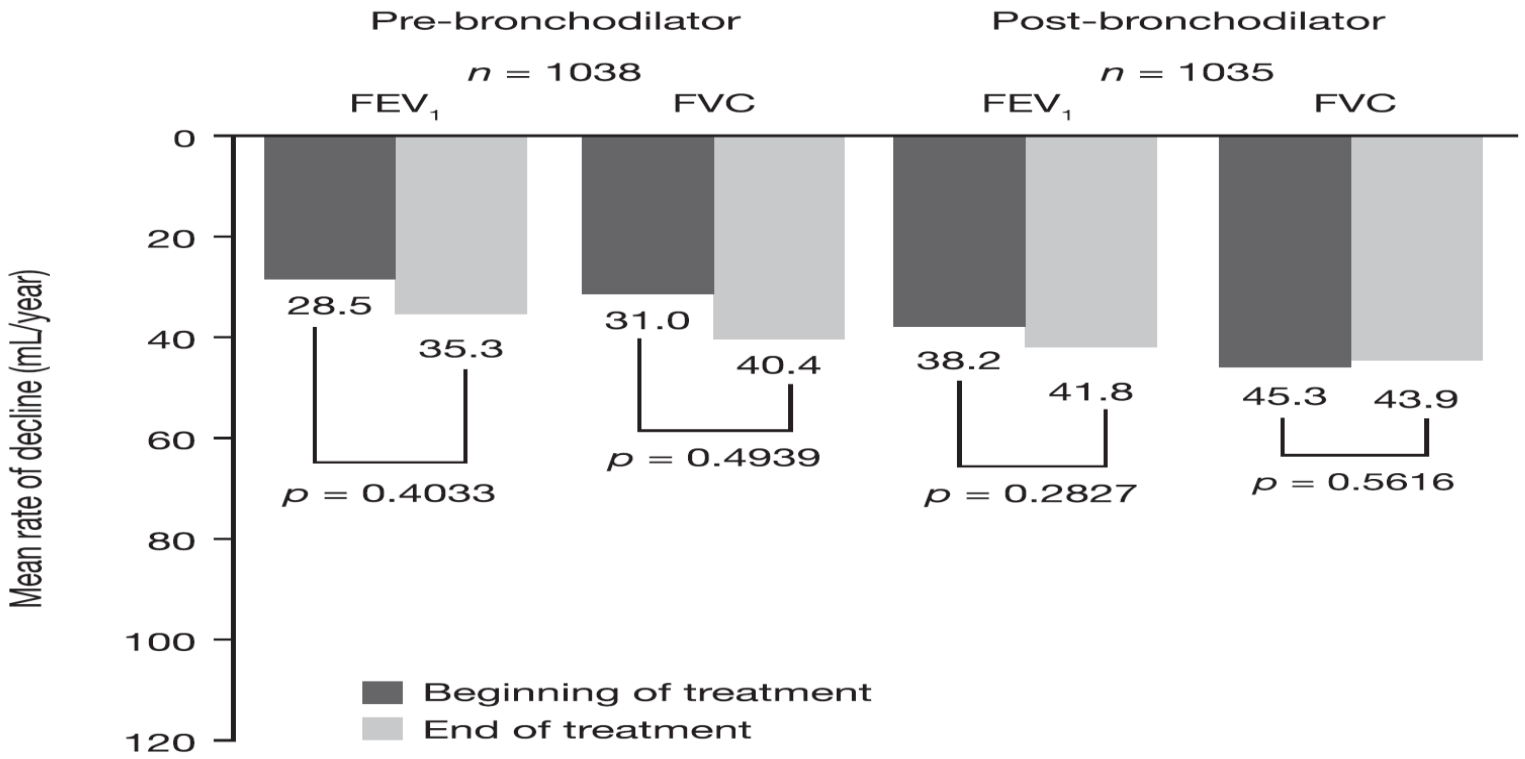
David M.G. Halpin [a, *], Marc Decramer [b], Bartolome R. Celli [c], Achim Mueller [d], Norbert Metzdorf [e], Donald P. Tashkin [f]



Respiratory Medicine 128 (2017) 85–91

Effect of a single exacerbation on decline in lung function in COPD

David M.G. Halpin [a, *], Marc Decramer [b], Bartolome R. Celli [c], Achim Mueller [d], Norbert Metzdorf [e], Donald P. Tashkin [f]

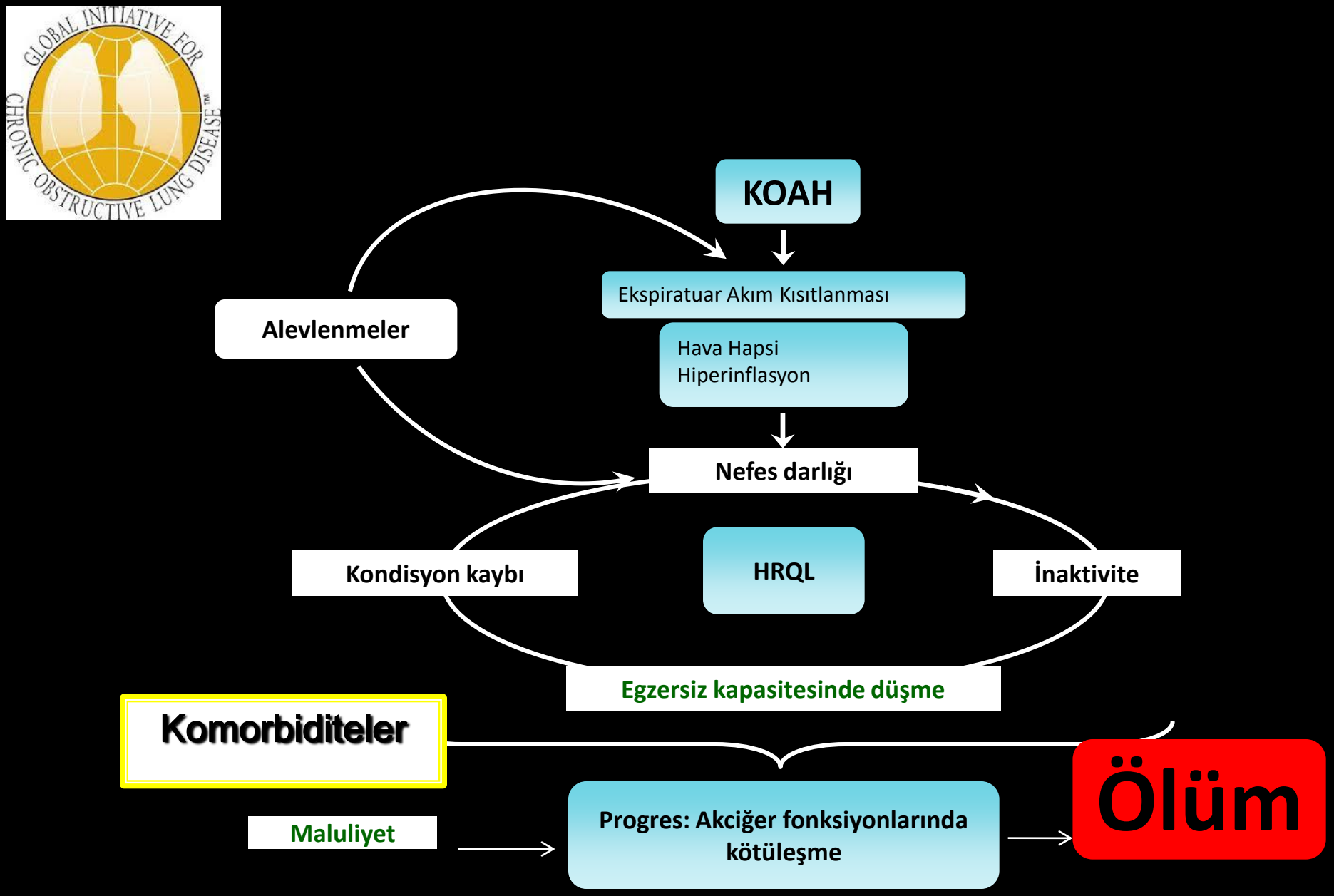


Respiratory Medicine 128 (2017) 85–91

FEV1 Kaybı ve Alevlenmeme İlişkisi

- Orta veya alevlenme geçirmeyen olgularda ise ilk 2 yıl ve takiben 3-4 yıl postbronkodilatör FEV1 de ve FVC de ortalama düşüş de fark yok
  - FEV1 38.2 ml/ yıl ile 41.8 mL/yıl
  - FVC 45.3 ml/yıl ile 43.9 mL/yıl

Respiratory Medicine 128 (2017) 85–91



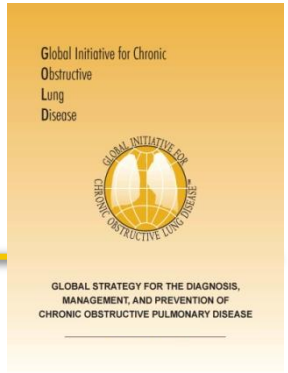
HRQL = Sağlıkla İlişkili Yaşam Kalitesinde Bozulma

Ferro T. Clinical Pulmonary Medicine 2005; Decramer M. Eur Respir Rev 2006

Bronkodilatörler

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Tedavinin Amaçları



- Semptomları iyileştir
- Egzersiz toleransınını iyileştir
- Yaşam kalitesini iyileştir

Semptomları azalt

- Hastalığın progresyonunu engelle
- Alevlenmeleri önle ve tedavi et
- Mortaliteyi azalt

Riskleri azalt

GOLD 2018

Semptomları Azaltılmasında Bronkodilatörler

KOAH TANISI

SEMPTOMLAR

Nefes darlığı

Kronik öksürük

Balgam

RİSK FAKTÖRLERİNE MARUZİYET

Sigara dumanı

meslek

İç/dış ortam kirliliği

SPİROMETRE

GOLD 2018

KOAH düşündüren semptomlar
- Nefes darlığı
- Kronik öksürük veya
- Balgam

Semptomlar:
- Nefes darlığı
- Kronik öksürük
- Balgam

Risk faktörleri:
- Hastaya spesifik
- Tütün
- Meslek
- İç mekan /dış mekan kirlilik

ve/veya
Risk faktörlerine maruziyet öyküsü

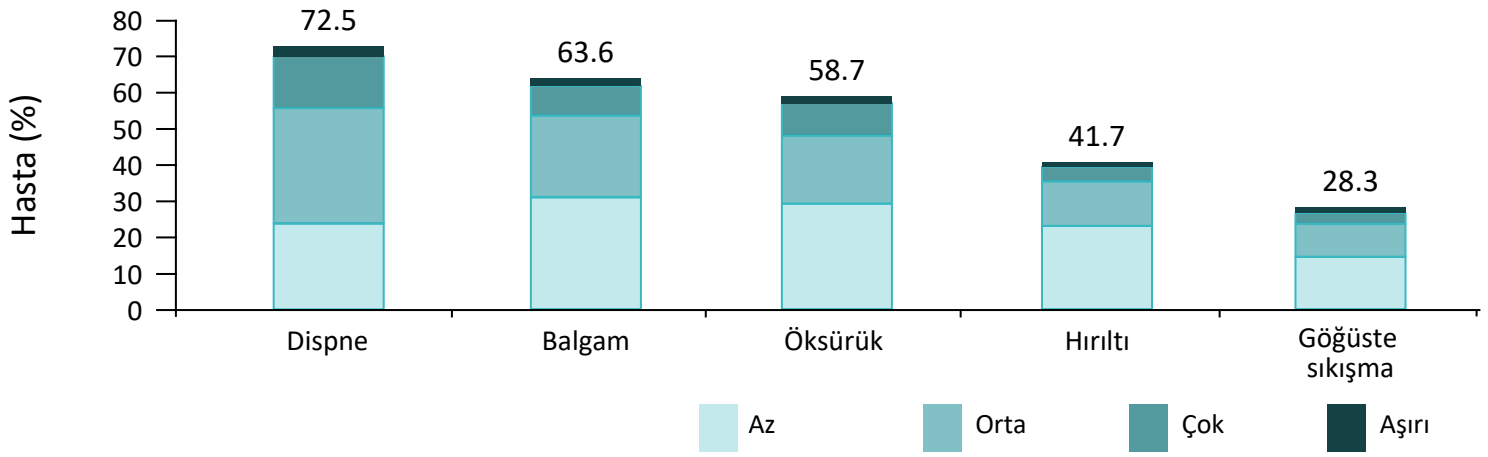
Spirometri: Tanı için gerekli

Spirometri(Post-brokodilatör)
Hava yolu darlığını gösteren FEV_1/FVC <0.7

Nefes darlığı KOAH'ta en sık görülen, en kritik semptom

- Dispne KOAH'ın kardinal bir semptomudur, ciddi bir anksiyete ve maluliyet sebebidir[1]
- 17 Avrupa ülkesinde 2441 KOAH hastasının değerlendirildiği çalışmada, en sık görülen semptomun dispne olduğu gösterilmiştir (%72.5)[2]
- SUNRISE (Türkiye, 2012) çalışmasında da dispne, %99 ile hastaların en çok şikayet ettikleri semptom olarak bildirilmiştir.[3]

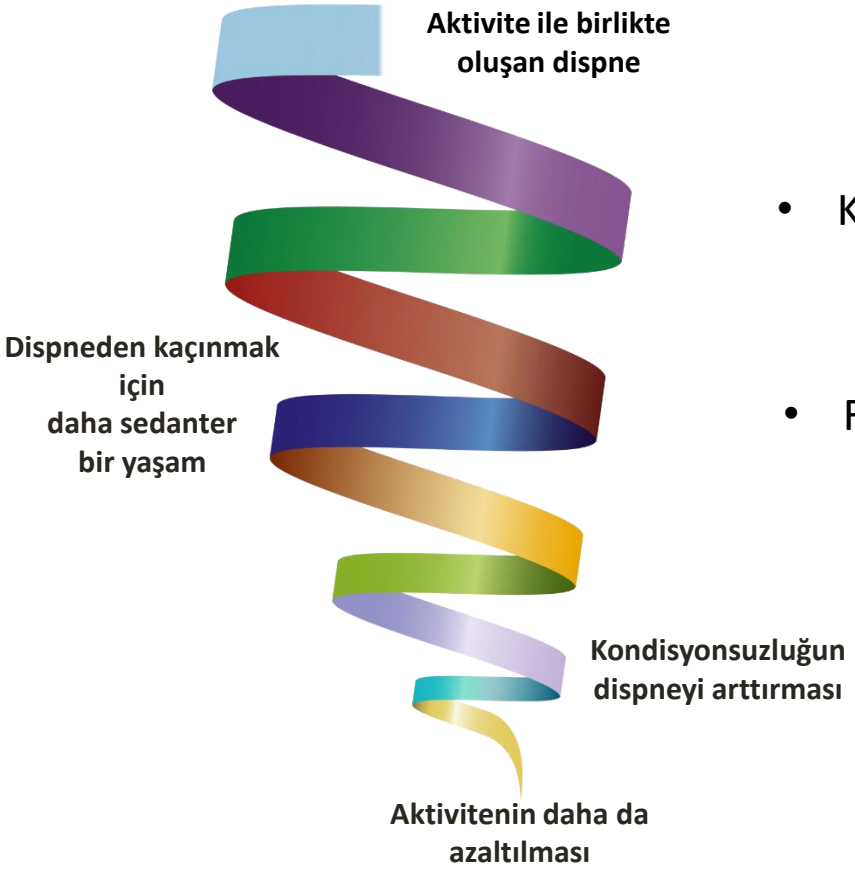
KOAH hastalarında semptom değişkenliği[2]



Grafik 2 numaralı referanstan uyarlanmıştır

1. GOLD 2017. http://goldcopd.org/. Erişim: Haziran 2017 2. Kessler R et al. Eur Respir J. 2011;37:264–272. 3. Kuyucu T et al Tüberküloz ve Toraks Dergisi 2011; 59(4): 328-339.

Dispne yaşam kalitesini azaltır



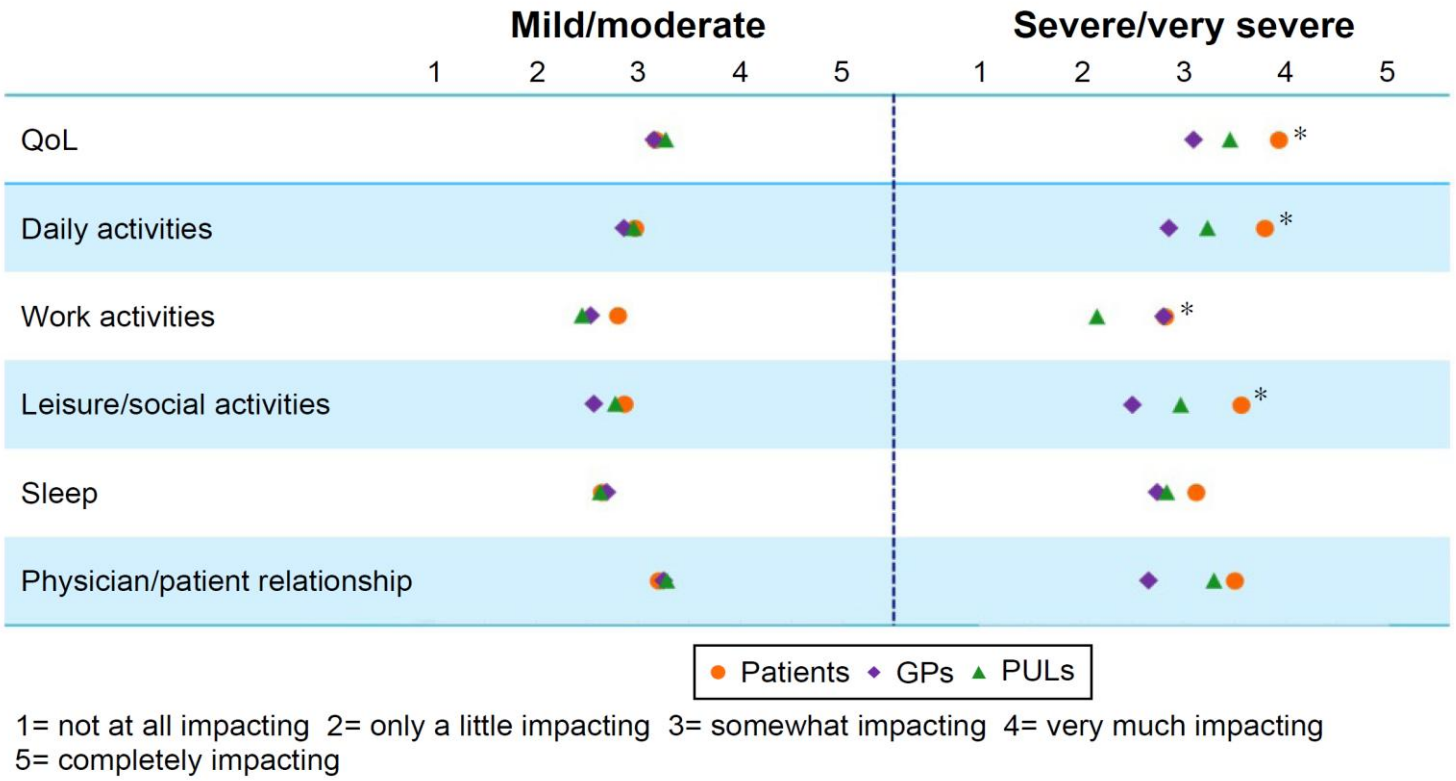
- KOAH hastaları dispne şikayetleri ile baş edebilmek için bilinçsiz olarak günlük aktivitelerini azaltırlar[1]
- Fiziksel aktivitedeki bu azalma nefes darlığını daha da arttıran kondisyonsuzluğa yol açmaktadır[1,2]

Şekil 1 numaralı referanstan uyarlanmıştır. KOAH: Kronik obstrüktif akciğer hastalığı

1. Reardon JZ et al. Am J Med. 2006;119:S32−S37. 2. ZuWallack R. COPD. 2007;4:293–297.

Perception of symptoms and quality of life – comparison of patients' and physicians' views in the COPD MIRROR study

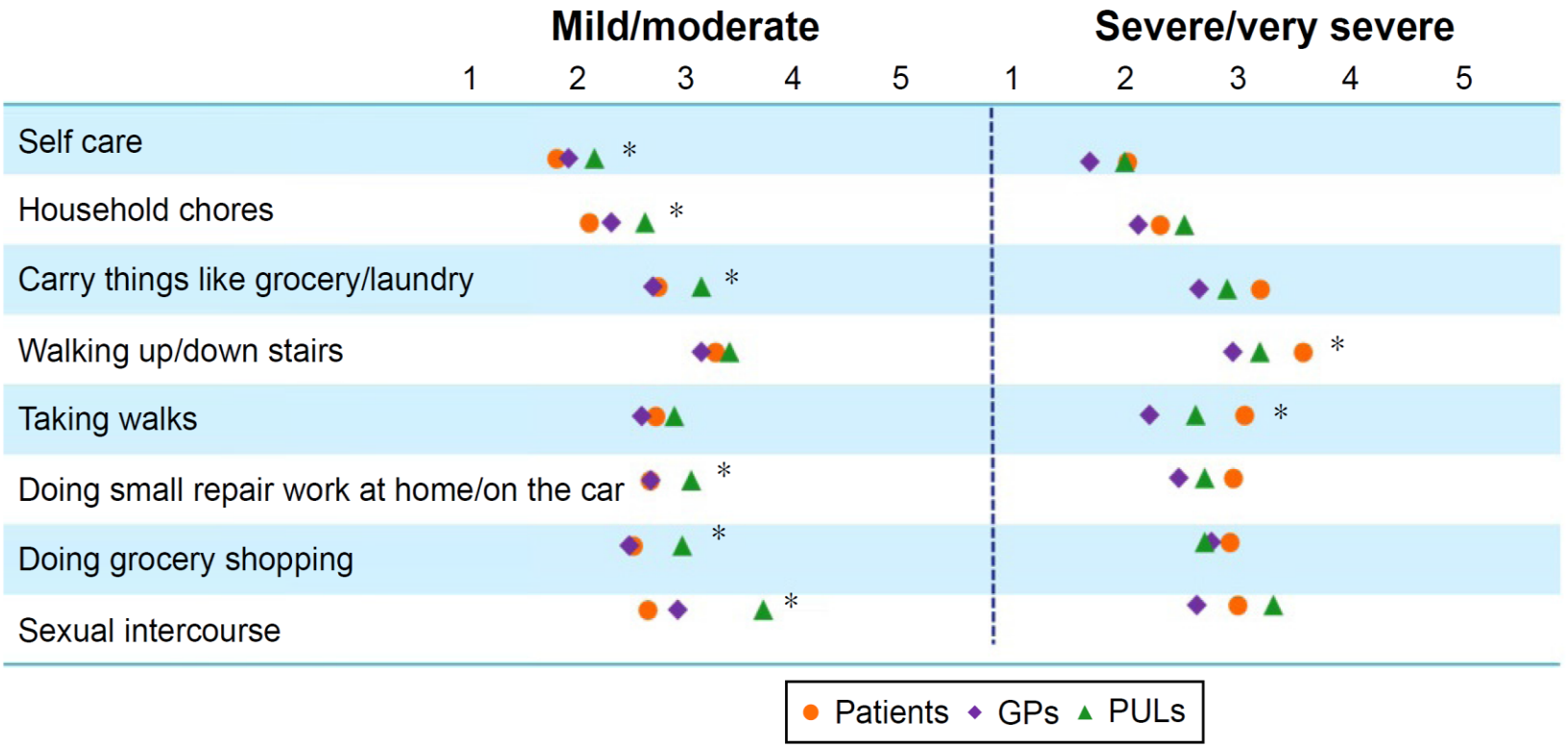
334 KOAH Hastası, 333 A.H ve 333 Göğüs Hastalıkları Uzmanı



Celli B, et.al. International Journal of COPD 2017:12 2189–2196

Perception of symptoms and quality of life – comparison of patients' and physicians' views in the COPD MIRROR study

334 KOAH Hastası, 333 A.H ve 333 Göğüs Hastalıkları Uzmanı



1= not at all impacting 2= only a little impacting 3= somewhat impacting 4= very much impacting
5= completely impacting

Celli B, et.al. International Journal of COPD 2017:12 2189–2196

KOAH ve Bronkodilatör Tedavi

Normal

KOAH

İnspirasyon

Inflammasyon

Küçük havayo

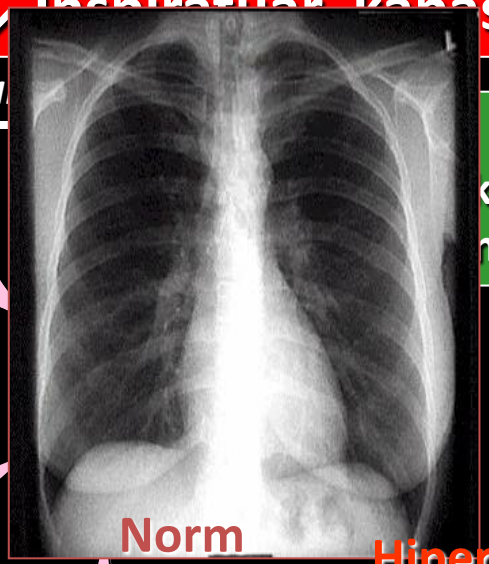
- Hava hapsi(hiperinflasyon)
- ↑ TLC
- ↑ Residual volum
- ↑ FRC
- ↓ İnspiratuar kapasite

↑ Egzersiz dispnesinde

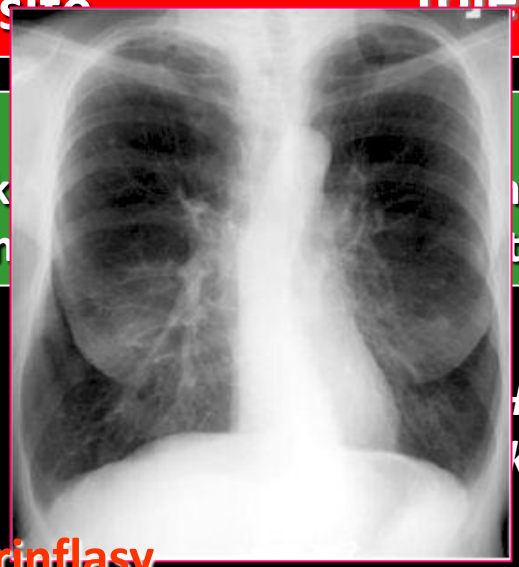
↓ Egzersiz toleransında

A tutama

, aklidinyum
terol, olandeterol....



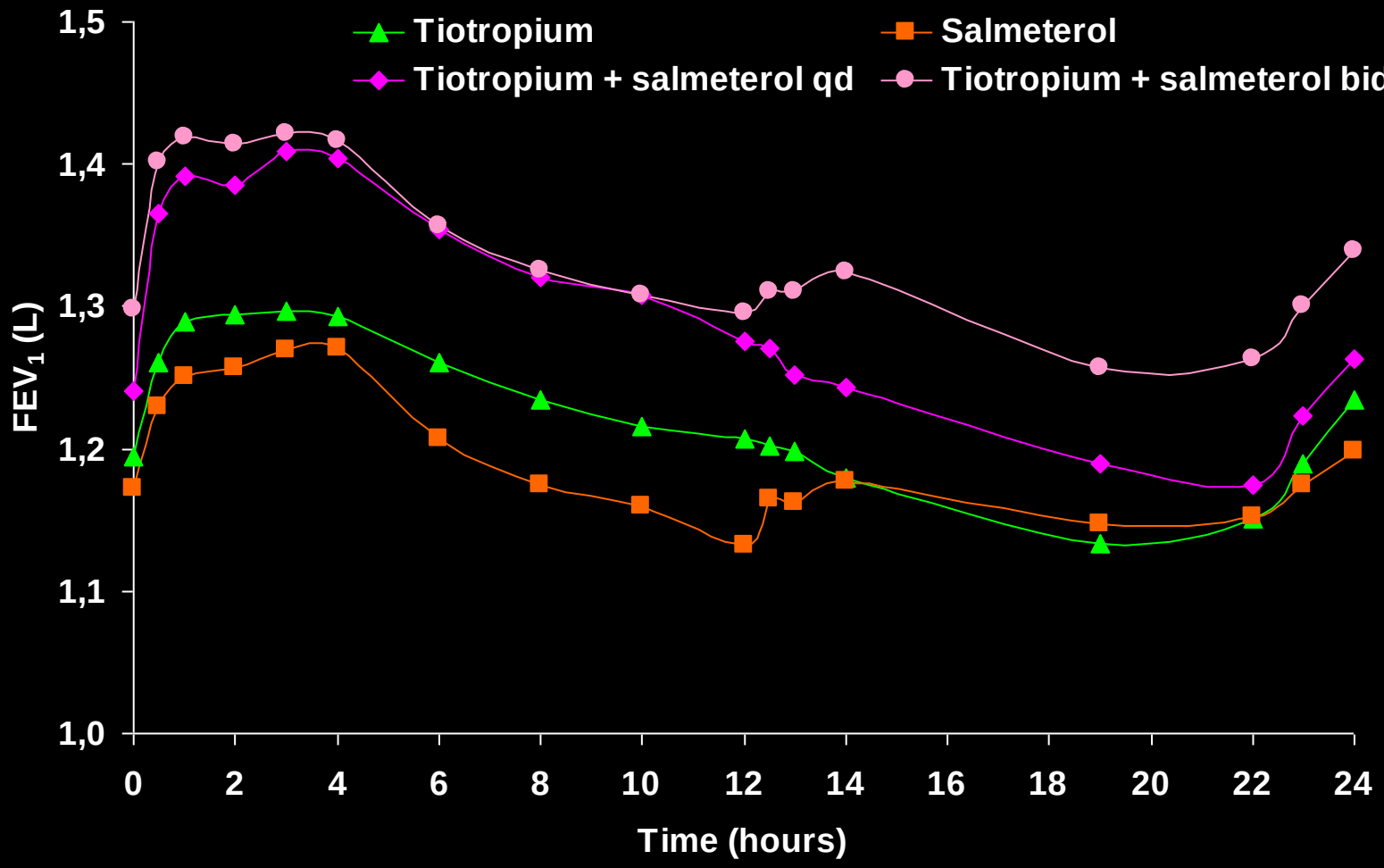
Norm al



Hiperinflasy

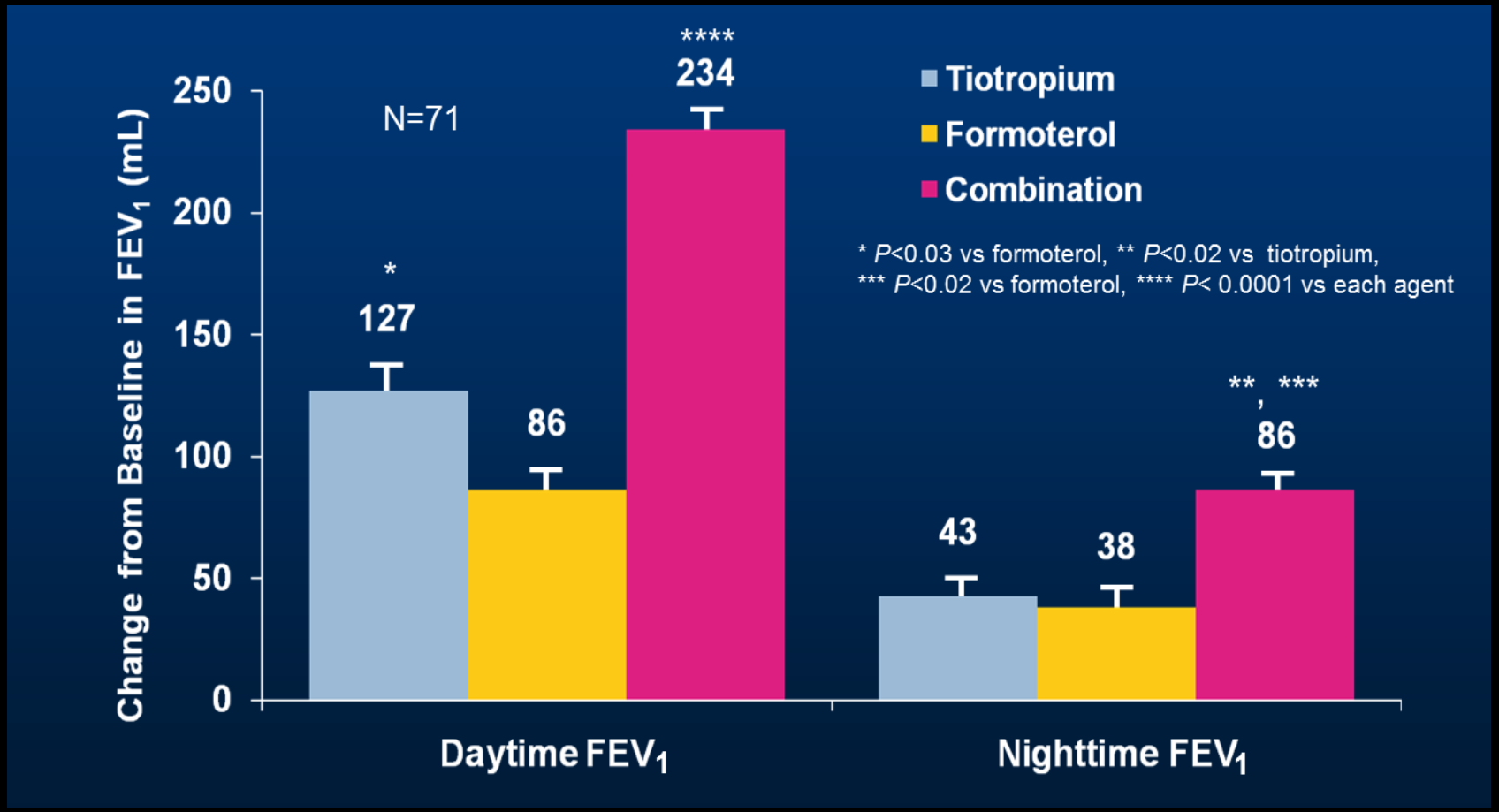
Havayolları kapanması

6 haftalık tedavi sonrası 24 saatlik FEV1 değerleri



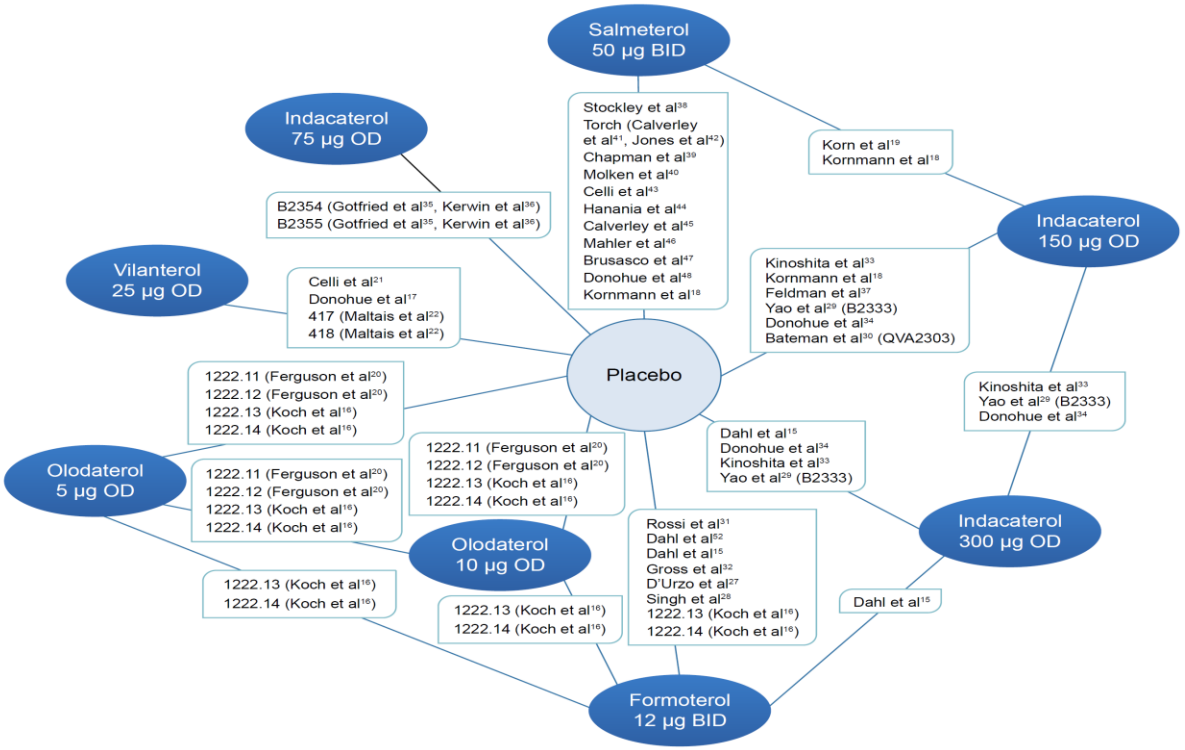
ATS 2005 Van Noord

Uzun etkili bronkodilatör



Van Nord JA, et al. ERJ 2005.

Comparative efficacy of long-acting β2-agonists as monotherapy for chronic obstructive pulmonary disease: a network meta-analysis



Donohue JF et al International Journal of COPD 2017:12 367–381

Comparative efficacy of long-acting β2-agonists as monotherapy for chronic obstructive pulmonary disease: a network meta-analysis

TDI

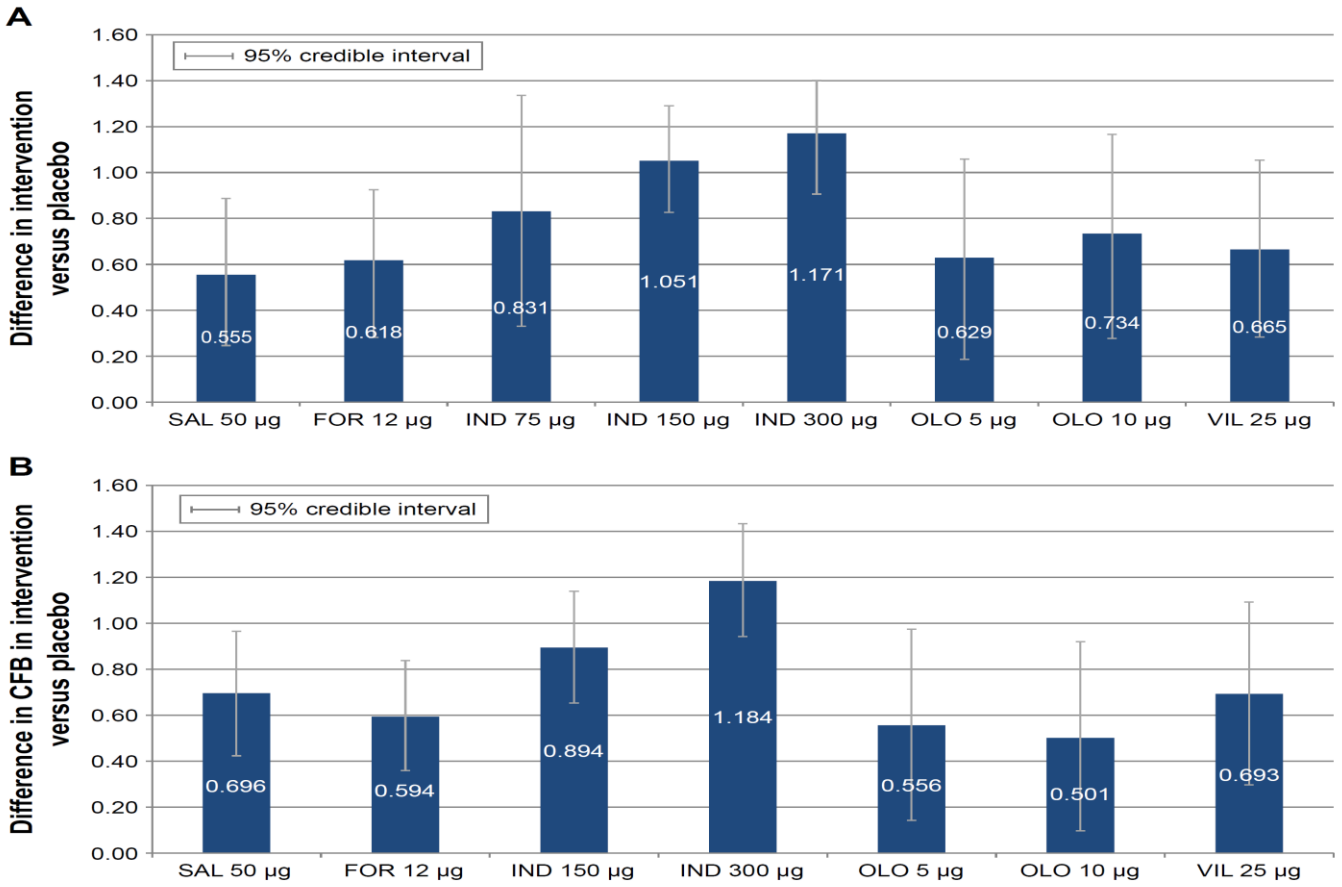


Figure 4 Difference in change from baseline TDI focal score of intervention versus placebo at 12 and 24 weeks. (**A**) TDI focal score at 12 weeks and (**B**) TDI focal score at 24 weeks.
Abbreviations: FOR, formoterol; IND, indacaterol; OLO, olodaterol; SAL, salmeterol; TDI, transition dyspnea index; VIL, vilanterol; CFB, change from baseline.

Donohue JF et al International Journal of COPD 2017:12 367–381

Comparative efficacy of long-acting β2-agonists as monotherapy for chronic obstructive pulmonary disease: a network meta-analysis

Trough FEV 1

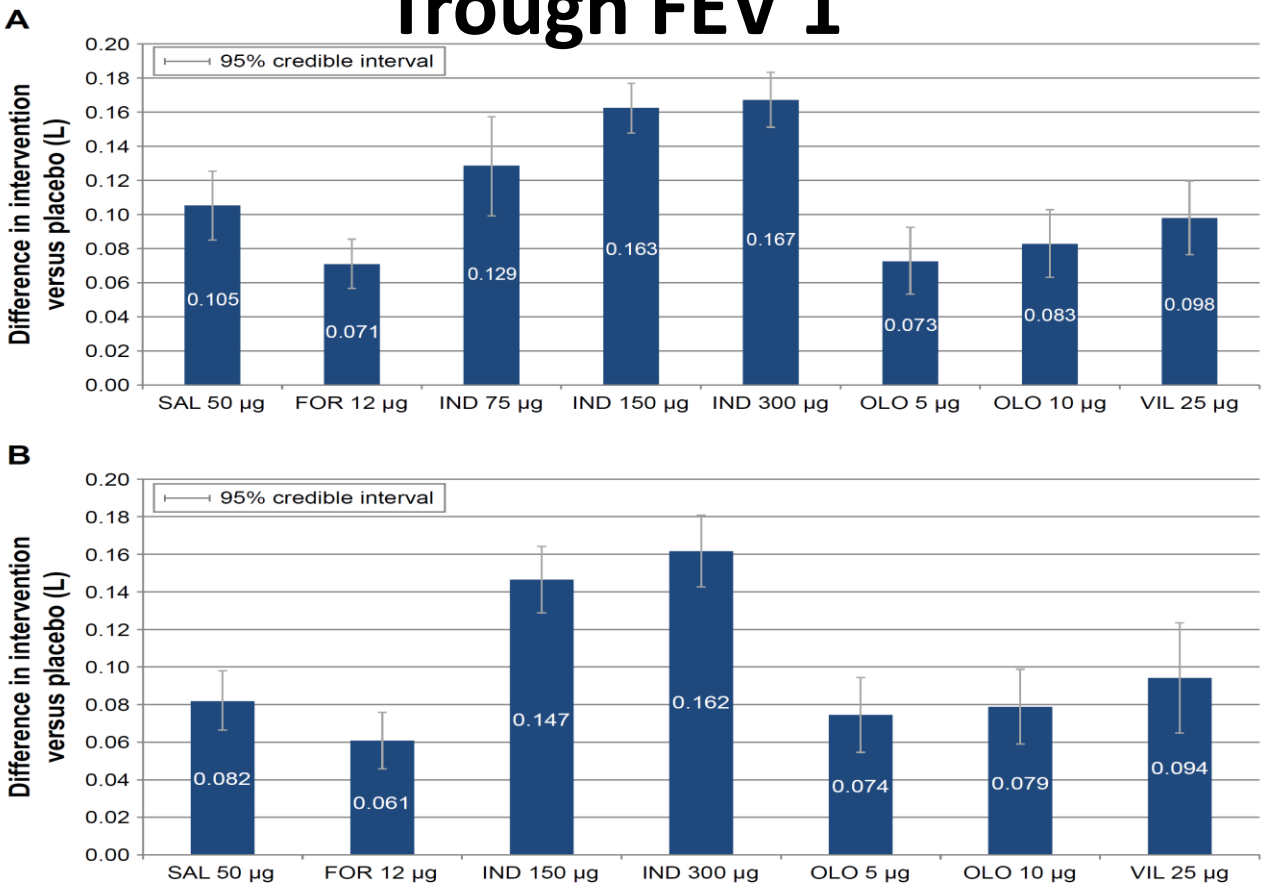


Figure 3 Change from baseline differences in trough FEV_1 (L) for intervention versus placebo at 12 and 24 weeks. (**A**) Trough FEV_1 at 12 weeks and (**B**) trough FEV_1 at 24 weeks.

Donohue JF et al International Journal of COPD 2017:12 367–381

Comparative efficacy of long-acting β2-agonists as monotherapy for chronic obstructive pulmonary disease: a network meta-analysis

SGRQ

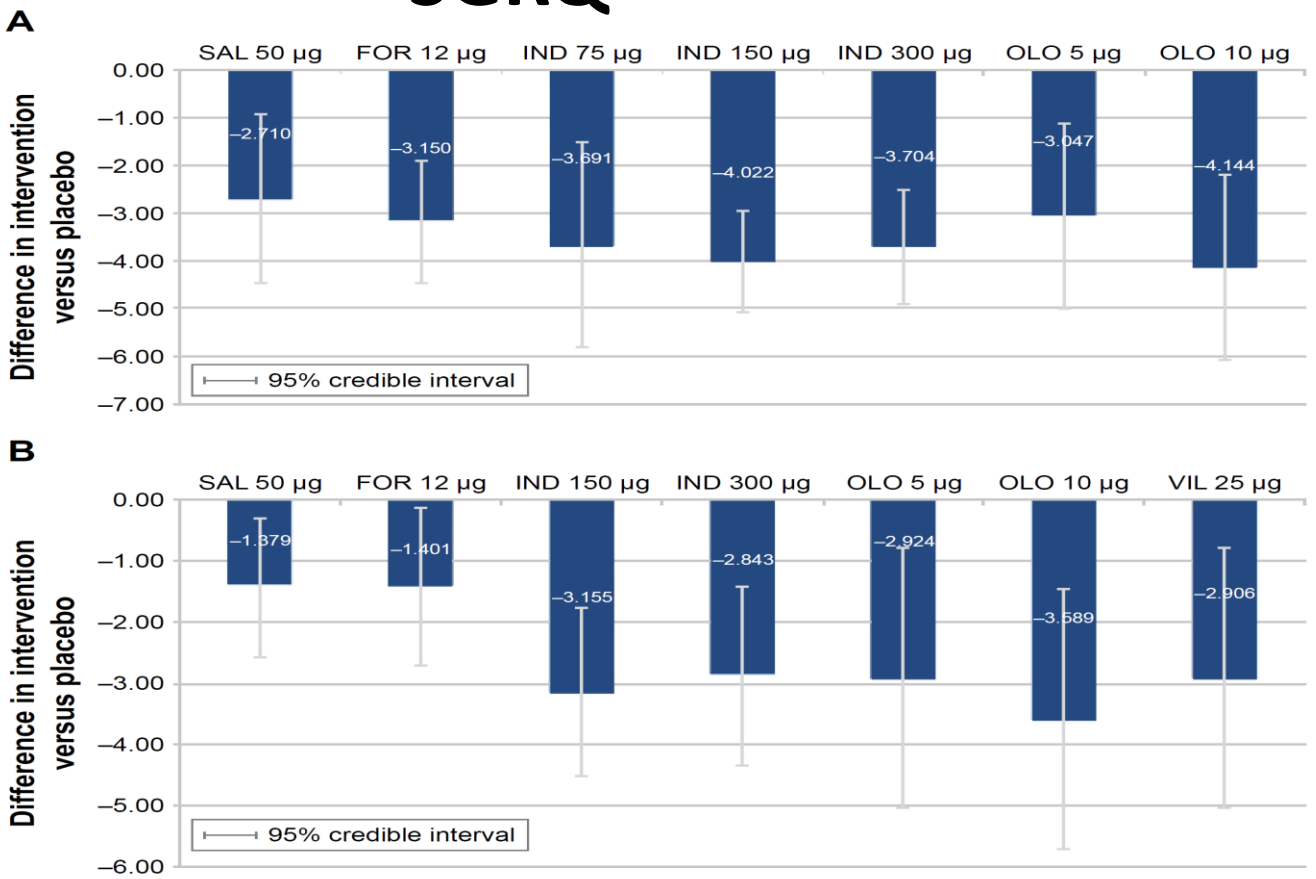
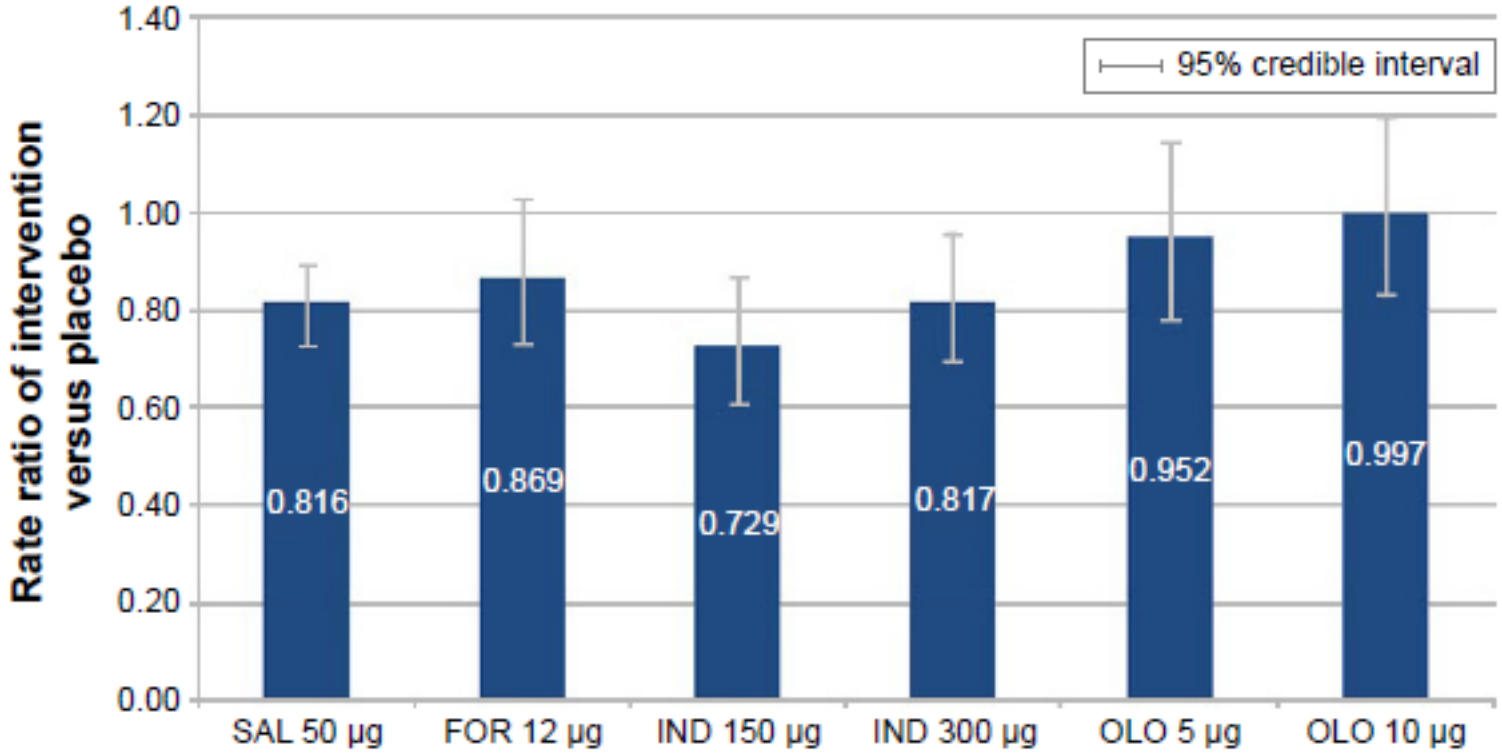


Figure 5 Change from baseline difference in SGRQ total score for intervention versus placebo at 12 and 24 weeks. (**A**) SGRQ total score at 12 weeks and (**B**) SGRQ total score at 24 weeks.

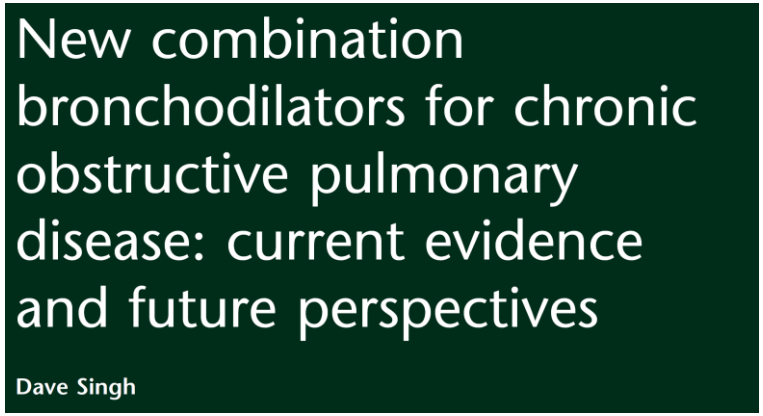
Donohue JF et al International Journal of COPD 2017:12 367–381

Comparative efficacy of long-acting β2-agonists as monotherapy for chronic obstructive pulmonary disease: a network meta-analysis

Alevlenme riskinde azalma



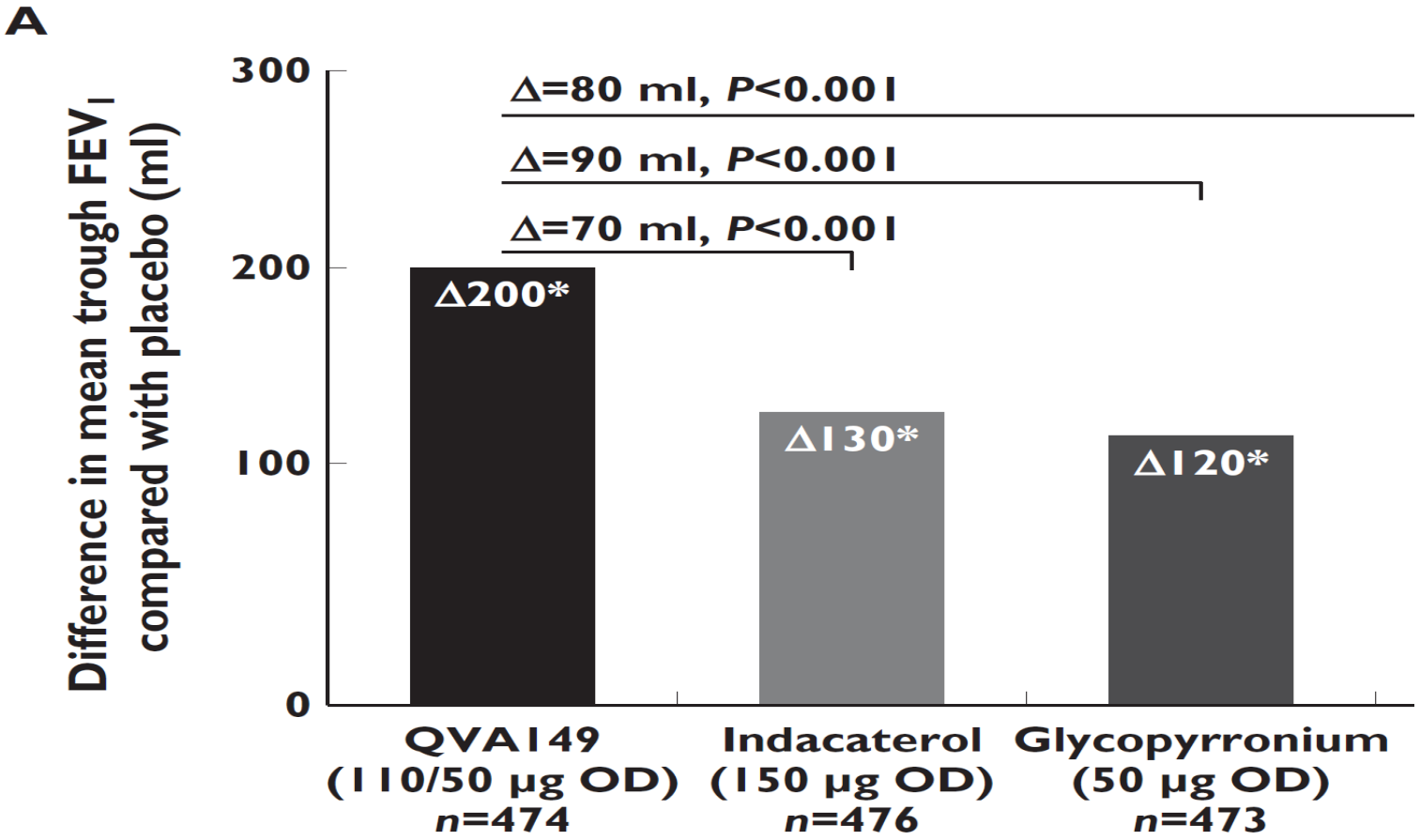
Donohue JF et al International Journal of COPD 2017:12 367–381



Bronkodilatör kombinasyonlarının semptom kontrolünde 6 ay değerlendirmeleri

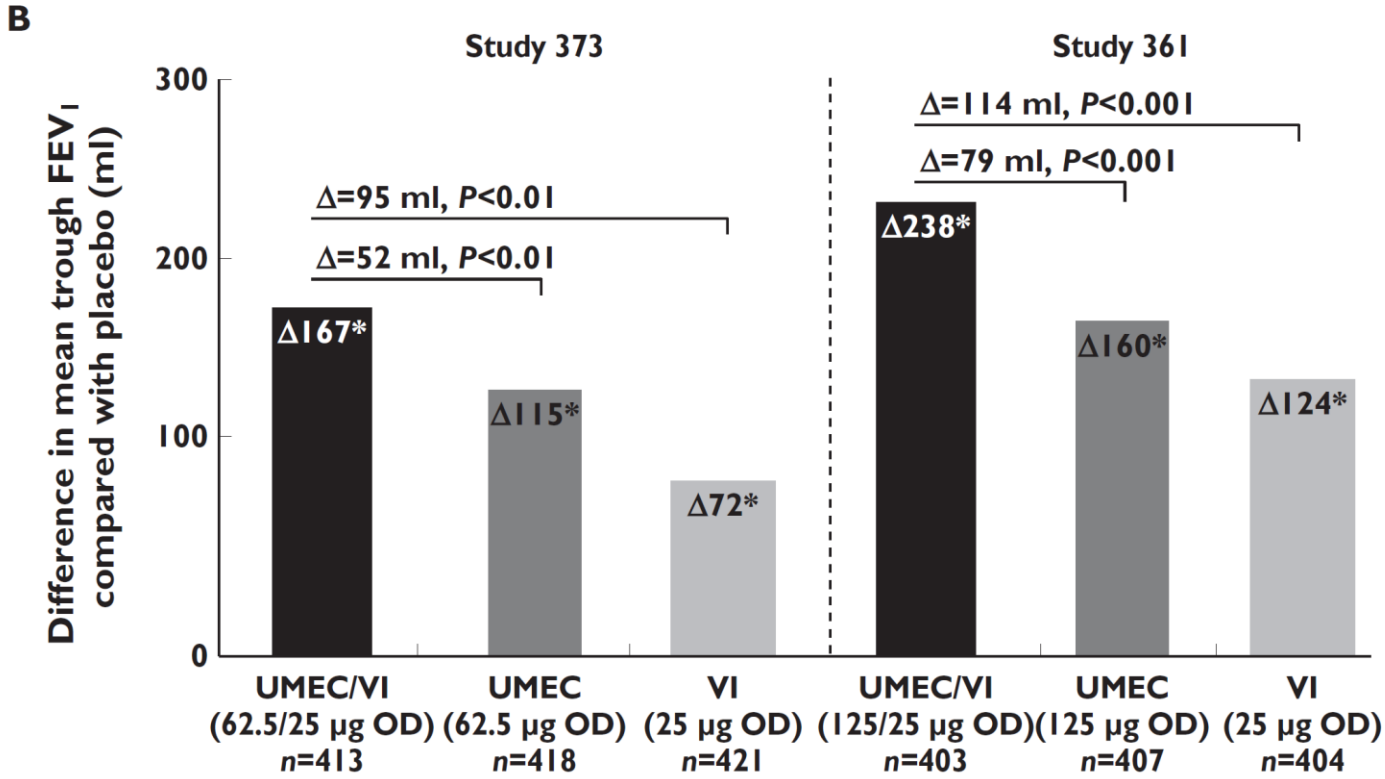
Singh D. Br J Clin Pharmacol 2014 / **79**:5 / 695–708 / 695

Trough FEV 1
26 Hafta



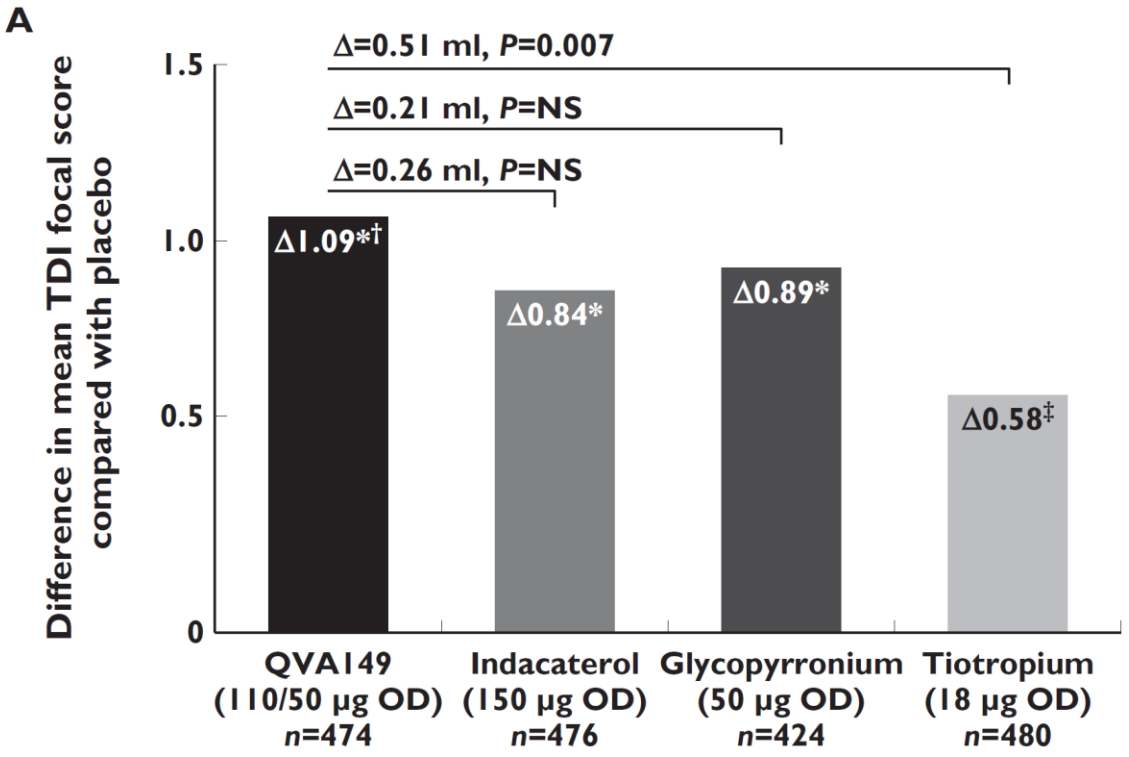
Singh D. Br J Clin Pharmacol 2014 / **79**:5 / 695–708 / 695

Trough FEV1
26 Hafta



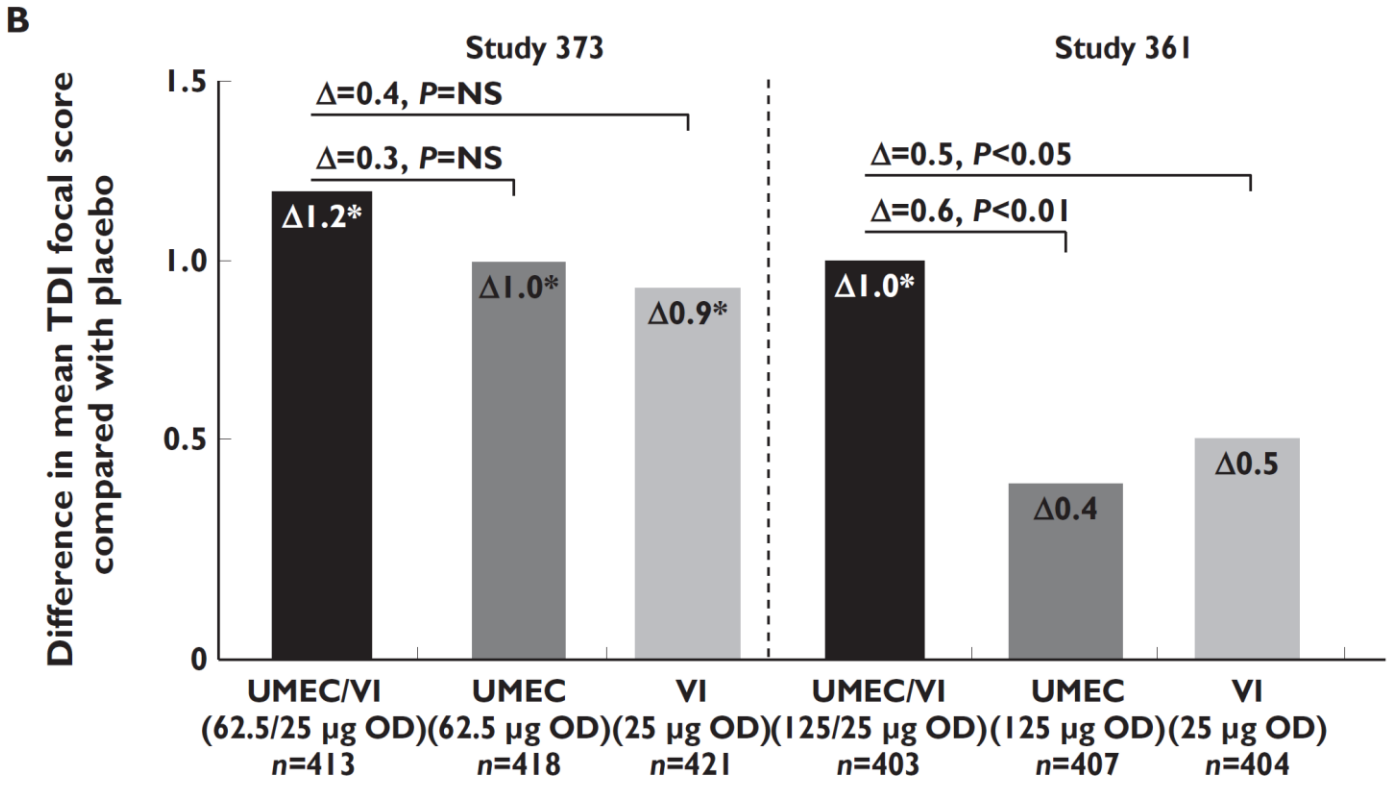
Singh D. Br J Clin Pharmacol 2014 / **79**:5 / 695–708 / 695

Dispnede Değişim İndeksi
TDI 26 Hafta



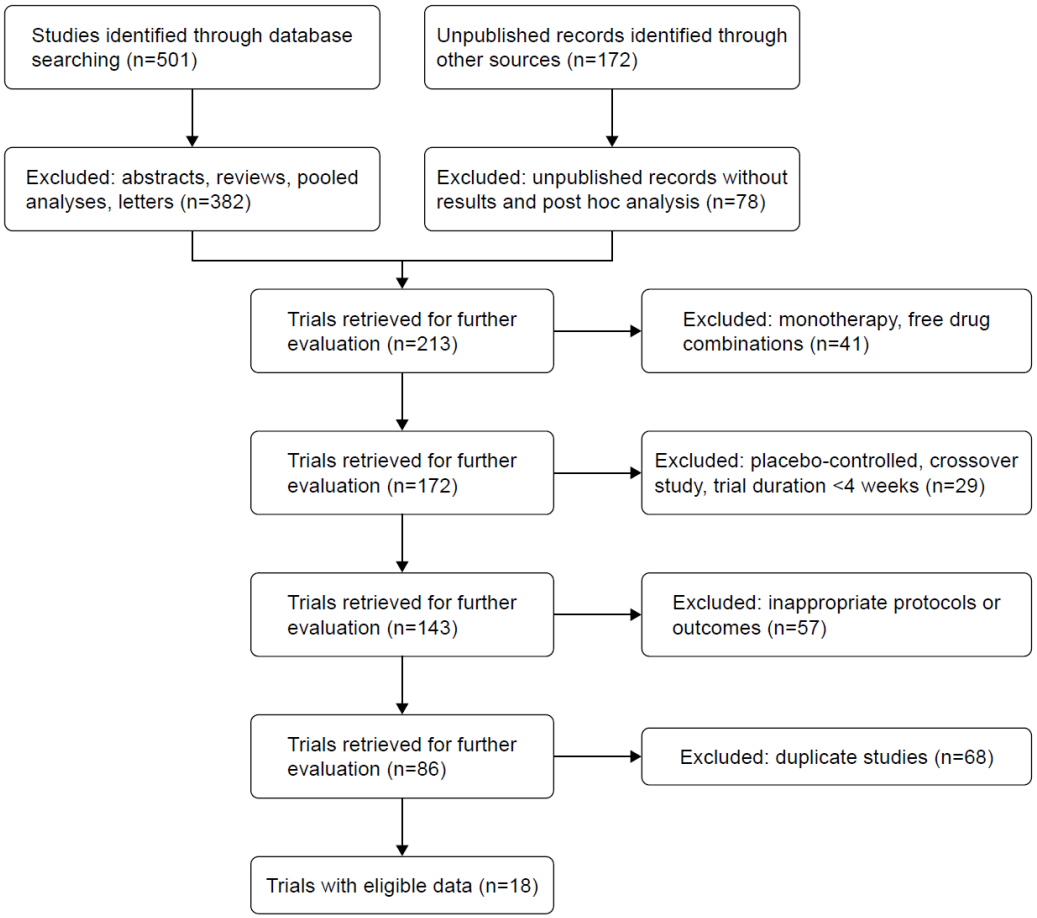
Singh D. Br J Clin Pharmacol 2014 / **79**:5 / 695–708 / 695

Dispnede Değişim İndeksi
26 Hafta



Singh D. Br J Clin Pharmacol 2014 / **79**:5 / 695–708 / 695

LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis

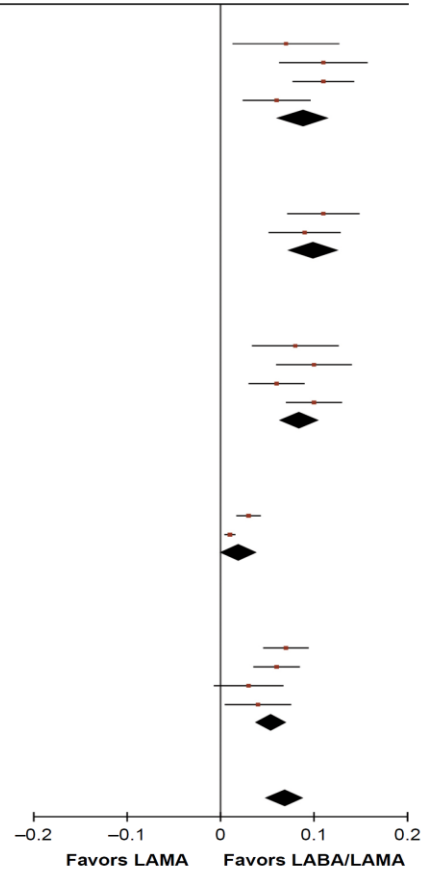


Rodrigo GJ et al . International Journal of COPD 2017:12 907–922

LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis

FEV 1

Study or subgroup	LABA/LAMA Mean, L	SD, L	Total	LAMA Mean, L	SD, L	Total	Weight (%)	Mean difference IV, random, 95% CI, L
Ind/Gly (110/50 µg od) vs Tio (18 µg od) and Gly (50 µg od)								
Asai et al[24]	0.21	0.17	113	0.14	0.15	38	4.8	0.07 (0.01, 0.13)
Bateman et al[25]	0.17	0.43	474	0.06	0.43	953	5.4	0.11 (0.06, 0.16)
Larbig et al[27]	0.3	0.23	376	0.19	0.23	371	6.4	0.11 (0.08, 0.14)
Wedzicha et al[26]	0.17	0.39	666	0.11	0.39	1,316	6.1	0.06 (0.02, 0.10)
Subtotal (95% CI)			**1,629**			**2,678**	**22.7**	**0.09 (0.06, 0.12)**
Heterogeneity: τ^2=0.00; χ^2=5.18, *df*=3 (*P*=0.16); I^2=42%								
Test for overall effect: *Z*=6.30 (*P*<0.0001)								
Ind/Gly (27.5/15.6 µg bid) vs Gly (15.6 µg bid)								
Mahler et al (FLIGHT 1)[28]	0.2	0.23	258	0.09	0.22	262	6.0	0.11 (0.07, 0.15)
Mahler et al (FLIGHT 2)[28]	0.21	0.22	250	0.12	0.22	251	6.0	0.09 (0.05, 0.13)
Subtotal (95% CI)			**508**			**513**	**12**	**0.10 (0.07, 0.13)**
Heterogeneity: τ^2=0.00; χ^2=0.52, *df*=1 (*P*=0.47); I^2=0%								
Test for overall effect: *Z*=7.18 (*P*<0.0001)								
Umec/Vi (62.5/25 µg od) vs Tio (18 µg od) and Umec (62.5 µg od)								
Decramer et al (Study 1)[29]	0.18	0.24	207	0.1	0.24	203	5.5	0.08 (0.03, 0.13)
Decramer et al (Study 2)[29]	0.2	0.22	217	0.1	0.21	215	5.9	0.10 (0.06, 0.14)
Donohue et al[30]	0.18	0.22	413	0.12	0.22	418	6.5	0.06 (0.03, 0.09)
Maleki-Yazdi et al[31]	0.18	0.23	454	0.08	0.23	451	6.5	0.10 (0.07, 0.13)
Subtotal (95% CI)			**1,291**			**1,287**	**24.4**	**0.08 (0.06, 0.11)**
Heterogeneity: τ^2=0.00; χ^2=4.19, *df*=3 (*P*=0.24); I^2=28%								
Test for overall effect: *Z*=7.85 (*P*<0.0001)								
Acli/For (400/12 µg bid) vs Acli (400 µg bid)								
D'Urzo et al[15]	0.11	0.1	335	0.08	0.07	337	7.4	0.03 (0.02, 0.04)
Singh et al[32]	0.06	0.05	385	0.05	0.03	385	7.6	0.01 (0.00, 0.02)
Subtotal (95% CI)			**720**			**722**	**15.0**	**0.02 (–0.00, 0.04)**
Heterogeneity: τ^2=0.00; χ^2=7.52, *df*=1 (*P*=0.006); I^2=87%								
Test for overall effect: *Z*=1.92 (*P*=0.06)								
Tio/Olo (5/5 µg od) vs Tio (5 µg od)								
Buhl et al (Study 1237.5)[7]	0.14	0.2	521	0.07	0.2	520	6.9	0.07 (0.05, 0.09)
Buhl et al (Study 1237.6)[7]	0.14	0.2	497	0.08	0.2	498	6.8	0.06 (0.04, 0.08)
Singh et al (OTEMTO 1)[33]	0.16	0.18	200	0.13	0.2	200	6.1	0.03 (–0.01, 0.07)
Singh et al (OTEMTO 2)[33]	0.16	0.18	199	0.12	0.18	197	6.2	0.04 (0.00, 0.08)
Subtotal (95% CI)			**1,417**			**1,415**	**26**	**0.05 (0.04, 0.07)**
Heterogeneity: τ^2=0.00; χ^2=4.02, *df*=3 (*P*=0.26); I^2=25%								
Test for overall effect: *Z*=6.27 (*P*<0.0001)								
Total (95% CI)			**5,565**			**6,615**	**100**	**0.07 (0.05, 0.09)**
Heterogeneity: τ^2=0.00; χ^2=165.90, *df*=15 (*P*<0.0001); I^2=91%								
Test for overall effect: *Z*=6.63 (*P*<0.0001)								
Test for subgroup differences: χ^2=34.57, *df*=4 (*P*<0.0001); I^2=88.4%								



! Pooled mean difference for trough FEV_1 (change from baseline, L) at week 12, with 95% CIs,

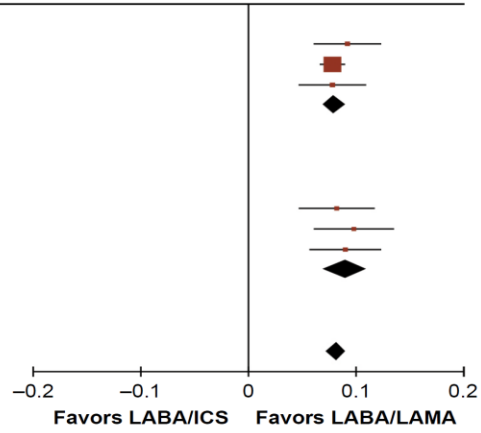
Rodrigo GJ et al . International Journal of COPD 2017:12 907–922

LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis

Trough FEV 1

A

Study or subgroup	Mean difference	SE	LABA/LAMA Total	LABA/ICS Total	Weight (%)	Mean difference IV, random, 95% CI
Ind/Gly (110/50 µg od) vs Sal/FP (50/500 µg bid)						
Vogelmeier et al[34]	0.092	0.016	230	235	8.7	0.09 (0.06, 0.12)
Wedzicha et al[36]	0.078	0.006	1,597	1,595	61.9	0.08 (0.07, 0.09)
Zhong et al[35]	0.078	0.016	342	332	8.7	0.08 (0.05, 0.11)
Subtotal (95% CI)			**2,169**	**2,162**	**79.3**	**0.08 (0.07, 0.09)**
Heterogeneity: τ^2=0.00; χ^2=0.68, *df*=2 (*P*=0.71); I^2=0%						
Test for overall effect: *Z*=15.00 (*P*<0.0001)						
Umec/Vi (62.5/25 µg od) vs Sal/FP (50/250 or 500 µg bid)						
Donohue et al (DB2114930)[37]	0.082	0.018	317	312	6.9	0.08 (0.05, 0.12)
Donohue et al (DB2114951)[37]	0.098	0.019	323	311	6.2	0.10(0.06, 0.14)
Singh et al[38]	0.09	0.017	333	338	7.7	0.09 (0.06, 0.12)
Subtotal (95% CI)			**973**	**961**	**20.7**	**0.09 (0.07, 0.11)**
Heterogeneity: τ^2=0.00; χ^2=0.37, *df*=2 (*P*=0.83); I^2=0%						
Test for overall effect: *Z*=8.66 (*P*<0.0001)						
Total (95% CI)			**3,142**	**3,123**	**100**	**0.08 (0.07, 0.09)**
Heterogeneity: τ^2=0.00; χ^2=1.82, *df*=5 (*P*=0.87); I^2=0%						
Test for overall effect: *Z*=17.30 (*P*<0.0001)						
Test for subgroup differences: χ^2=0.77, *df*=1 (*P*=0.38); I^2=0%						



B

Study or subgroup	Mean difference	SE	LABA/LAMA Total	LABA/ICS Total	Weight (%)	Mean difference IV, random, 95% CI
Ind/Gly (110/50 µg od) vs Sal/FP (50/500 µg bid)						
Vogelmeier et al[34]	0.103	0.019	212	216	25.2	0.10 (0.07, 0.14)
Wedzicha et al[36]	0.086	0.027	1,597	1,595	22.7	0.09 (0.03, 0.14)
Zhong et al[35]	0.075	0.016	352	340	26.0	0.07 (0.04, 0.11)
Subtotal (95% CI)			**2,161**	**2,151**	**73.8**	**0.09 (0.06, 0.11)**
Heterogeneity: τ^2=0.00; χ^2=1.27, *df*=2 (*P*=0.53); I^2=0%						
Test for overall effect: *Z*=7.76 (*P*<0.0001)						
Acli/For (400/12 µg bid) vs Sal/FP (50/500 µg bid)						
Vogelmeier et al[39]	−0.014	0.015	402	386	26.2	−0.01 (−0.04, 0.02)
Subtotal (95% CI)			**402**	**386**	**26.2**	**−0.01 (−0.04, 0.02)**
Heterogeneity: not applicable						
Test for overall effect: *Z*=0.93 (*P*=0.35)						
Total (95% CI)			**2,563**	**2,537**	**100**	**0.06 (0.00, 0.12)**
Heterogeneity: τ^2=0.00; χ^2=30.20, *df*=3 (*P*<0.0001); I^2=90%						
Test for overall effect: *Z*=2.09 (*P*=0.04)						
Test for subgroup differences: χ^2=28.93, *df*=1 (*P*<0.0001); I^2=96.5%						

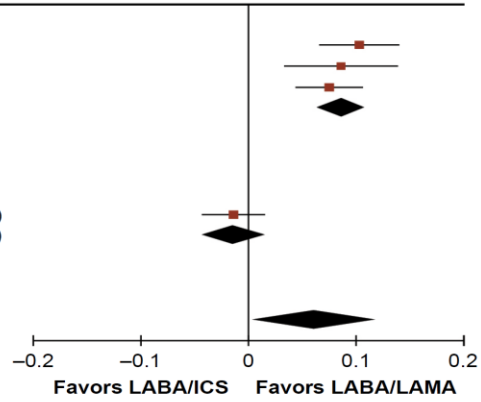


Figure 3 Pooled mean difference for trough FEV_1 (change from baseline, L) at (**A**) week 12 and (**B**) weeks 24–26, with 95% CIs, for eligible studies comparing approved LABA/LAMA combinations with approved LABA/ICS combinations.

Rodrigo GJ et al . International Journal of COPD 2017:12 907–922

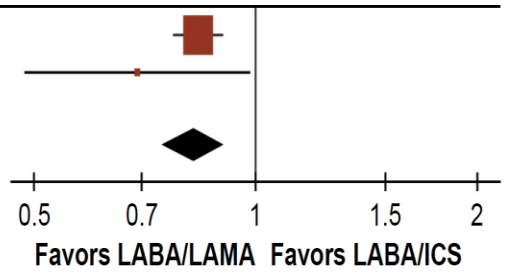
LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis

ALEVLENME

A

Study or subgroup	Log (risk ratio)	SE	LABA/ LAMA Total	LABA/ ICS Total	Weight (%)	Risk ratio IV, random, 95% CI
Wedzicha et al[36]	–0.18	0.04	1,651	1,656	92.7	0.84 (0.77, 0.90)
Zhong et al[35]	–0.37	0.18	372	369	7.3	0.69 (0.49, 0.98)
Total (95% CI)			**2,023**	**2,025**	**100**	**0.82 (0.75, 0.91)**

Heterogeneity: τ^2=0.00; χ^2=1.06, *df*=1 (*P*=0.30); I^2=6%
Test for overall effect: *Z*=3.91 (*P*<0.0001)



B

Study or subgroup	Log (risk ratio)	SE	LABA/ LAMA Total	LABA/ ICS Total	Weight (%)	Risk ratio IV, random, 95% CI
Wedzicha et al[36]	–0.13	0.11	1,651	1,656	61.9	0.88 (0.71, 1.09)
Zhong et al[35]	–1.17	0.52	372	369	38.1	0.31 (0.11, 0.86)
Total (95% CI)			**2,023**	**2,025**	**100**	**0.59 (0.22, 1.59)**

Heterogeneity: τ^2=0.40; χ^2=3.83, *df*=1 (*P*=0.05); I^2=74%
Test for overall effect: *Z*=1.04 (*P*=0.30)

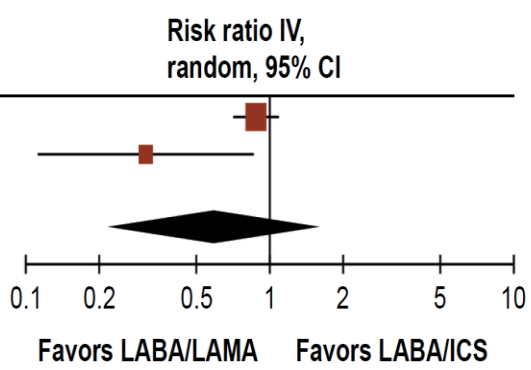


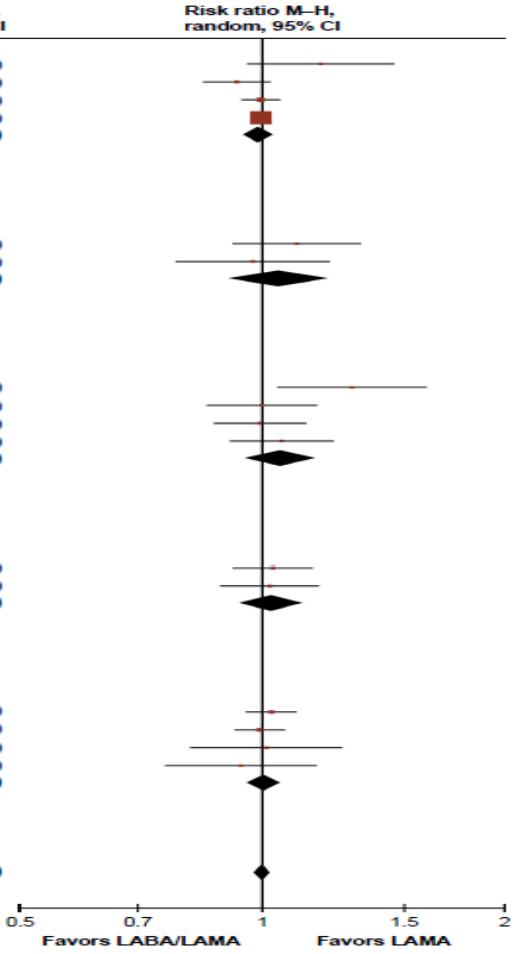
Figure 4 Pooled relative risk of annualized rates of (**A**) moderate and/or severe exacerbations or (**B**) severe exacerbations, with 95% CIs, for eligible studies comparing approved LABA/LAMA combinations with approved LABA/ICS combinations.

Rodrigo GJ et al . International Journal of COPD 2017:12 907–922

LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis

Pooled relative risk of AE incidence at end of treatment,

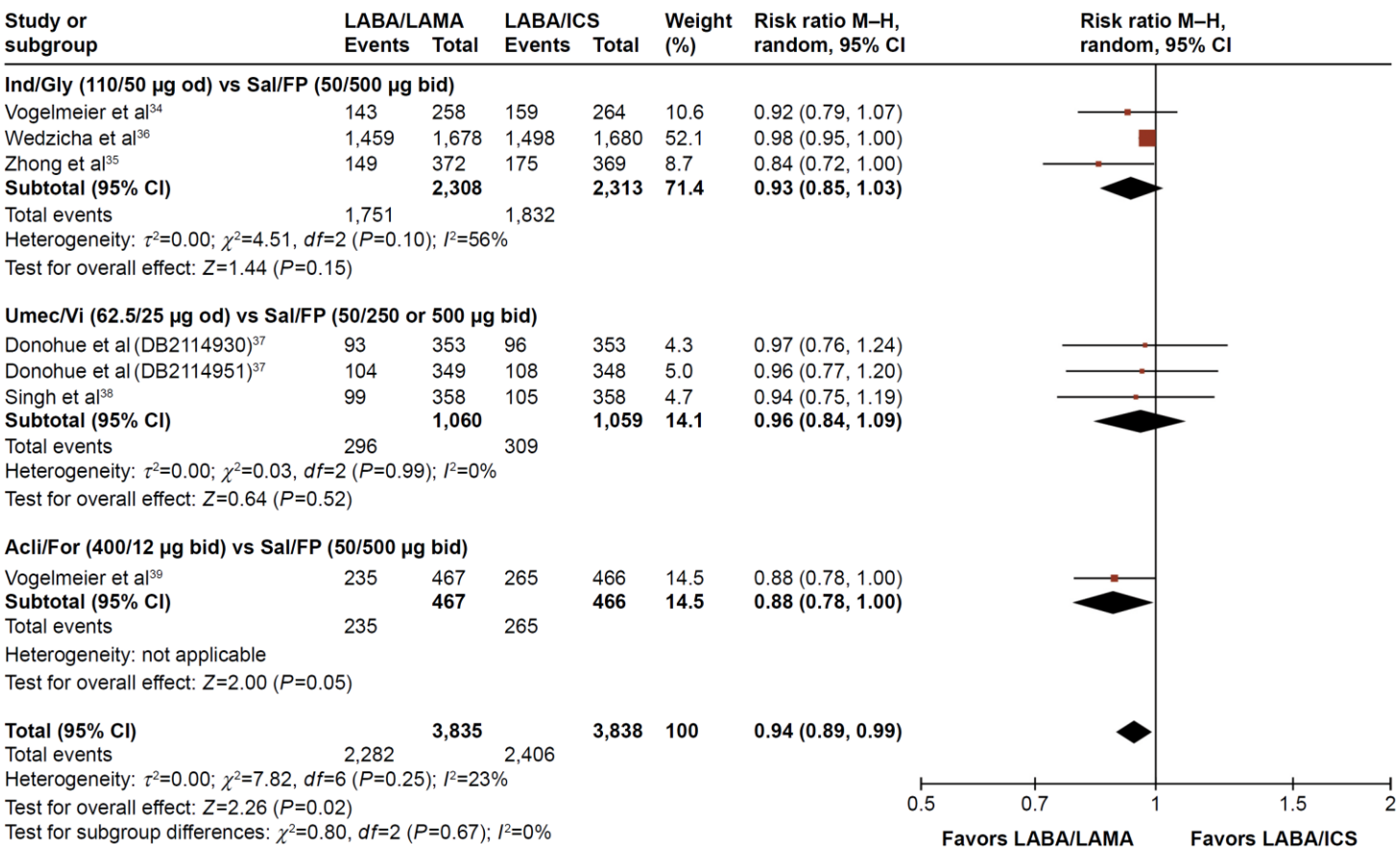
Study or subgroup	LABA/LAMA Events	LABA/LAMA Total	LAMA Events	LAMA Total	Weight (%)	Risk ratio M–H, random, 95% CI
Ind/Gly (110/50 µg od) vs Tio (18 µg od) and Gly (50 µg od)						
Asai et al[24]	101	119	28	39	0.8	1.18 (0.96, 1.46)
Bateman et al[25]	261	474	565	953	3.6	0.93 (0.84, 1.02)
Larbig et al[27]	349	407	349	405	11.0	1.00 (0.94, 1.05)
Wedzicha et al[26]	678	729	1,380	1,477	58.8	1.00 (0.97, 1.02)
Subtotal (95% CI)		**1,729**		**2,874**	**74.3**	**0.99 (0.95, 1.03)**
Total events	1,389		2,322			
Heterogeneity: τ^2=0.00; χ^2=5.13, *df*=3 (*P*=0.16); I^2=42%						
Test for overall effect: *Z*=0.39 (*P*=0.70)						
Ind/Gly (27.5/15.6 µg bid) vs Gly (15.6 µg bid)						
Mahler et al (FLIGHT 1)[28]	126	258	116	262	1.0	1.10 (0.92, 1.33)
Mahler et al (FLIGHT 2)[28]	95	250	98	251	0.7	0.97 (0.78, 1.21)
Subtotal (95% CI)		**508**		**513**	**1.7**	**1.05 (0.91, 1.21)**
Total events	221		214			
Heterogeneity: τ^2=0.00; χ^2=0.73, *df*=1 (*P*=0.39); I^2=0%						
Test for overall effect: *Z*=0.65 (*P*=0.52)						
Umec/Vi (62.5/25 µg od) vs Tio (18 µg od) and Umec (62.5 µg od)						
Decramer et al (Study 1)[29]	108	212	82	208	0.7	1.29 (1.04, 1.60)
Decramer et al (Study 2)[29]	127	217	126	215	1.4	1.00 (0.85, 1.17)
Donohue et al[30]	212	413	216	418	2.0	0.99 (0.87, 1.13)
Maleki-Yazdi et al[31]	202	454	190	451	1.5	1.06 (0.91, 1.23)
Subtotal (95% CI)		**1,296**		**1,292**	**5.6**	**1.06 (0.96, 1.17)**
Total events	649		614			
Heterogeneity: τ^2=0.00; χ^2=4.70, *df*=3 (*P*=0.20); I^2=36%						
Test for overall effect: *Z*=1.08 (*P*=0.28)						
Acli/For (400/12 µg bid) vs Acli (400 µg bid)						
D'Urzo et al[15]	215	335	210	337	2.6	1.03 (0.92, 1.16)
Singh et al[32]	194	385	190	385	1.7	1.02 (0.89, 1.18)
Subtotal (95% CI)		**720**		**722**	**4.3**	**1.03 (0.94, 1.12)**
Total events	409		400			
Heterogeneity: τ^2=0.00; χ^2=0.01, *df*=1 (*P*=0.93); I^2=0%						
Test for overall effect: *Z*=0.57 (*P*=0.57)						
Tio/Olo (5/5 µg od) vs Tio (5 µg od)						
Buhl et al (Study 1237.5)[7]	387	522	381	527	6.4	1.03 (0.95, 1.10)
Buhl et al (Study 1237.6)[7]	374	507	376	506	6.4	0.99 (0.92, 1.07)
Singh et al (OTEMTO 1)[33]	91	203	90	203	0.7	1.01 (0.81, 1.26)
Singh et al (OTEMTO 2)[33]	87	202	93	203	0.7	0.94 (0.76, 1.17)
Subtotal (95% CI)		**1,434**		**1,439**	**14.2**	**1.01 (0.96, 1.06)**
Total events	939		940			
Heterogeneity: τ^2=0.00; χ^2=0.78, *df*=3 (*P*=0.85); I^2=0%						
Test for overall effect: *Z*=0.22 (*P*=0.83)						
Total (95% CI)		**5,687**		**6,840**	**100**	**1.00 (0.98, 1.02)**
Total events	3,607		4,490			
Heterogeneity: τ^2=0.00; χ^2=13.73, *df*=15 (*P*=0.55); I^2=0%						
Test for overall effect: *Z*=0.07 (*P*=0.95)						
Test for subgroup differences: χ^2=1.87, *df*=4 (*P*=0.76); I^2=0%						



Rodrigo GJ et al . International Journal of COPD 2017:12 907–922

LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis

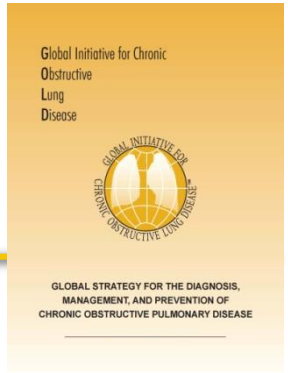
Pooled relative risk of AE incidence at end of treatment,



Rodrigo GJ et al . International Journal of COPD 2017:12 907–922

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Tedavinin Amaçları



- **Semptomları iyileştir**
- **Egzersiz toleransınını iyileştir**
- **Yaşam kalitesini iyileştir**

Semptomları azalt

- Hastalığın progresyonunu engelle
- Alevlenmeleri önle ve tedavi et
- Mortaliteyi azalt

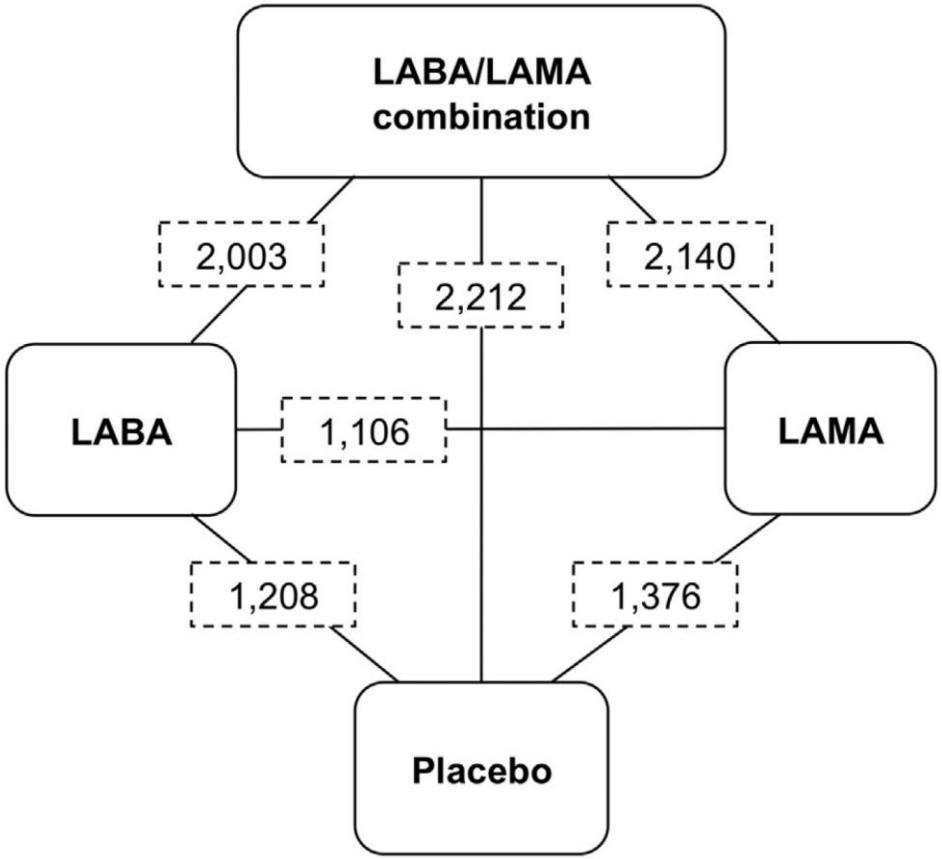
Riskleri azalt

GOLD 2018

Egzersiz Dayanıklılığını İyileştirmede Bronkodilatörler

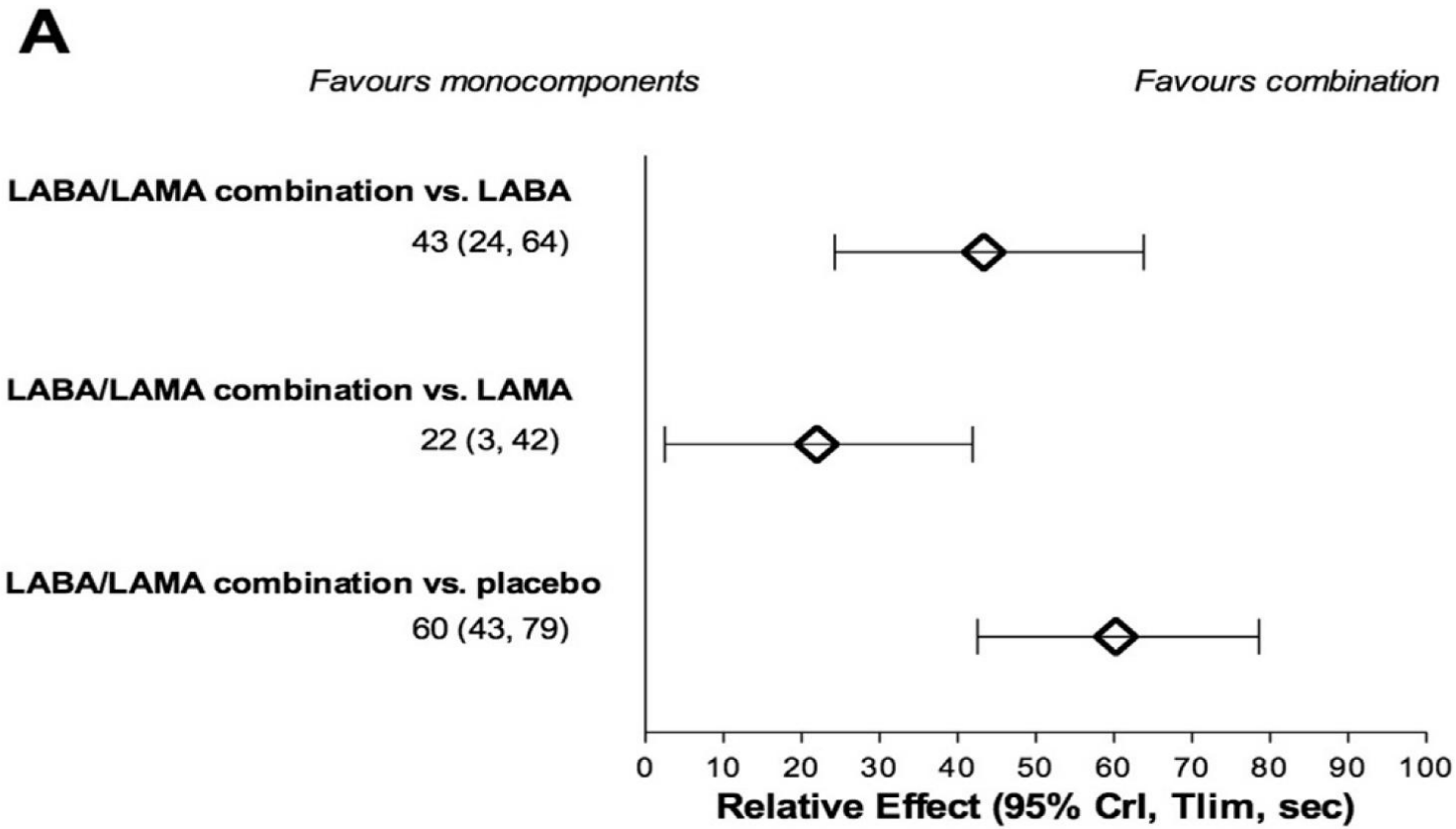
Impact of LABA/LAMA combination on exercise endurance and lung hyperinflation in COPD: A pair-wise and network meta-analysis

Luigino Calzetta [a], Josuel Ora [b], Francesco Cavalli [a], Paola Rogliani [a, b], Denis E. O'Donnell [c], Mario Cazzola [a, *]



Impact of LABA/LAMA combination on exercise endurance and lung hyperinflation in COPD: A pair-wise and network meta-analysis

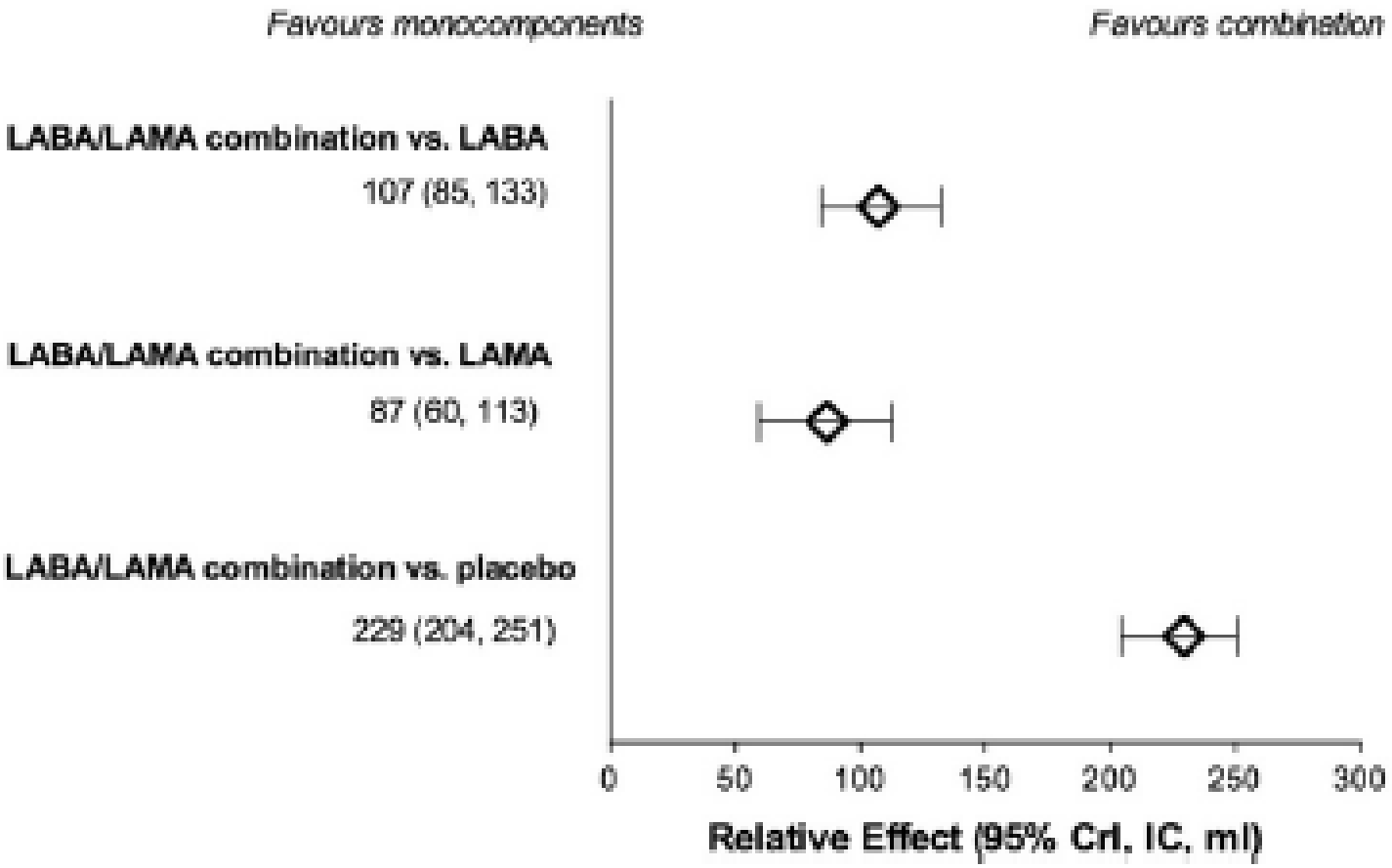
Luigino Calzetta [a], Josuel Ora [b], Francesco Cavalli [a], Paola Rogliani [a, b], Denis E. O'Donnell [c], Mario Cazzola [a, *]



Respiratory Medicine 129 (2017) 189–198

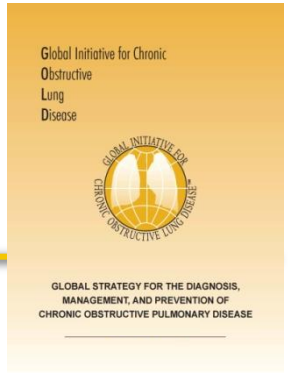
Impact of LABA/LAMA combination on exercise endurance and lung hyperinflation in COPD: A pair-wise and network meta-analysis

Luigino Calzetta [a], Josuel Ora [b], Francesco Cavalli [a], Paola Rogliani [a, b], Denis E. O'Donnell [c], Mario Cazzola [a, *]



Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Tedavinin Amaçları



- **Semptomları iyileştir**
- **Egzersiz toleransınını iyileştir**
- **Yaşam kalitesini iyileştir**

Semptomları azalt

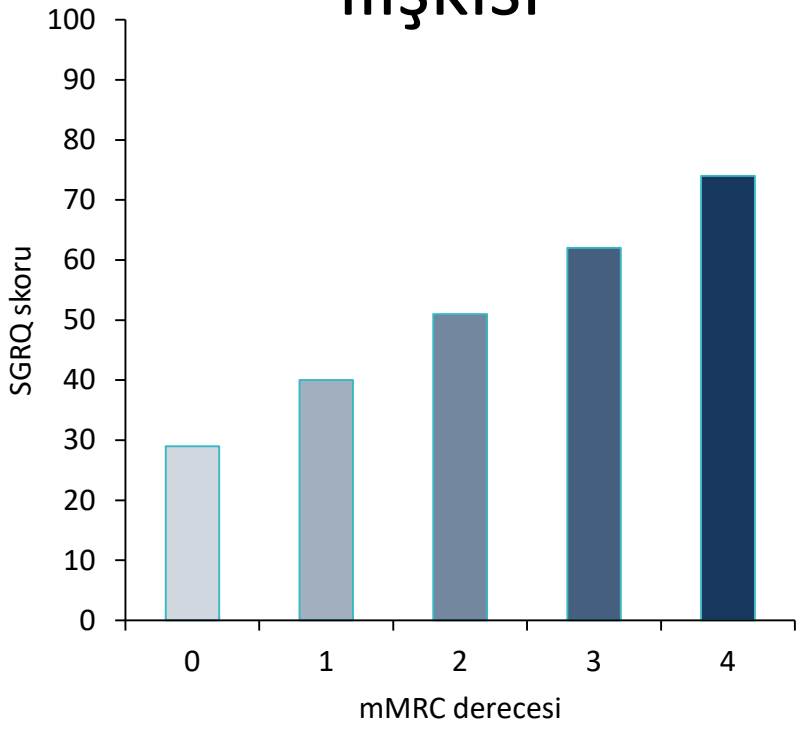
- Hastalığın progresyonunu engelle
- Alevlenmeleri önle ve tedavi et
- Mortaliteyi azalt

Riskleri azalt

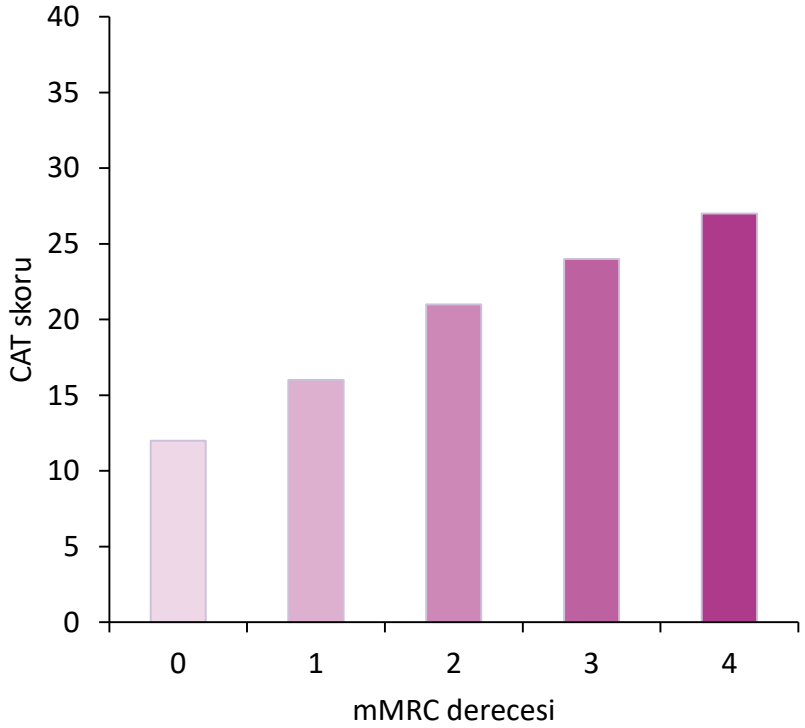
GOLD 2018

Yaşam Kalitesini İyileştirmede Bronkodilatörler

Dispne ve SGRQ ilişkisi



Dispne ve CAT ilişkisi



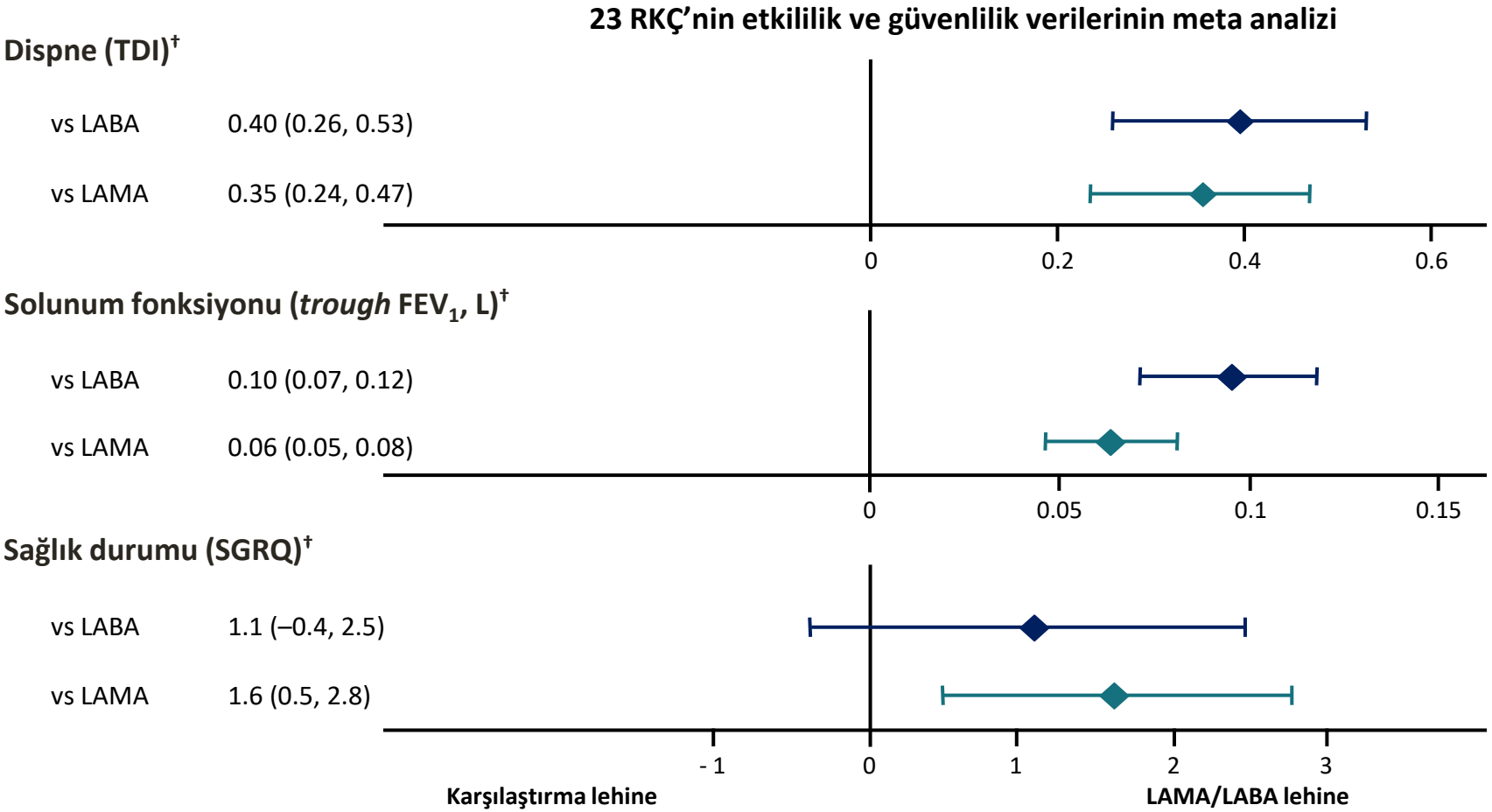
- 1817 hastadan elde edilen veriler, mMRC dereceleri ile sağlık durumu puanları arasında anlamlı bir ilişki olduğunu göstermiştir.

Grafik 1 numaralı referanstan uyarlanmıştır.

KOAH: Kronik obstrüktif akciğer hastalığı; CAT: KOAH değerlendirme testi; mMRC: modifiye Medical Research Council dispne skalası

1. Jones PW et al. Eur Respir J. 2013;42:647–654.

6 aylık tedavide, LAMA/LABA, mono bronkodilatörlere göre, klinik sonuçları iyileştirmiştir[1]

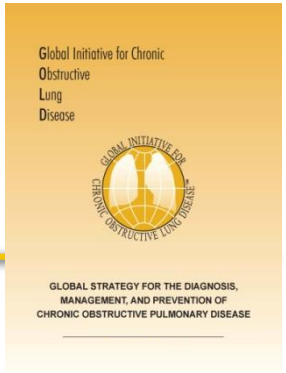


†Ortalama fark (%95 kabul edilebilir aralık). Grafik 1 numaralı referanstan uyarlanmıştır FEV_1: 1. saniyede zorlu ekspiratuar volüm; FVC: Zorlu vital kapasite; LABA: Uzun etkili beta agonist; LAMA: Uzun etkili antikolinerjik; SGRQ: St george solunum anketi; TDI: Geçiş dispne indeksi; RKÇ: Randomize kontrollü çalışma

1. Oba Y et al. Thorax 2016, 71, 15–25

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Tedavinin Amaçları



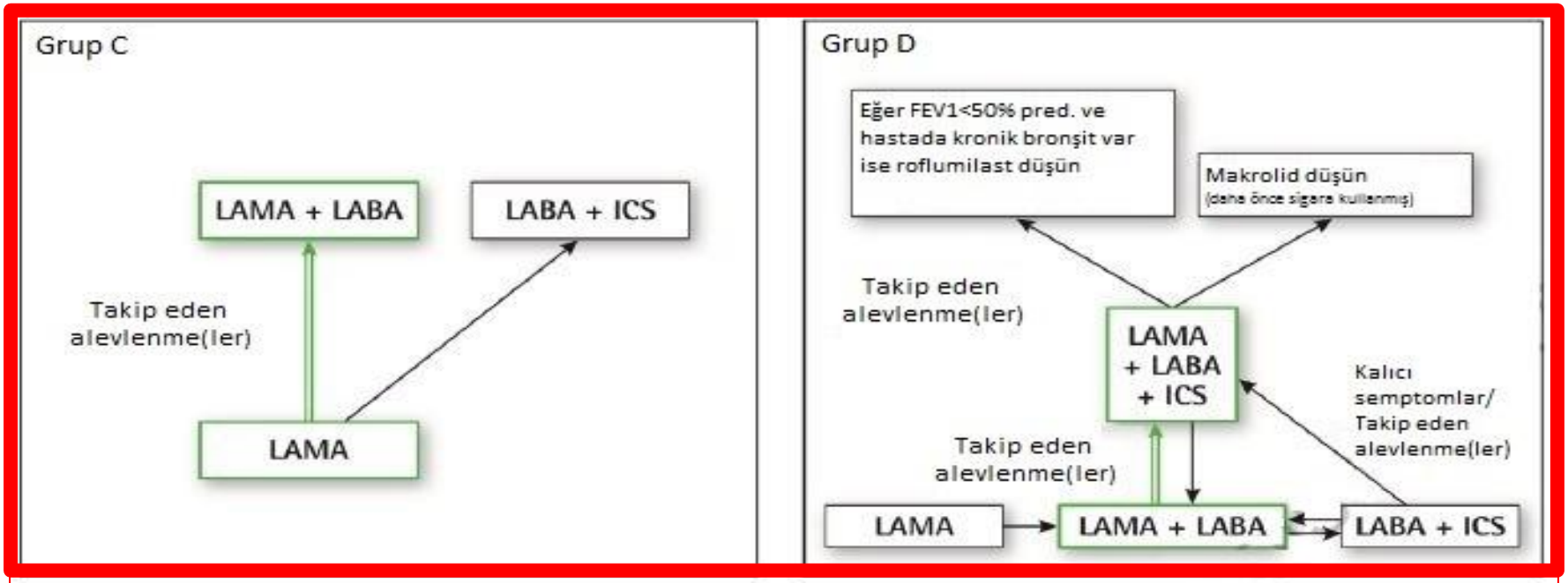
- Semptomları iyileştir
- Egzersiz toleransınını iyileştir
- Yaşam kalitesini iyileştir

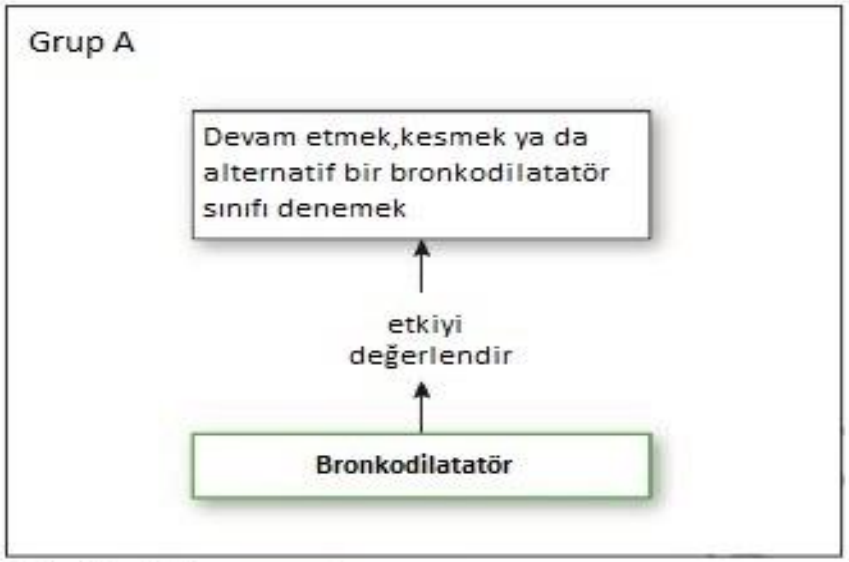
Semptomları azalt

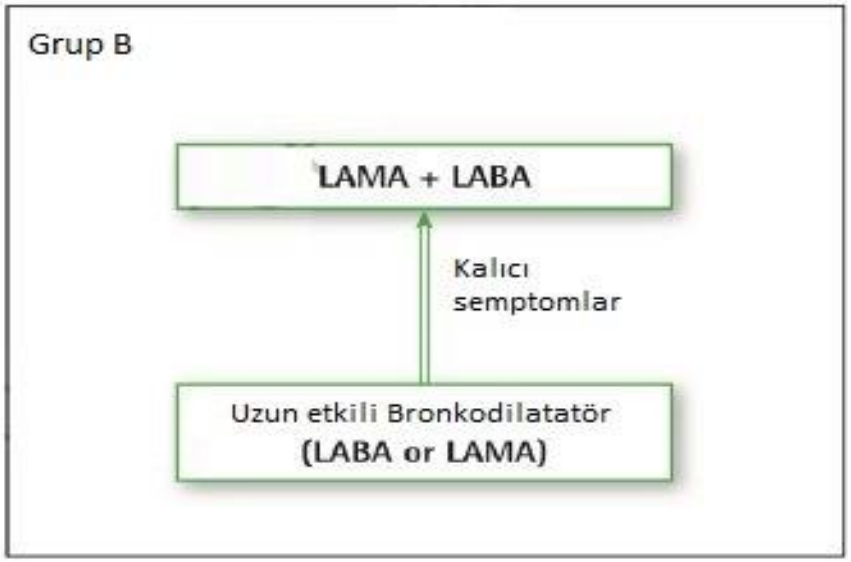
- Hastalığın progresyonunu engelle
- **Alevlenmeleri önle ve tedavi et**
- Mortaliteyi azalt

Riskleri azalt

GOLD 2018





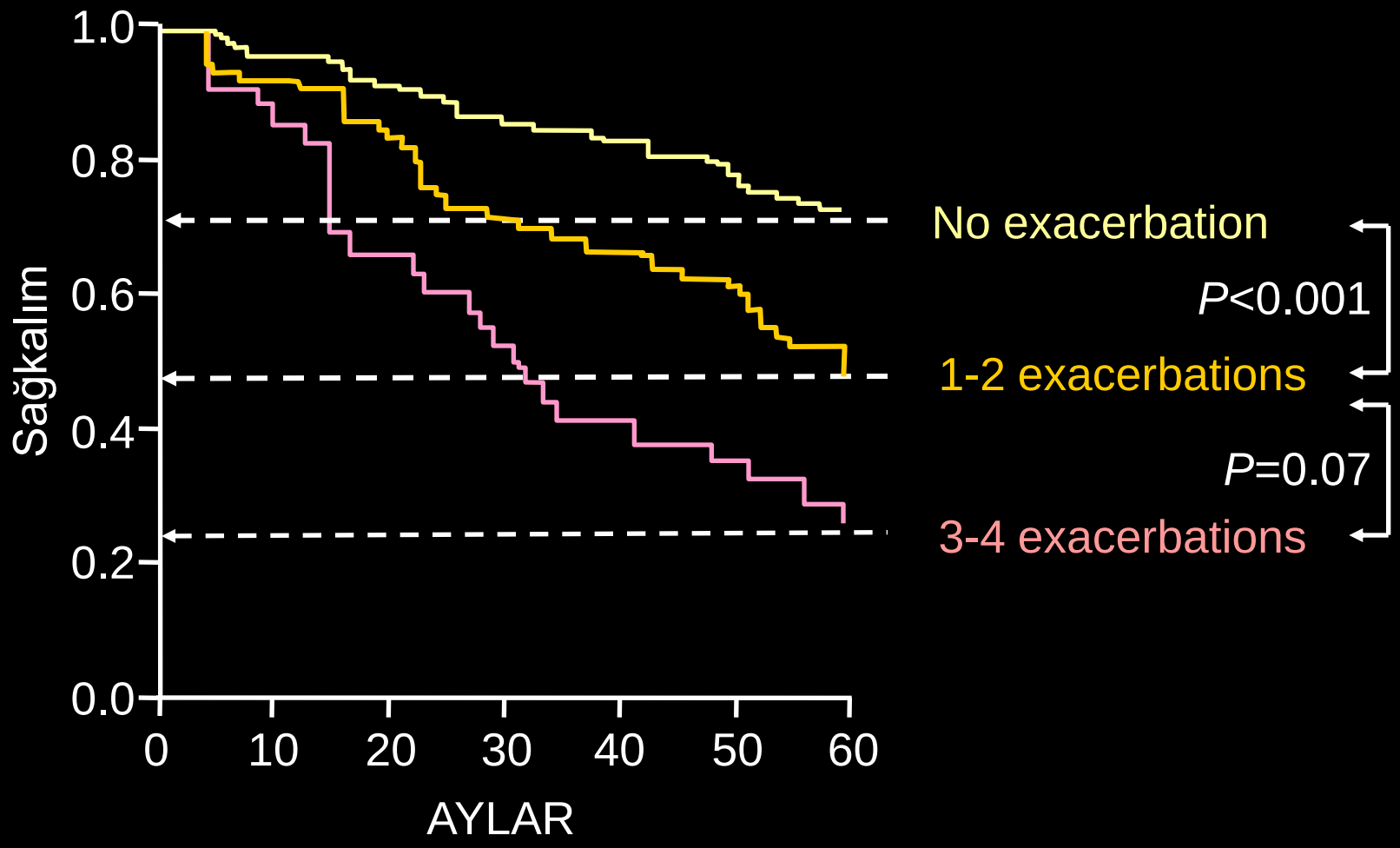


Tercih edilen tedavi →

Hastalarda hissedilen semptom dereceleri ve havayolu kısıtlılığı ağırlığı arasında majör bir tutarsızlık mevcut olup daha ileri bir değerlendirme gereklidir.

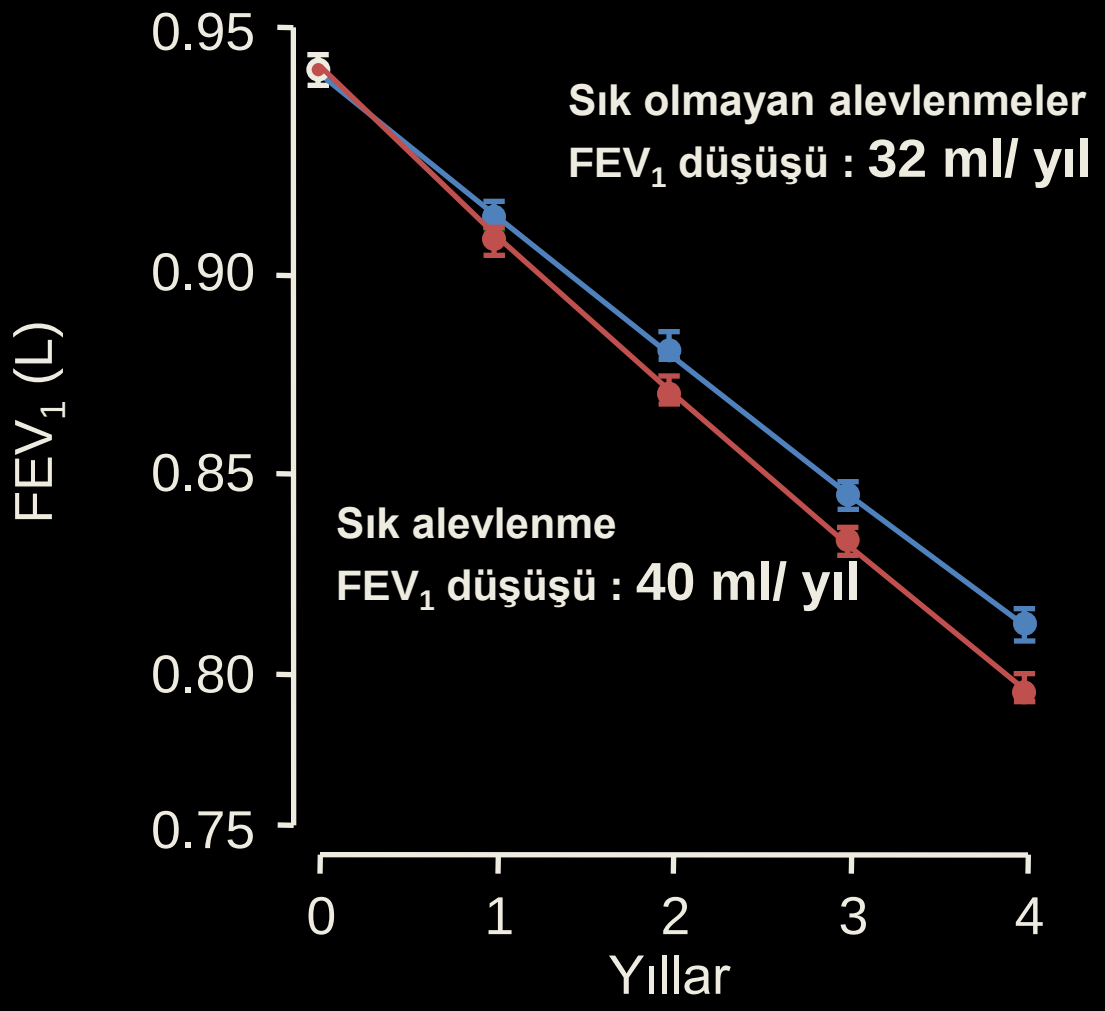
Ref: GOLD 2017 son rapor – 16 Kasım 2016' da yayınlanmıştır.

Tekrarlayan Alevlenmeler ve Sağkalım



Soler-Cataluña JJ et al. Thorax 2005;64:925-31

Sık Alevlenmelerin FEV_1 düşüşü üzerine etkisi



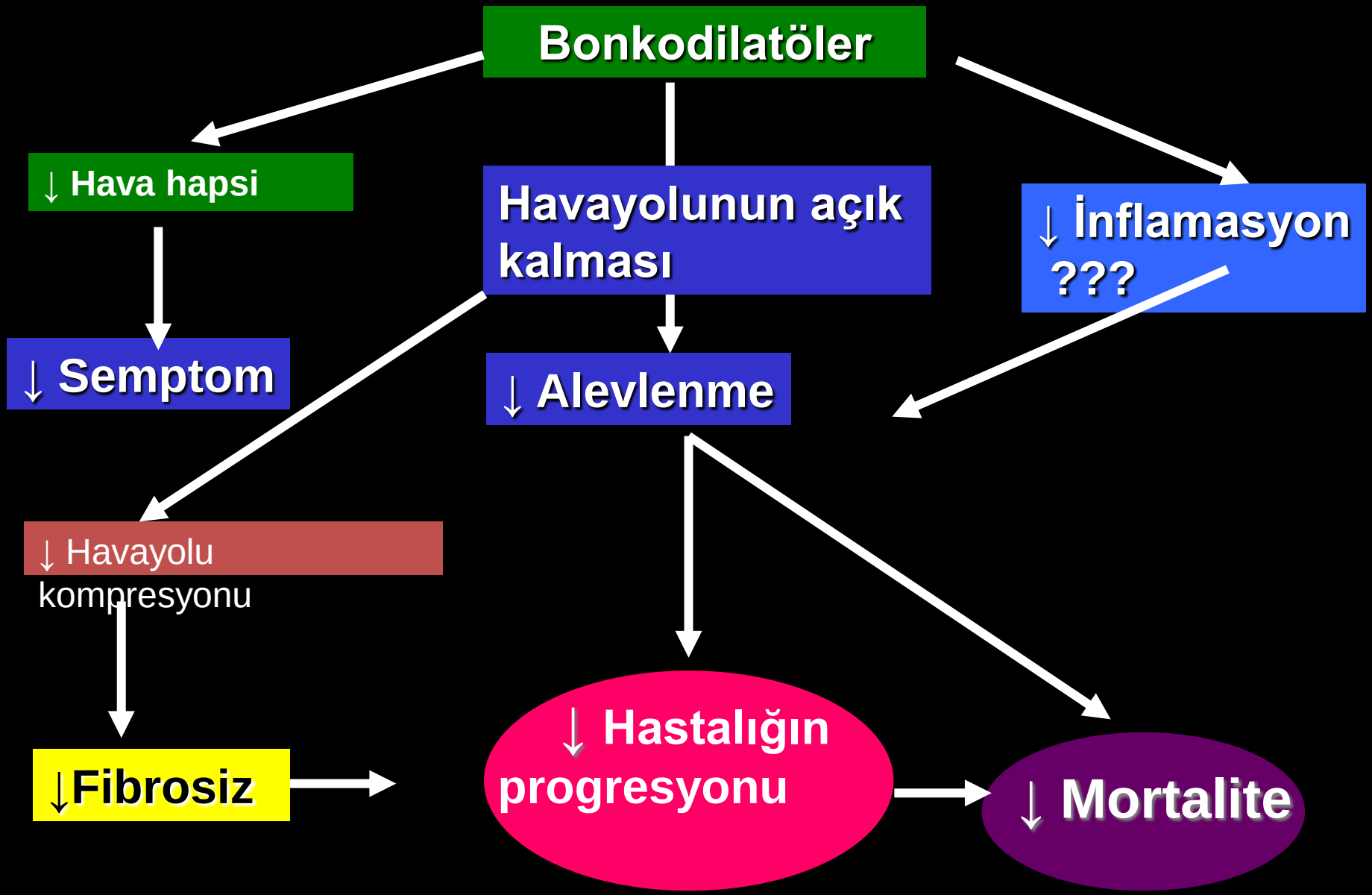
Donaldson GC et al. Thorax 2002

FEV 1 ve Kardiyak Mortalite

- FEV1 düşüşü kardiyovasküler mortalite belirteci
- KOAH olgularında FEV 1'de her % 10'luk düşüş
    - Kardiyovasküler mortaliteyi % 28
    - Non- fatal koroner olayları % 20 arttırır

Anthonisen NR, et al. Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002;166:333–339.

KOAH'da Bronkodilatörler



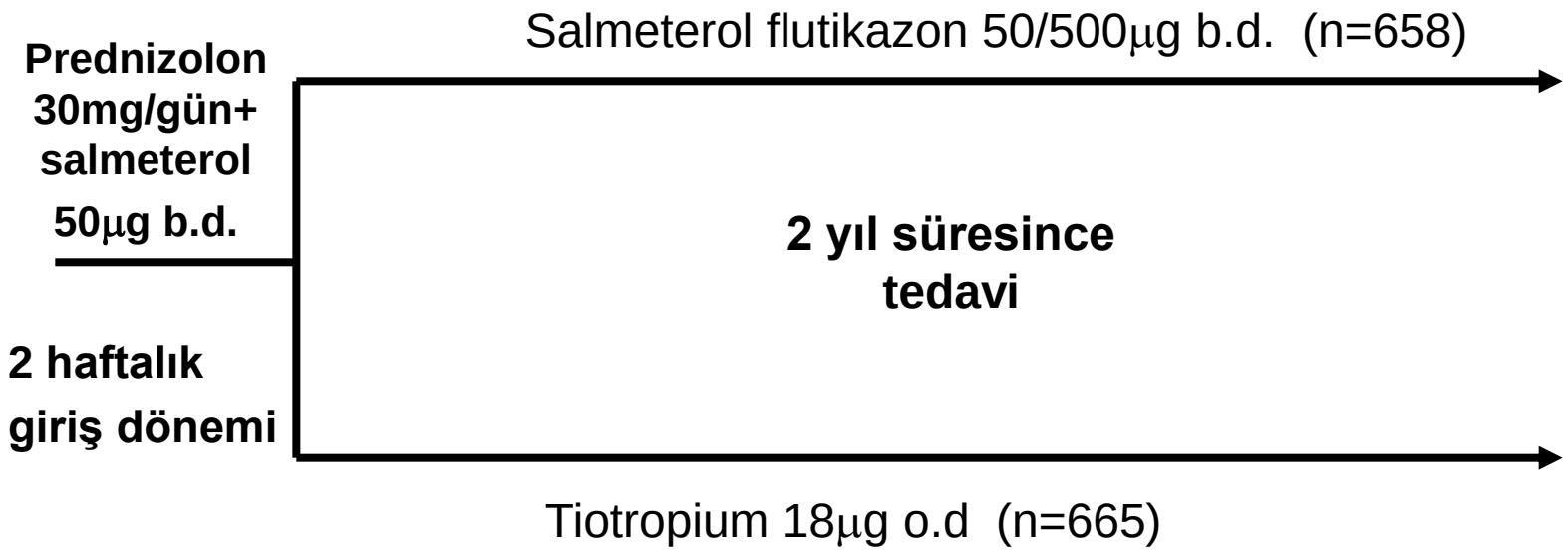
The Prevention of Chronic Obstructive Pulmonary Disease Exacerbations by Salmeterol/Fluticasone Propionate or Tiotropium Bromide

Jadwiga A. Wedzicha[1], Peter M. A. Calverley[2], Terence A. Seemungal[3], Gerry Hagan[4], Zainab Ansari[4], and Robert A. Stockley[5], for the INSPIRE Investigators

Am J Respir Crit Care Med. 2008, 1;177:19-26

Çalışma dizaynı

Randomize, çift kör, paralel grup çalışması



Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA; INSPIRE Investigators.The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008, 1;177:19-26

Alevlenme Sıklığı

	Salmeterol/ Flutikazon (n = 658)	Tiotropium (n = 665)
Alevlenme	1.28	1.32
p-değeri	0.656	

RR, 0.967; % 95 [CI],0.836-1.119]; P = 0.656

Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA; INSPIRE Investigators.The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008, 1;177:19-26

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

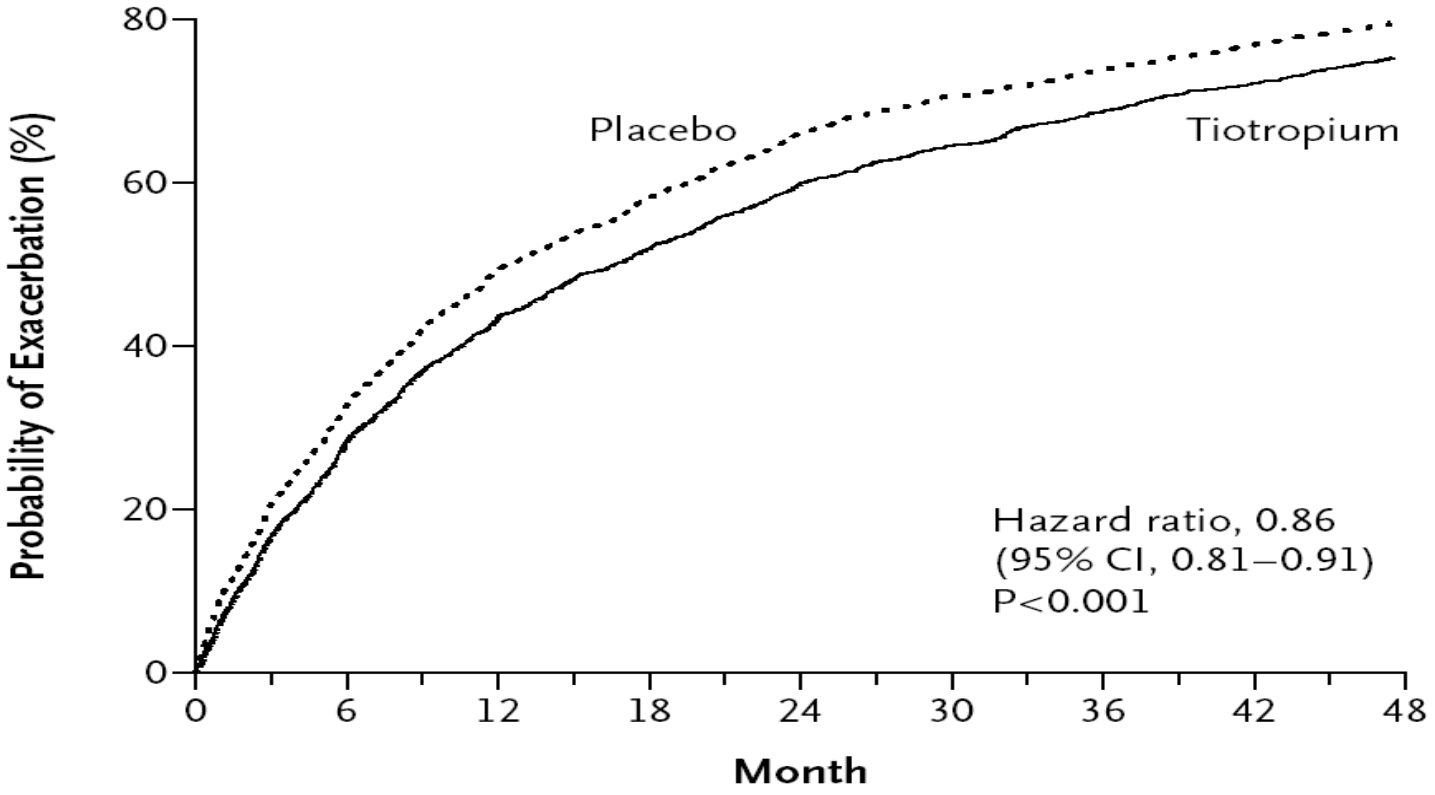
Donald P. Tashkin, M.D., Bartolome Celli, M.D., Stephen Senn, Ph.D., Deborah Burkhart, B.S.N., Steven Kesten, M.D., Shailendra Menjoge, Ph.D., and Marc Decramer, M.D., Ph.D., for the UPLIFT Study Investigators*

Amaç

- Birincil sonlanım
  - FEV 1 azalması
- İkincil sonlanım
  - Alevlenme
  - Alevlenme nedeni ile hastaneye yatış
  - Yaşam kalitesi (St. George’s Respiratory Questionnaire)
  - Mortalite (Tedavi ve izlemde)

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*



No. at Risk

Tiotropium	2986	1996	1496	1223	983	838	709	610	26
Placebo	3006	1815	1284	1010	776	634	545	460	21

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

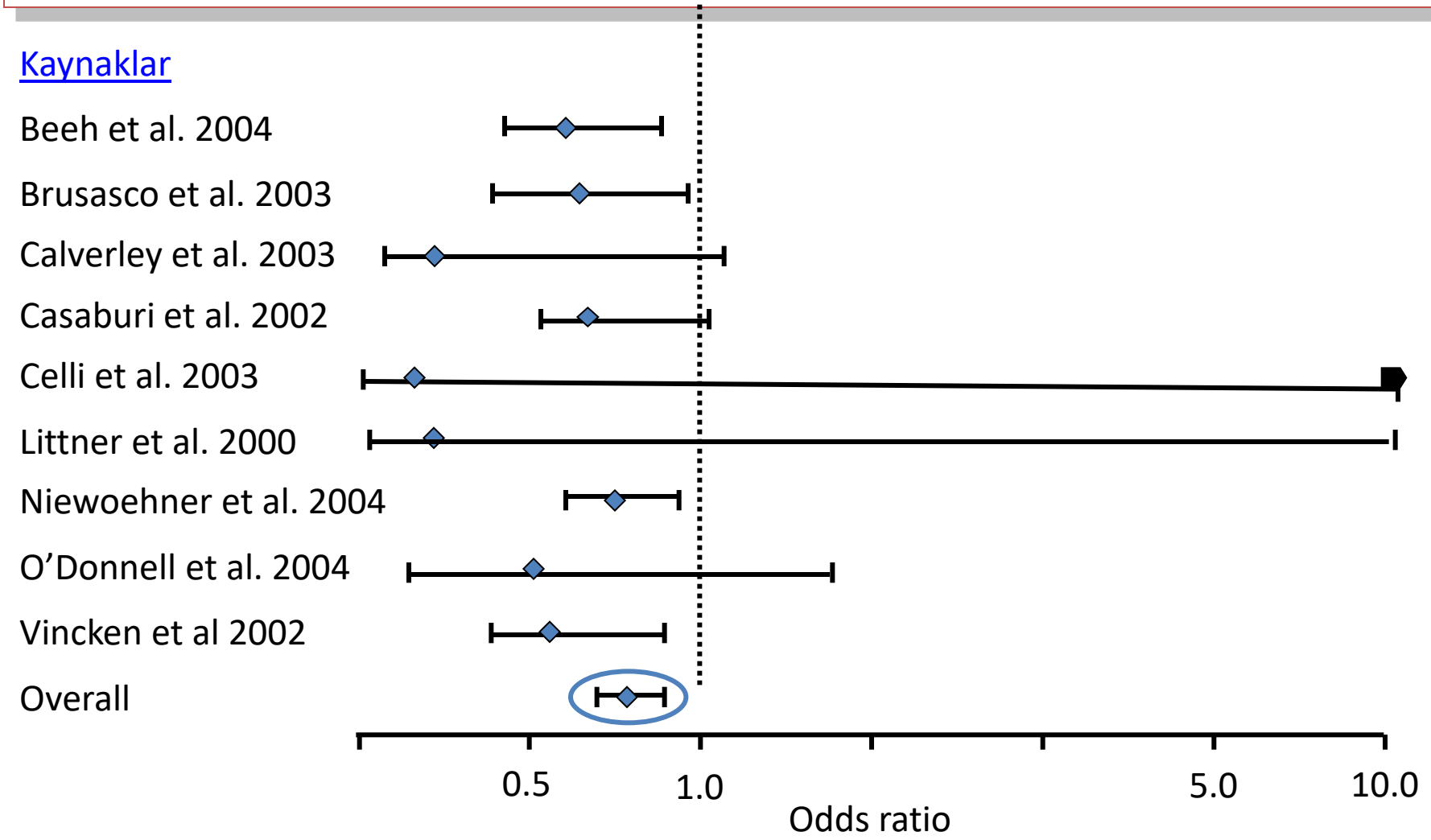
Donald P. Tashkin, M.D., Bartolome Celli, M.D., Stephen Senn, Ph.D., Deborah Burkhart, B.S.N., Steven Kesten, M.D., Shailendra Menjoge, Ph.D., and Marc Decramer, M.D., Ph.D., for the UPLIFT Study Investigators*

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
Patients with exacerbation — no. (%)‡				
Total	2001 (67.0)	2049 (68.2)	NA	0.35
Leading to hospitalization	759 (25.4)	811 (27.0)	NA	0.18

Antikolinerjikler Alevlenmeleri Azaltmada Etkilidir

Kaynaklar



Barr et al. *Cochrane Database of Systematic Reviews.* 2005, Issue 2

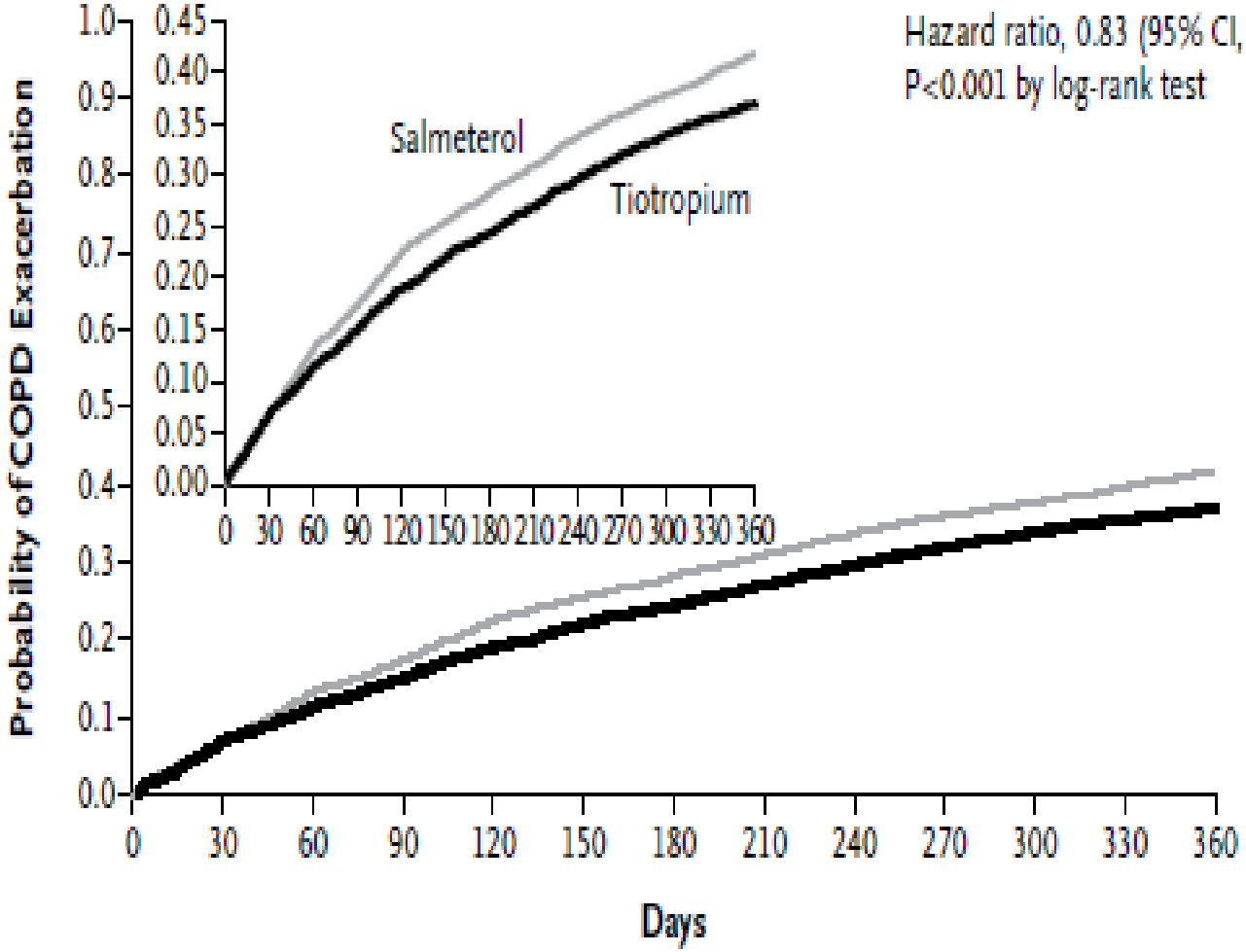
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 24, 2011 VOL. 364 NO. 12

Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD

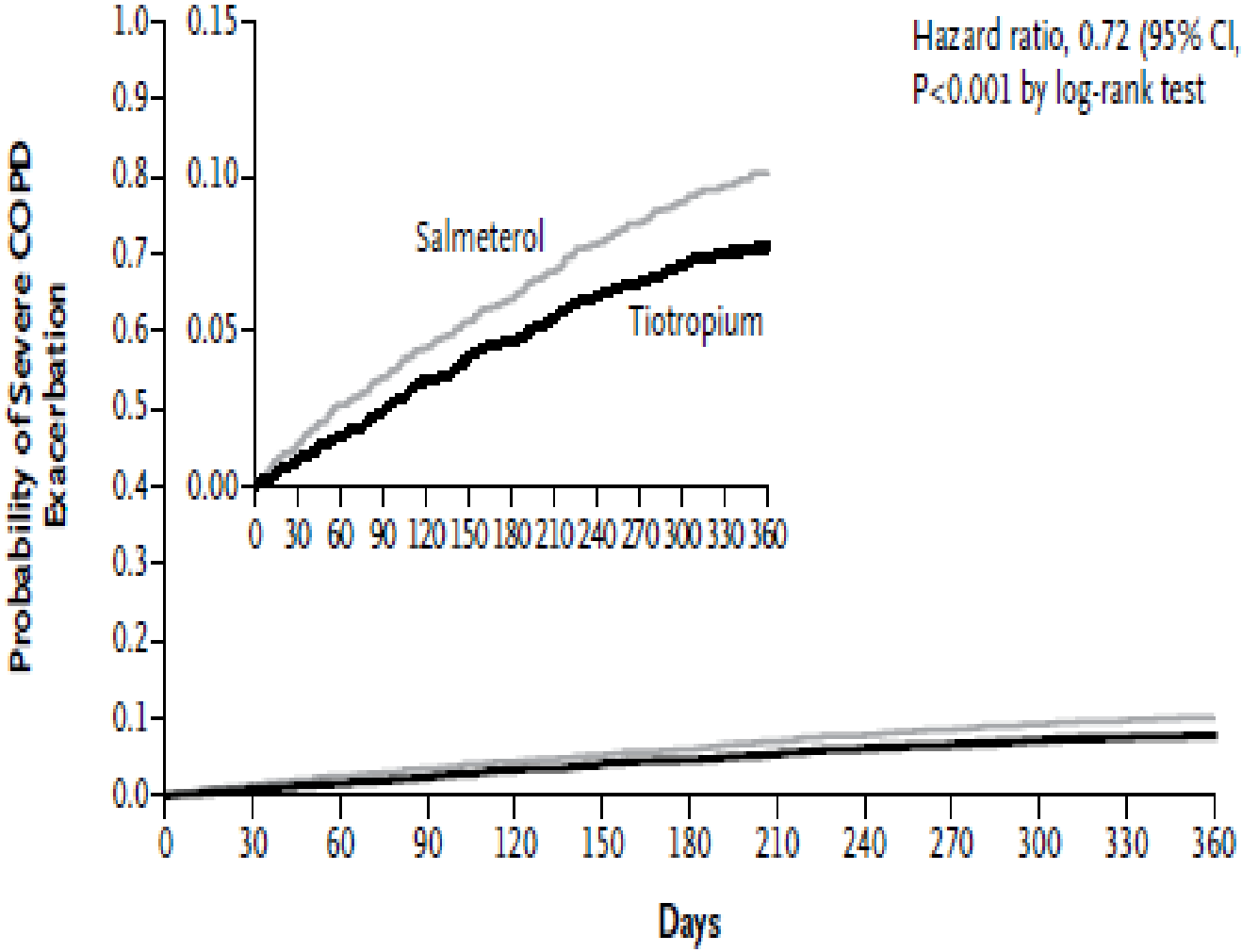
Claus Vogelmeier, M.D., Bettina Hederer, M.D., Thomas Glaab, M.D., Hendrik Schmidt, Ph.D., Maureen P.M.H. Rutten-van Mölken, Ph.D., Kai M. Beeh, M.D., Klaus F. Rabe, M.D., and Leonardo M. Fabbri, M.D., for the POET-COPD Investigators*

Characteristic	Tiotropium (N = 3707)	Salmeterol (N = 3669)
Male sex (%)	74.4	74.9
Age (yr)	62.9±9.0	62.8±9.0
Smoking status		
Current smoker (%)	48.0	48.3
Smoking history (pack-yr)	38.8±20.0	37.8±19.2
Duration of COPD (yr)†	8.0±6.7	7.9±6.5
GOLD stage (%)‡		
II	47.8	49.6
III	43.1	42.1
IV	8.9	7.9
Spirometry after bronchodilation§		
FEV_1 (liters)	1.41±0.47	1.41±0.45
FEV_1 (% of predicted value)	49.2±13.3	49.4±13.1
FVC (liters)	2.71±0.81	2.75±0.82
Ratio of FEV_1 to FVC (%)	52.5±10.8	52.4±11.2
Pulmonary medications (%)		
Any	90.0	89.9
Anticholinergic drug		
Tiotropium	30.5	30.3
Short-acting	29.3	29.6
β_2-Agonists		
Long-acting¶	51.5	51.5
Short-acting	52.5	53.4
Glucocorticoids		
Inhaled¶	53.6	53.3
With tiotropium	18.7	18.2
With long-acting β_2-agonists	43.3	43.5
Oral	2.4	2.3
Methylxanthines	23.0	21.2



No. at Risk

Tiotropium	3707	3369	3136	2955	2787	2647	2561	2455	2343	2242	2169	2107	1869
Salmeterol	3669	3328	3028	2802	2605	2457	2351	2251	2137	2050	1982	1915	1657


Hazard ratio, 0.72 (95% CI, 0.61–0.85)
P<0.001 by log-rank test
Probability of Severe COPD Exacerbation
Salmeterol
Tiotropium
Days
No. at Risk
Tiotropium 3707 3564 3453 3359 3285 3217 3177 3125 3066 3017 2977 2948 2663
Salmeterol 3669 3502 3362 3244 3172 3080 3032 2982 2921 2870 2834 2806 2489

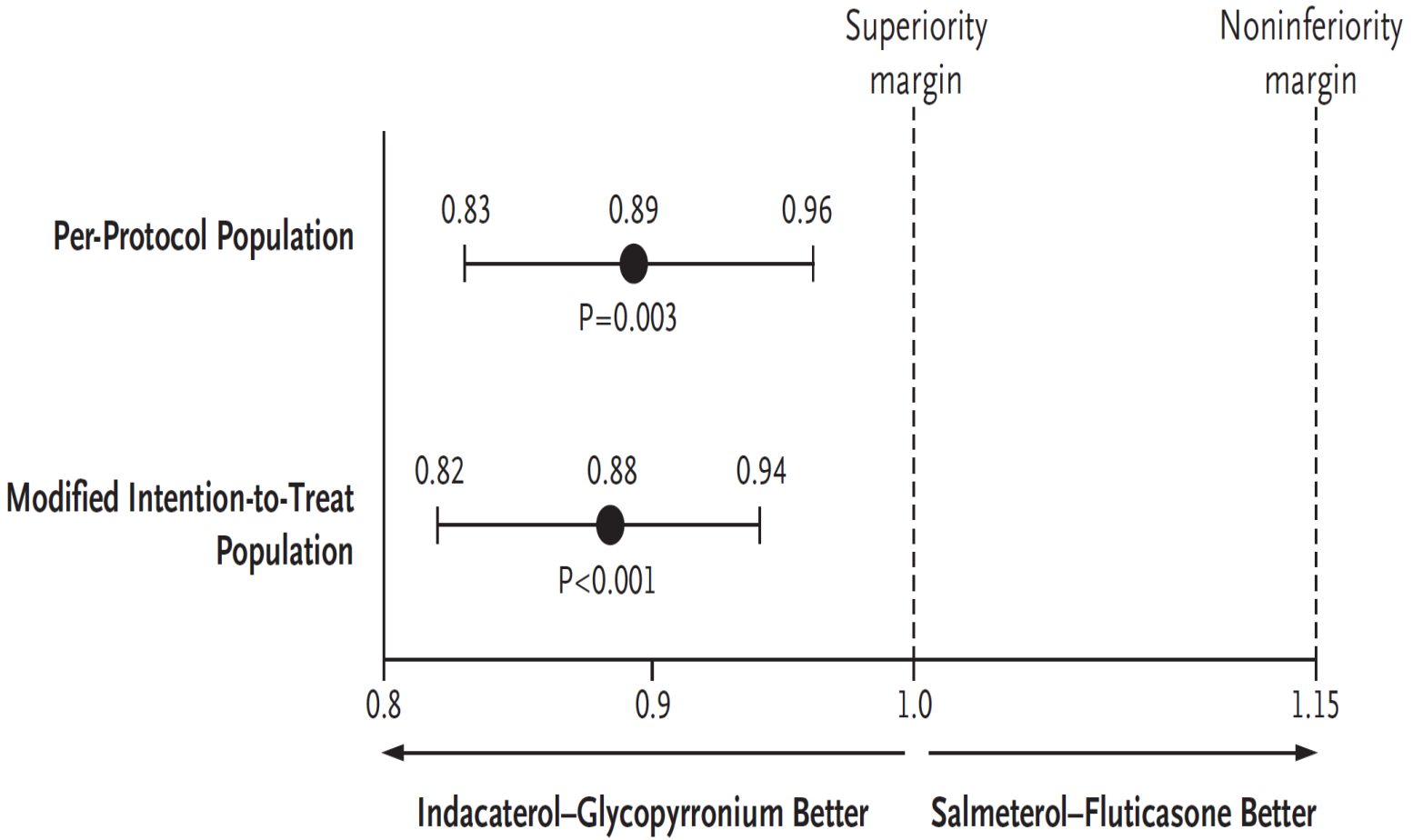
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

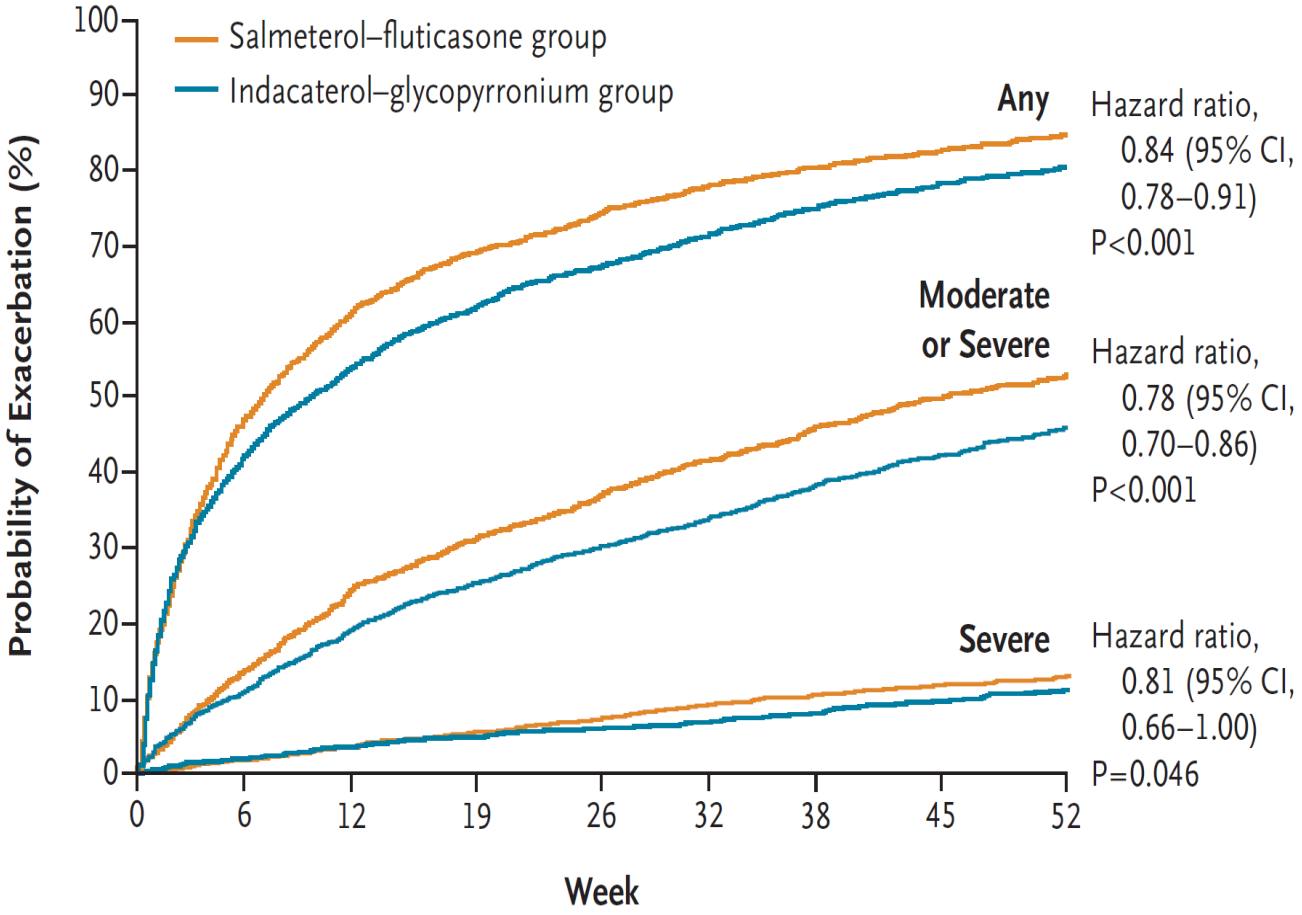
Jadwiga A. Wedzicha, M.D., Donald Banerji, M.D., Kenneth R. Chapman, M.D., Jørgen Vestbo, M.D., D.M.Sc., Nicolas Roche, M.D., R. Timothy Ayers, M.Sc., Chau Thach, Ph.D., Robert Fogel, M.D., Francesco Patalano, M.D., and Claus F. Vogelmeier, M.D., for the FLAME Investigators*

Wedzicha J et al N Engl J Med. 2016 Jun 9;374(23):2222-34



Wedzicha J et al N Engl J Med. 2016 Jun 9;374(23):2222-34

Time to First Exacerbation



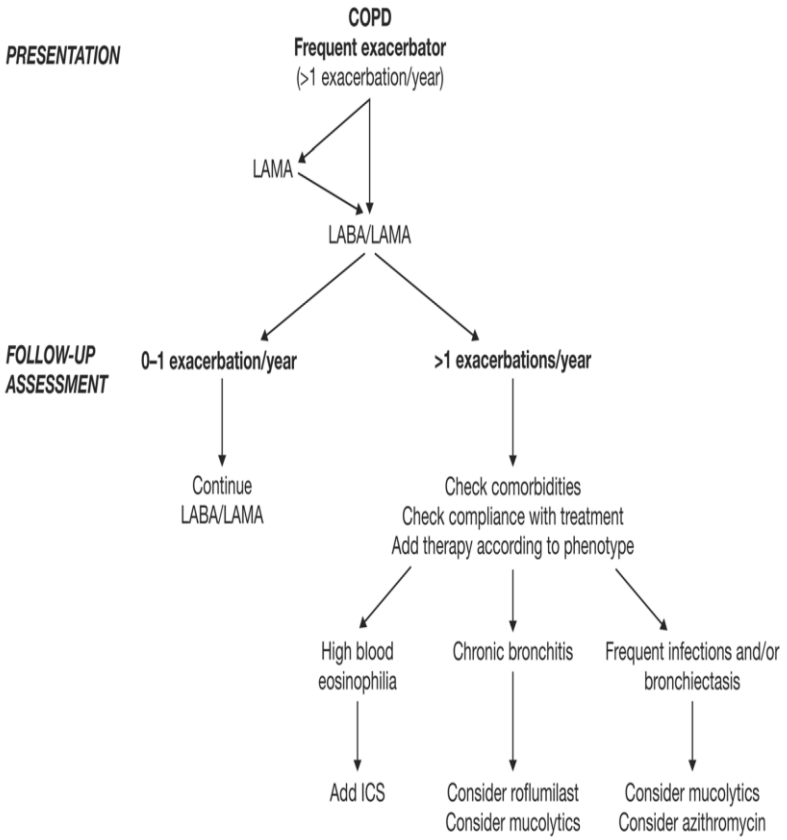
Wedzicha J et al N Engl J Med. 2016 Jun 9;374(23):2222-34

Pharmacological strategies to reduce exacerbation risk in COPD: a narrative review

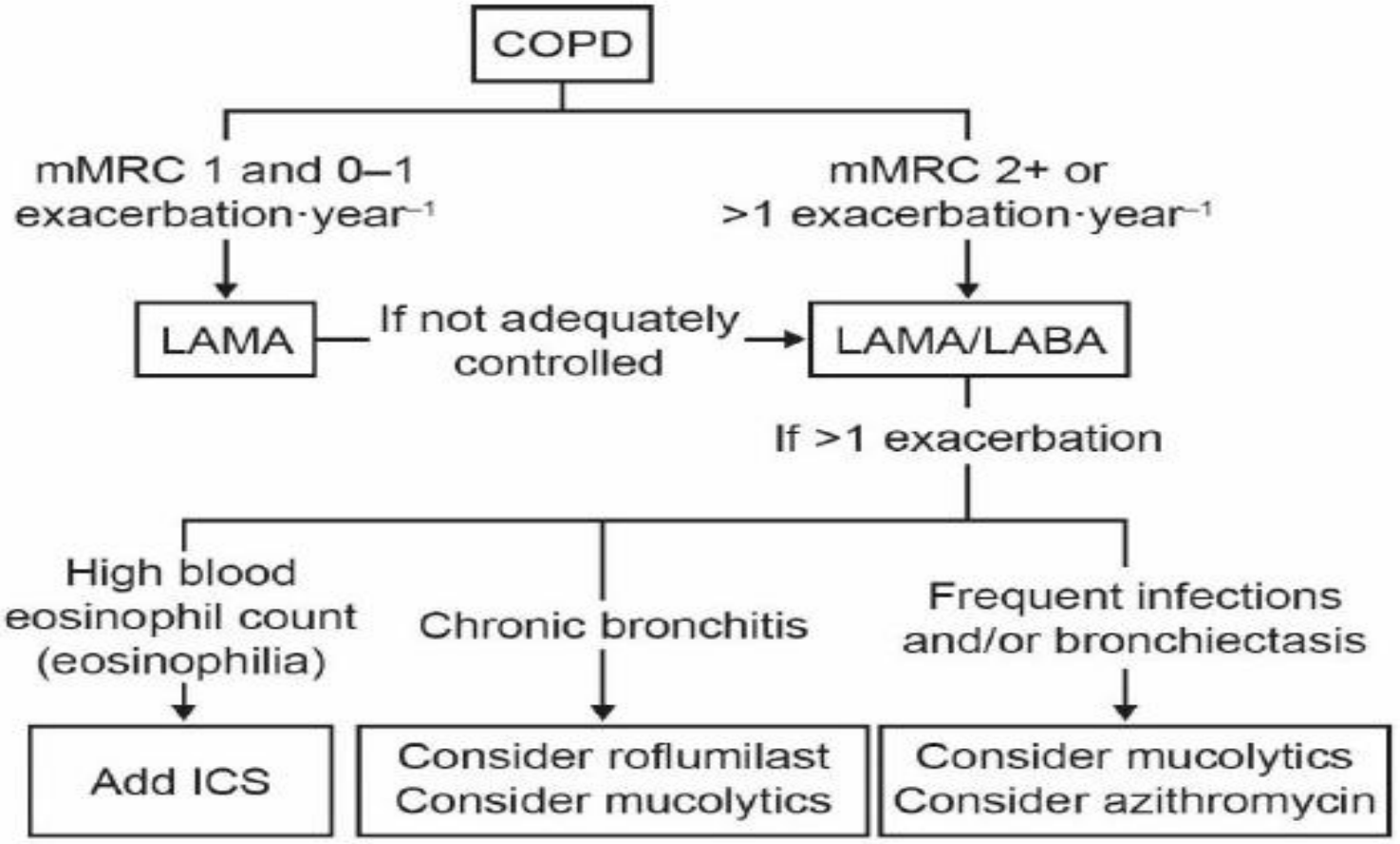
Marc Miravitlles[1*], Anthony D'Urzo[2], Dave Singh[3] and Vladimir Koblizek[4]

Table 1 Risk factors for exacerbations of chronic obstructive pulmonary disease [6, 21–23, 25, 122]

Risk factors
• Older age
• Lower body mass index
• Continued smoking
• Poor exercise capacity
• Severity of airflow obstruction
• Previous exacerbations (including hospitalizations for exacerbations)
• Longer duration of chronic obstructive pulmonary disease
• Co-morbidities (e.g. bronchiectasis, cardiovascular disease, pulmonary hypertension, gastroesophageal reflux)
• Respiratory tract infections (viral and bacterial
• Chronic bronchial mucus production
• Environmental pollutants
• Colder weather/temperature



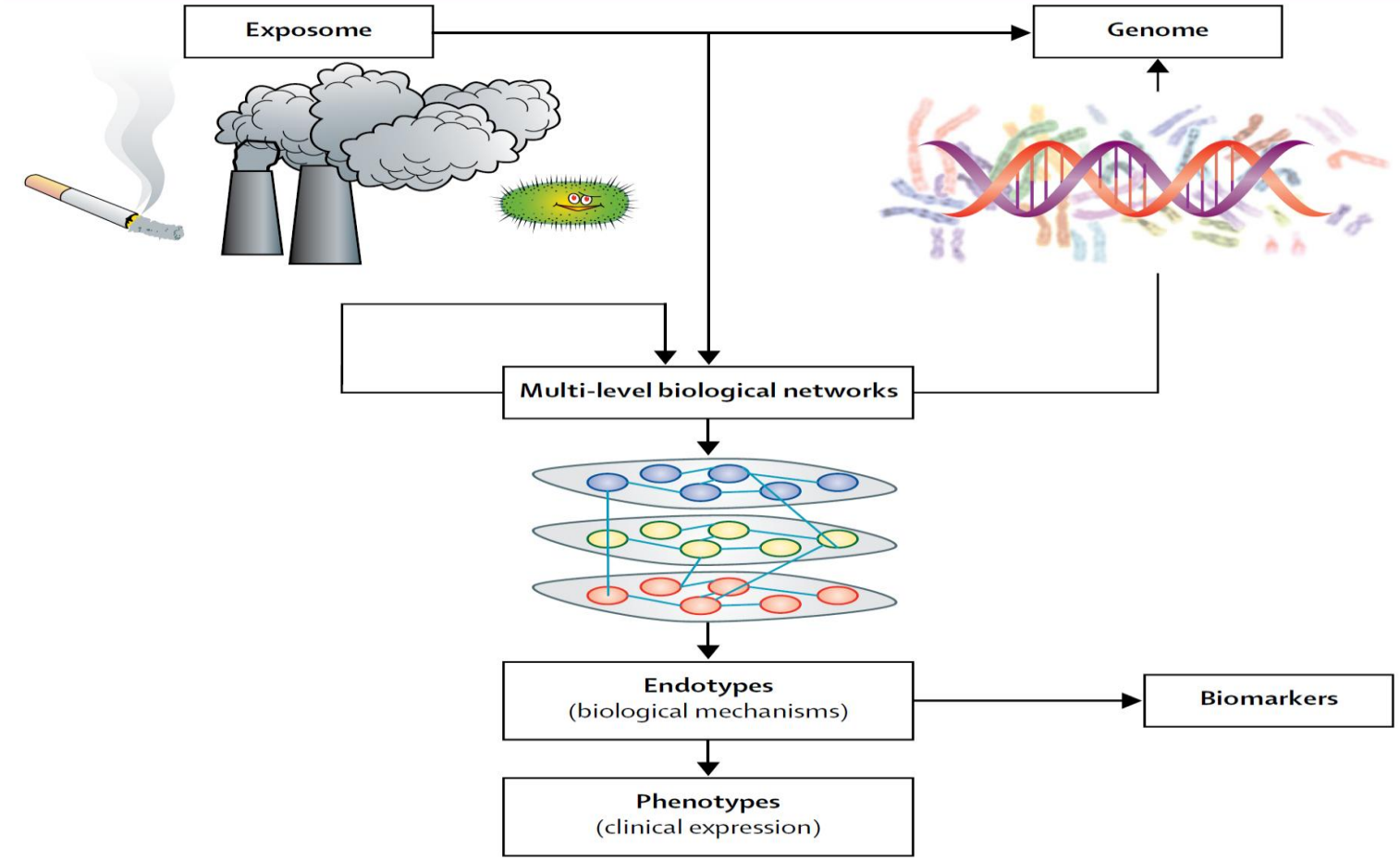
Therapeutic recommendations based on exacerbation phenotype



Miravitlles et al., 2017

What does endotyping mean for treatment in chronic obstructive pulmonary disease?

Alvar Agustí, Bartolome Celli, Rosa Faner

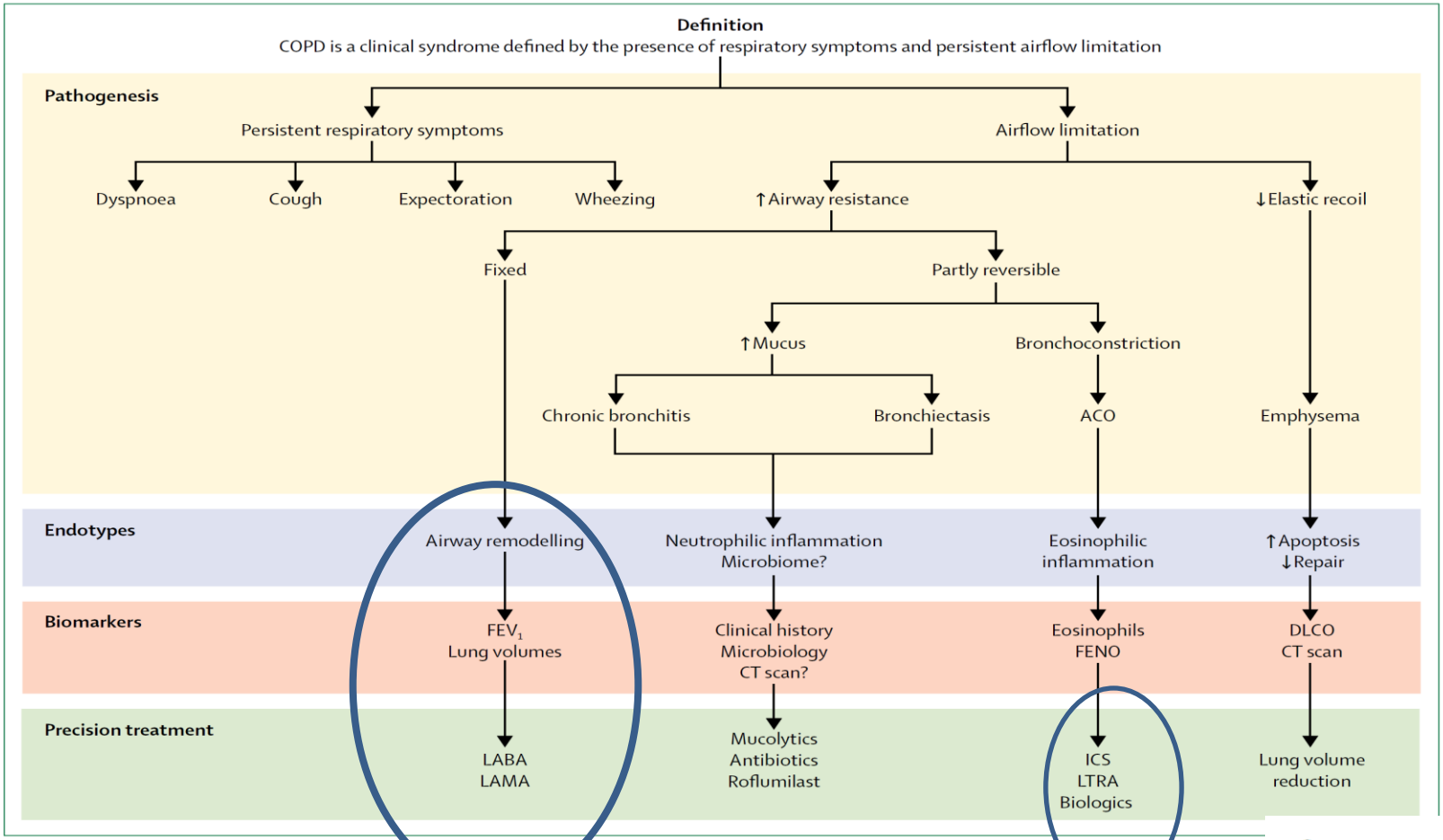


Lancet 2017; 390: 980–87

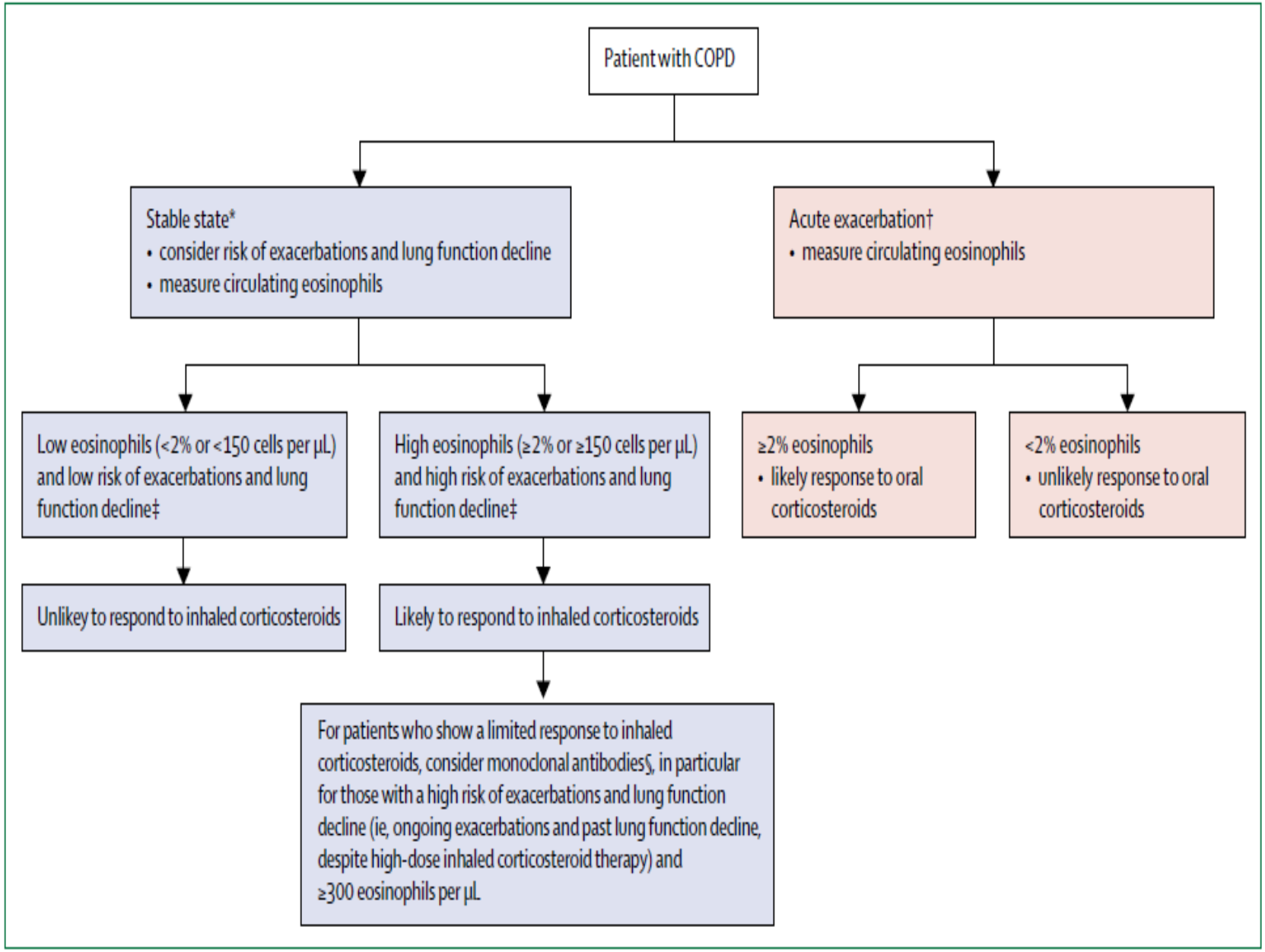
What does endotyping mean for treatment in chronic obstructive pulmonary disease?

Alvar Agustí, Bartolome Celli, Rosa Faner

: A potential approach to COPD treatment based on endotypes and biomarkers, as per available therapeutic recommendations[3]



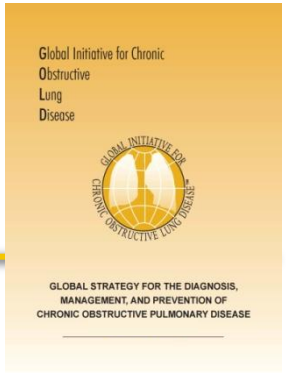
Lancet 2017; 390: 980–87



Lancet Respir Med 2017; 5: 747–59

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Tedavinin Amaçları



- Semptomları iyileştir
- Egzersiz toleransınını iyileştir
- Yaşam kalitesini iyileştir

Semptomları azalt

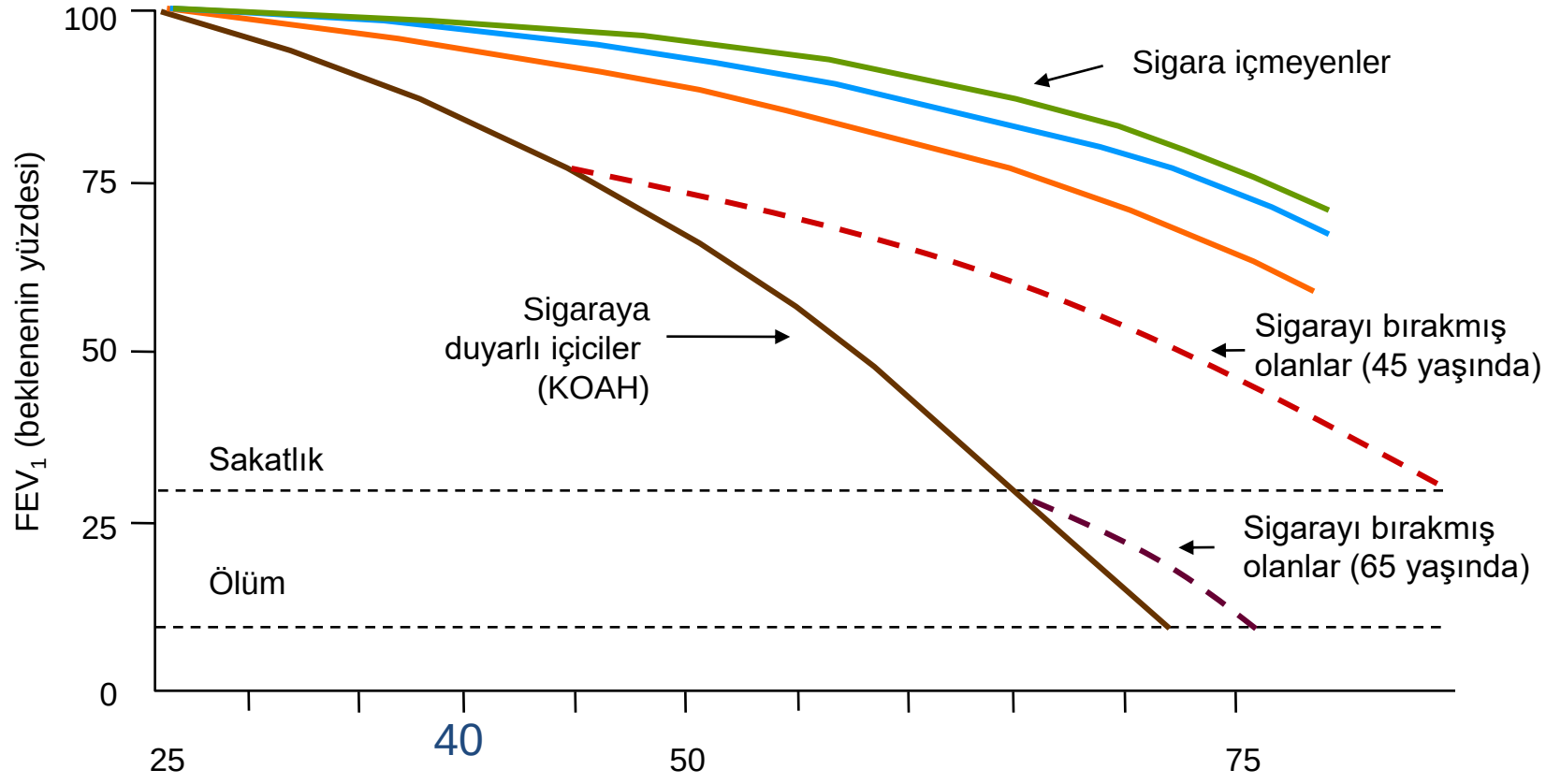
- **Hastalığın progresyonunu engelle**
- Alevlenmeleri önle ve tedavi et
- Mortaliteyi azalt

Riskleri azalt

GOLD 2018

Progresyonu ne kadar engelleyebiliriz?

Sigara İçimi İle Akciğer Fonksiyonu ve Yaş Arasındaki İlişki



Fletcher C, Peto R. Br Med J 1977; 1:1645-1648

The Natural History of Chronic Airflow Obstruction Revisited

An Analysis of the Framingham Offspring Cohort

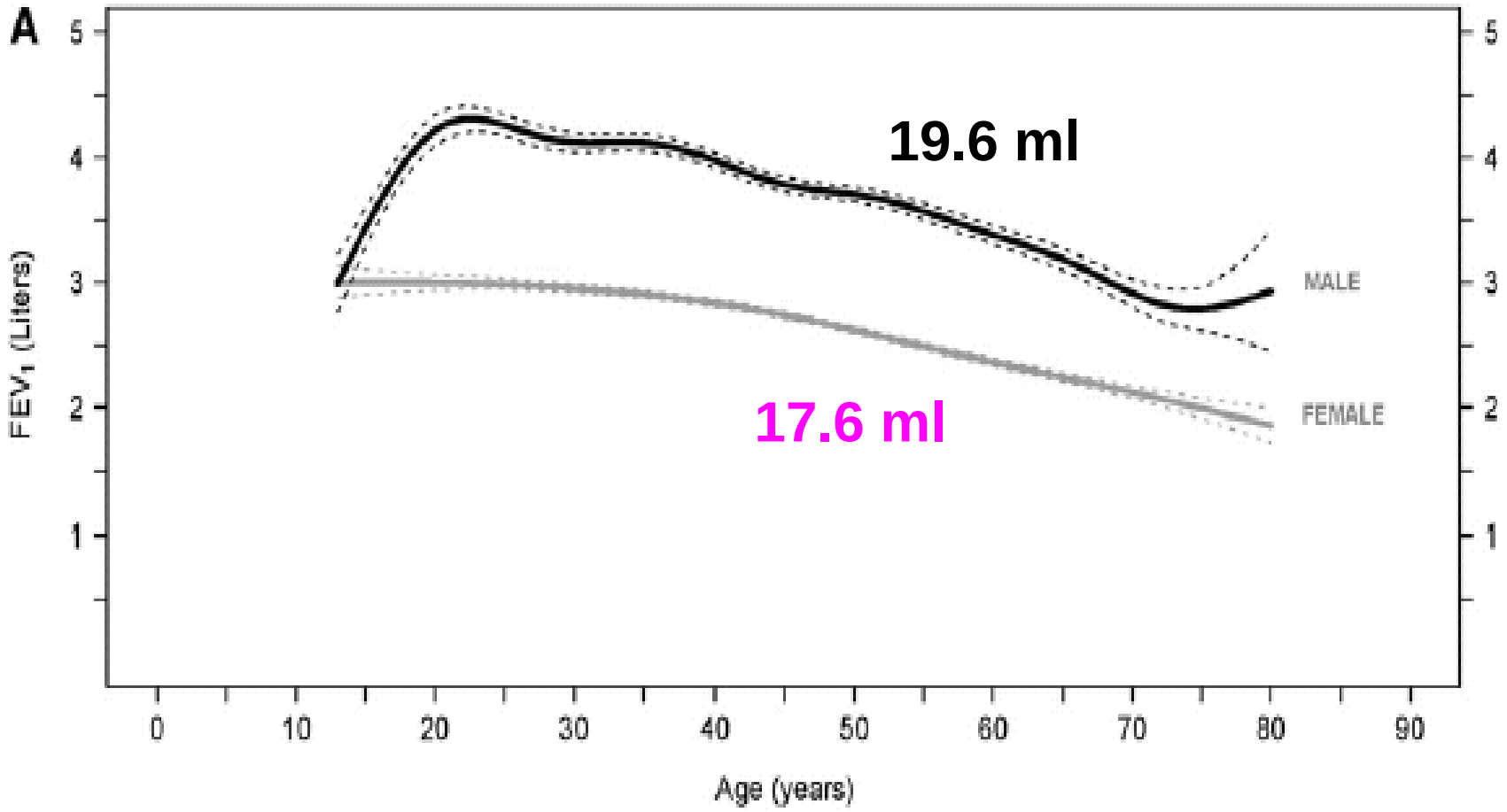
Robab Kohansal[1,2], Pablo Martinez-Camblor[1,3], Alvar Agustí[1,4,5], A. Sonia Buist[6], David M. Mannino[7], and Joan B. Soriano[1,4]

- İncelenen populasyon erkekler (n=2121), kadınları (n=2270) içeriyor
- Yaş grubu 13-80 arasında değişiyor (n=4391)
- İzlem süresi 26 yıl
- Adelosandan ileri yaşa kadar takip
- Spirometre standardize

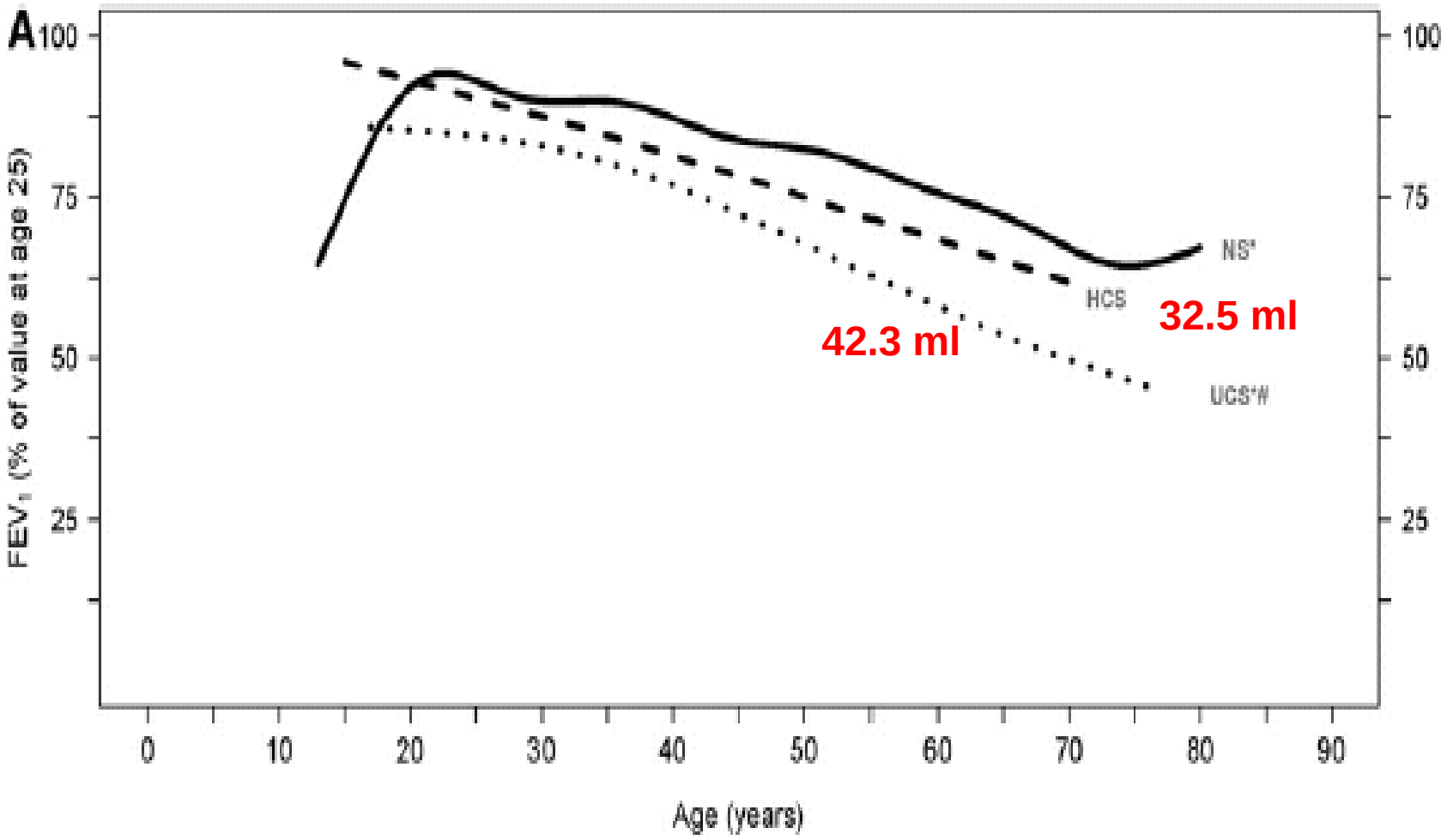
TABLE 1. BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PARTICIPANTS WITH TWO OR MORE SPIROMETRIES, AT EXAM 1 OF THE FRAMINGHAM OFFSPRING COHORT

	Male (n = 2,121)	Female (n = 2,270)
Follow-up, years	22.7 ± 2.7	23.1 ± 1.8
Age, years	36.5 ± 10.5	35.6 ± 10.1
Height, cm	176.3 ± 7.2	162.3 ± 6.1
Weight, kg	81.9 ± 12.5	63.3 ± 11.8
BMI, kg/m^2	26.4 ± 3.6	24.0 ± 4.3
Smoker, n (%)		
Current	361 (17.0%)	393 (17.3%)
Former	1,094 (51.6%)	965 (42.5%)
Never	666 (31.4%)	912 (40.0%)
Pack-years*	31.2 ± 24.1	19.0 ± 17.0
FEV_1, L	3.7 ± 0.7	2.7 ± 0.5
FEV_1,% pred	87.8 ± 13.9	90.0 ± 17.5
FVC, L	4.3 ± 0.8	3.2 ± 0.5
FVC, % pred	83.6 ± 11.7	85.6 ± 11.3
FEV_1/FVC	0.85 ± 0.1	0.86 ± 0.1
FEV_1, % pred at age 25	81.7 ± 14.3	83.1 ± 14.0

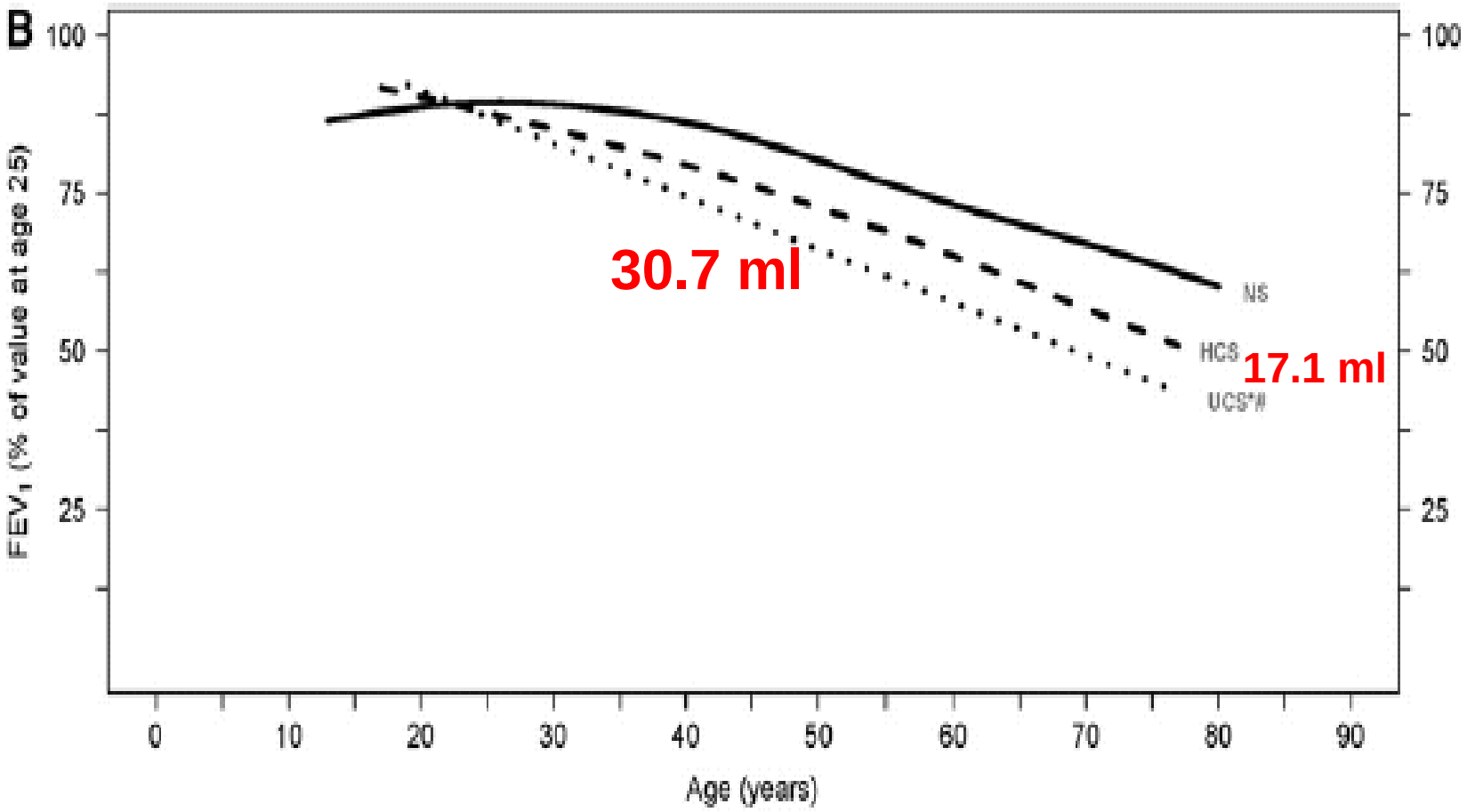
Sigara içmeyenlerin FEV 1 Kaybı



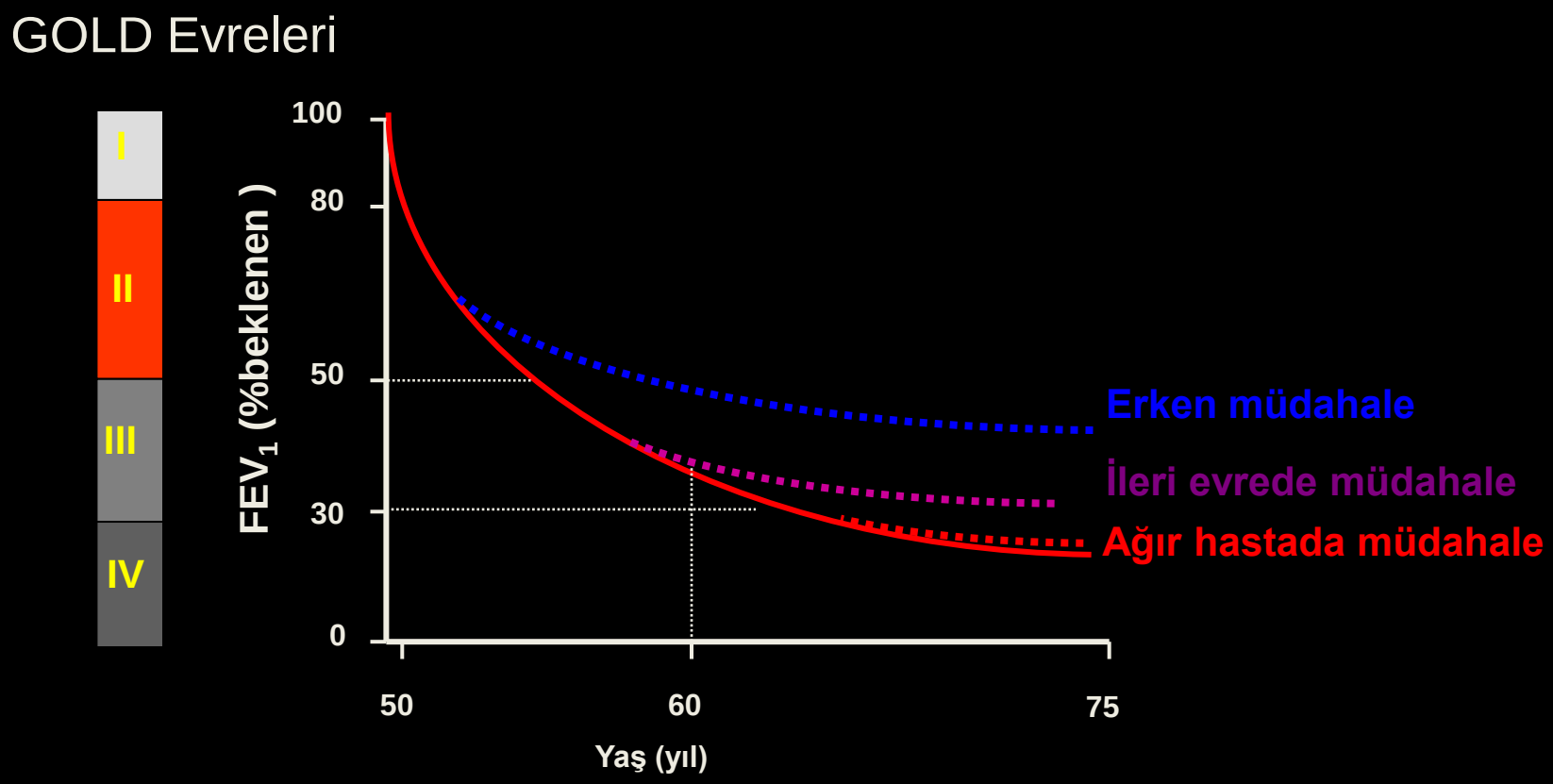
Sigara İçen Erkeklerin FEV 1 Kaybı (38.2ml/yıl)



Sigara İçen Kadınların FEV 1 Kaybı (23.9ml/yıl)



KOAH Evreleri ve FEV 1 Kaybı



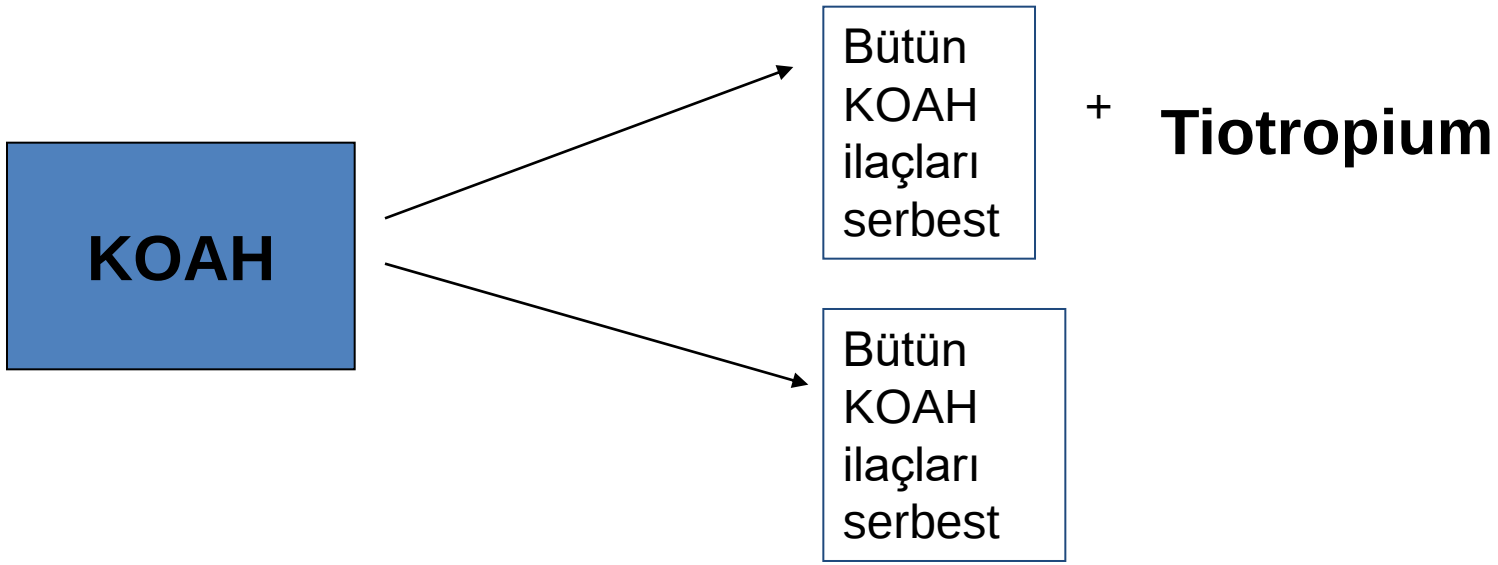
The NEW ENGLAND JOURNAL of MEDICINE

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

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

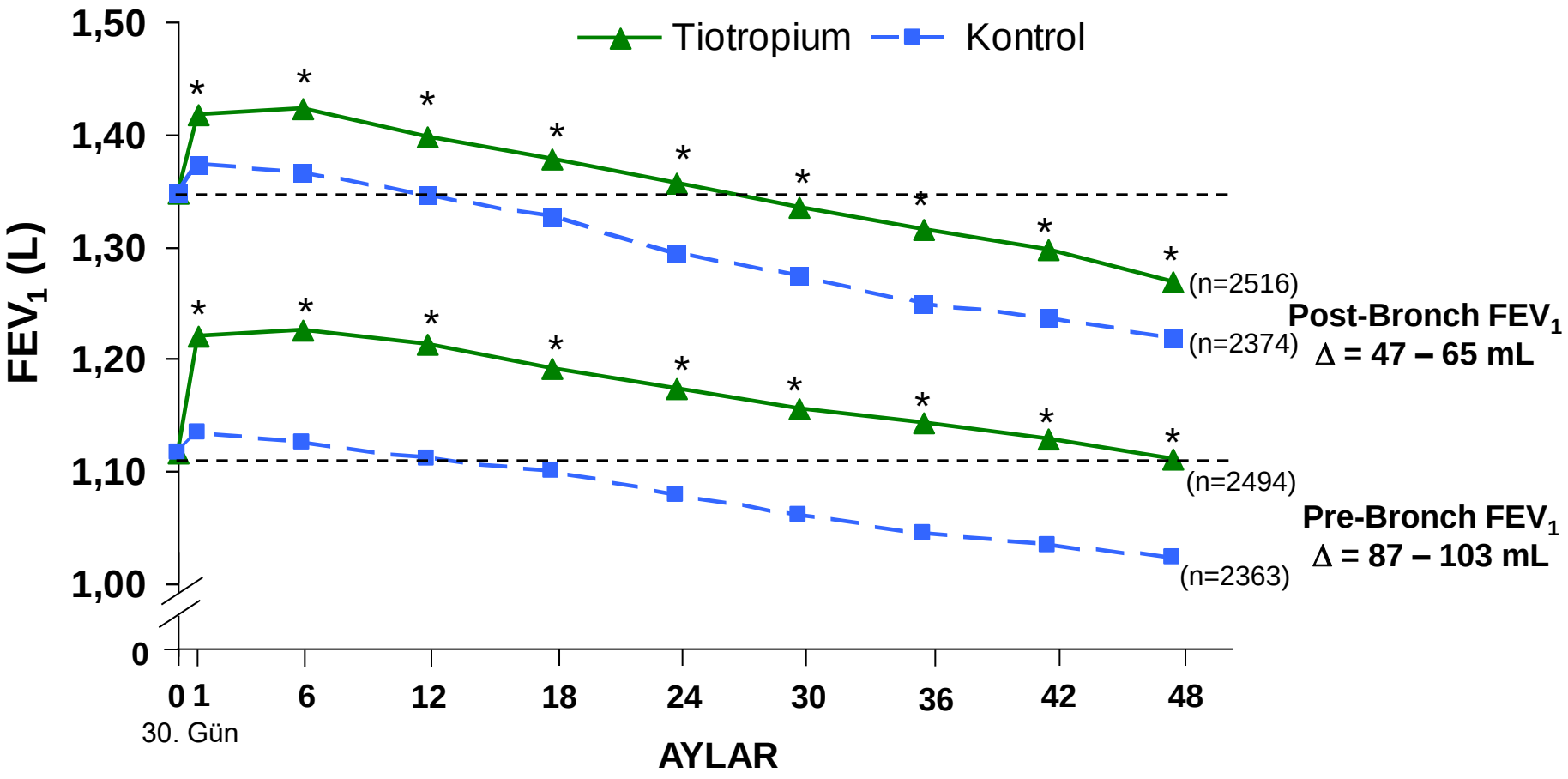
Donald P. Tashkin, M.D., Bartolome Celli, M.D., Stephen Senn, Ph.D., Deborah Burkhart, B.S.N., Steven Kesten, M.D., Shailendra Menjoge, Ph.D., and Marc Decramer, M.D., Ph.D., for the UPLIFT Study Investigators*

TEDAVİ PROTOKOLÜ



Kullanılmayan: Çalışma süresince inhale kısa etkili antikolinerjikler

Bronkodilatör-öncesi ve -sonrası FEV_1
(Zaman noktalarındaki ortalama değerler)

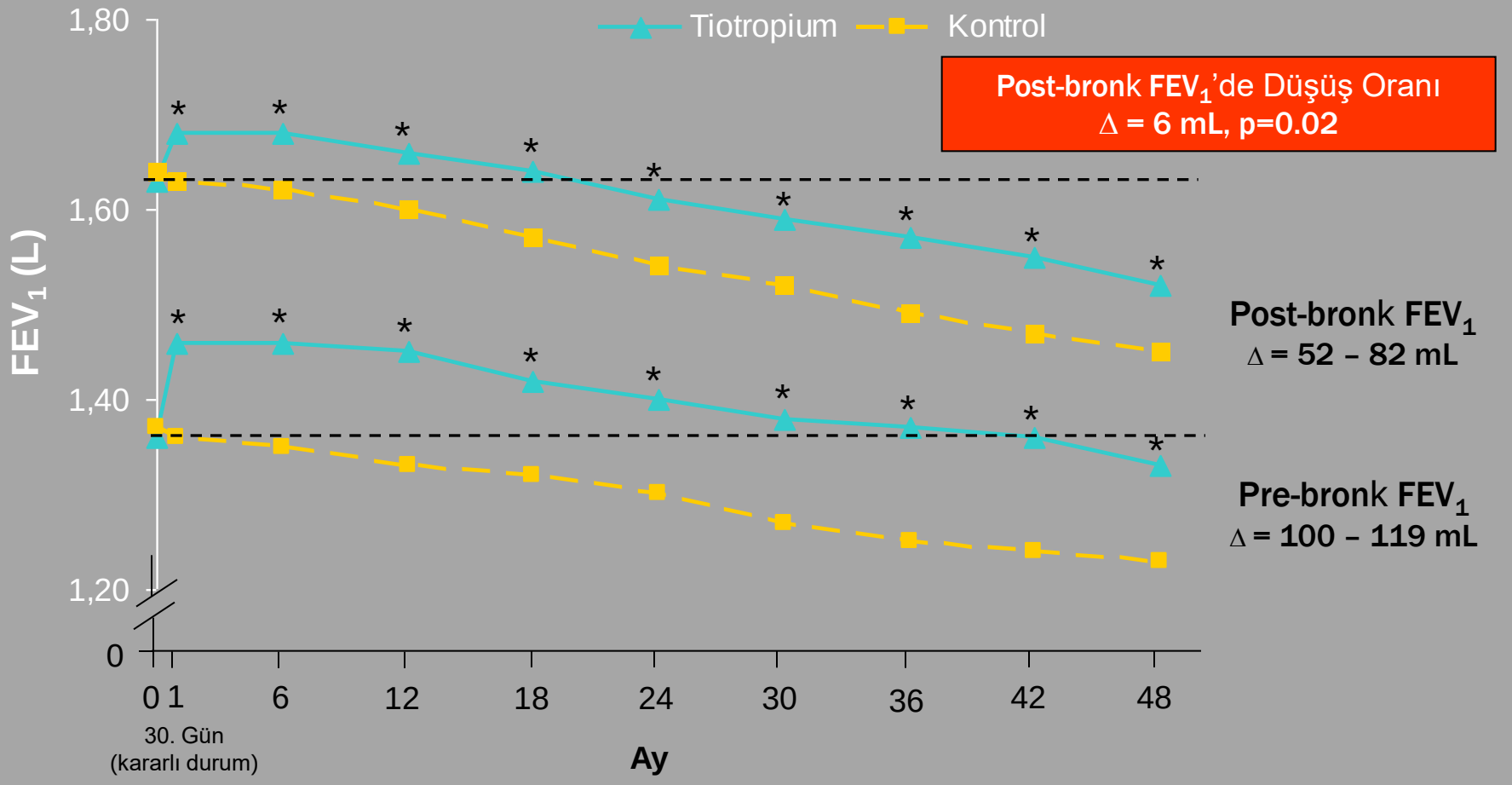


*P<0.0001 vs. control. Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements.
Baseline trough FEV_1 (observed mean) = 1.116 (trough), 1.347 (peak). Patients with ≥3 acceptable PFTs after day 30 were included in the analysis.

FEV_1'deki Gerileme Oranı

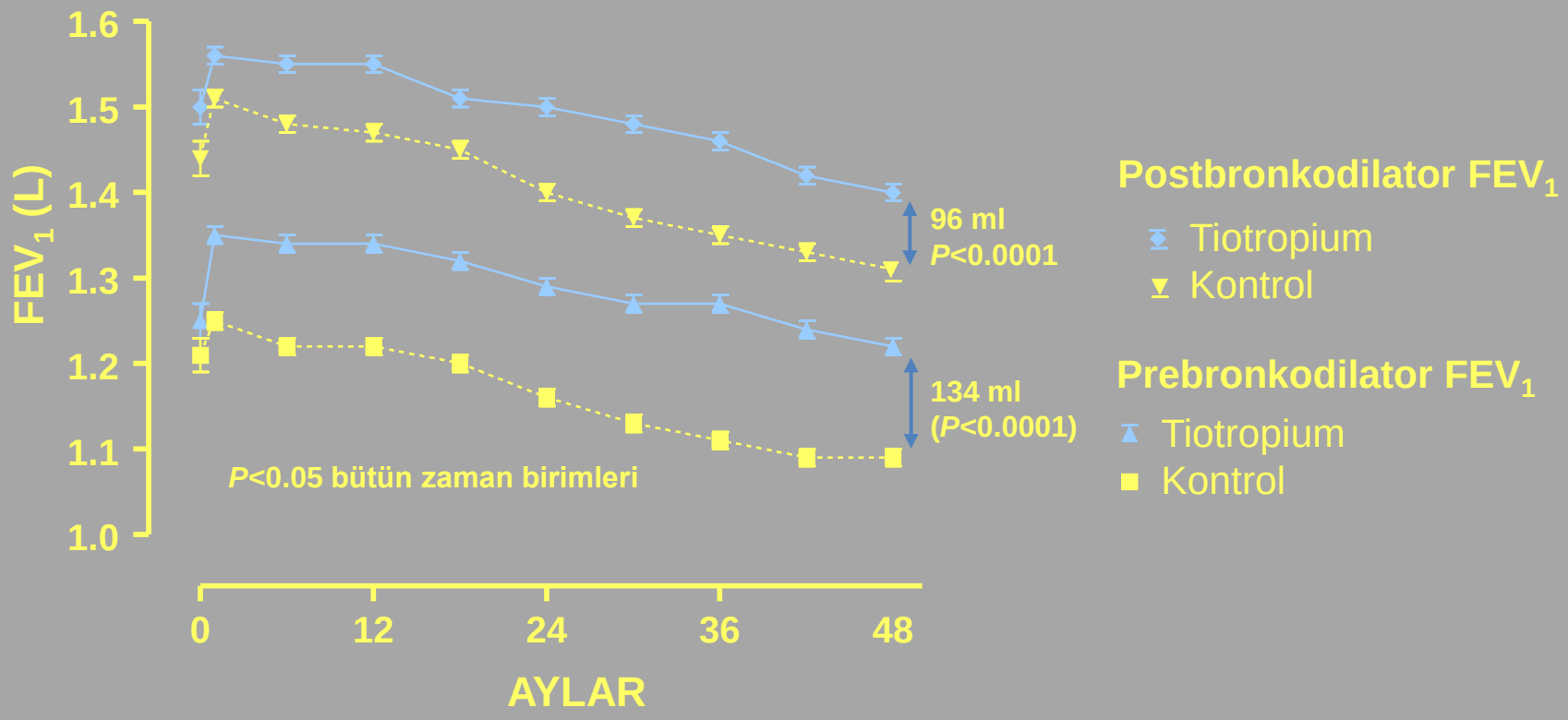
	Tiotropium (mL/yıl)		**Kontrol (mL/yıl)**		**∆ Tio – Kon**	**%95 GA**	**P-değeri***
	n	Ortalama (SE)	n	Ortalama (SE)	Ortalama (SE)		
Bronk-öncesi	2557	30 (1)	2413	30 (1)	0 (2)	-4, 4	0.95
Bronk-sonrası	2554	40 (1)	2410	42 (1)	2 (2)	-6, 2	0.20

GOLD Evre II: FEV_1



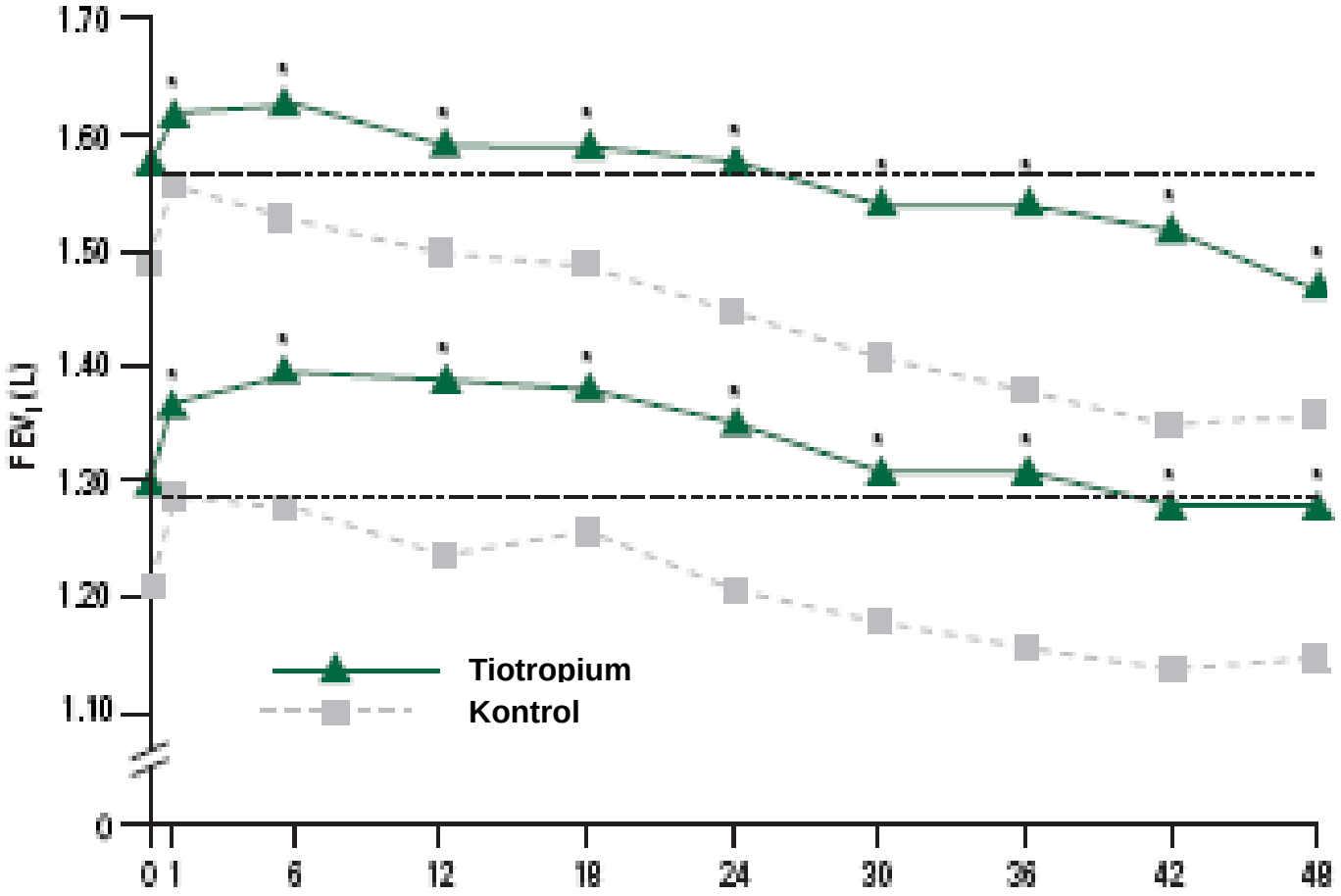
*P<0.0001 vs. kontrol.

İdame tedavisi almayan olgularda her klinik vizitde saptanan FEV_1

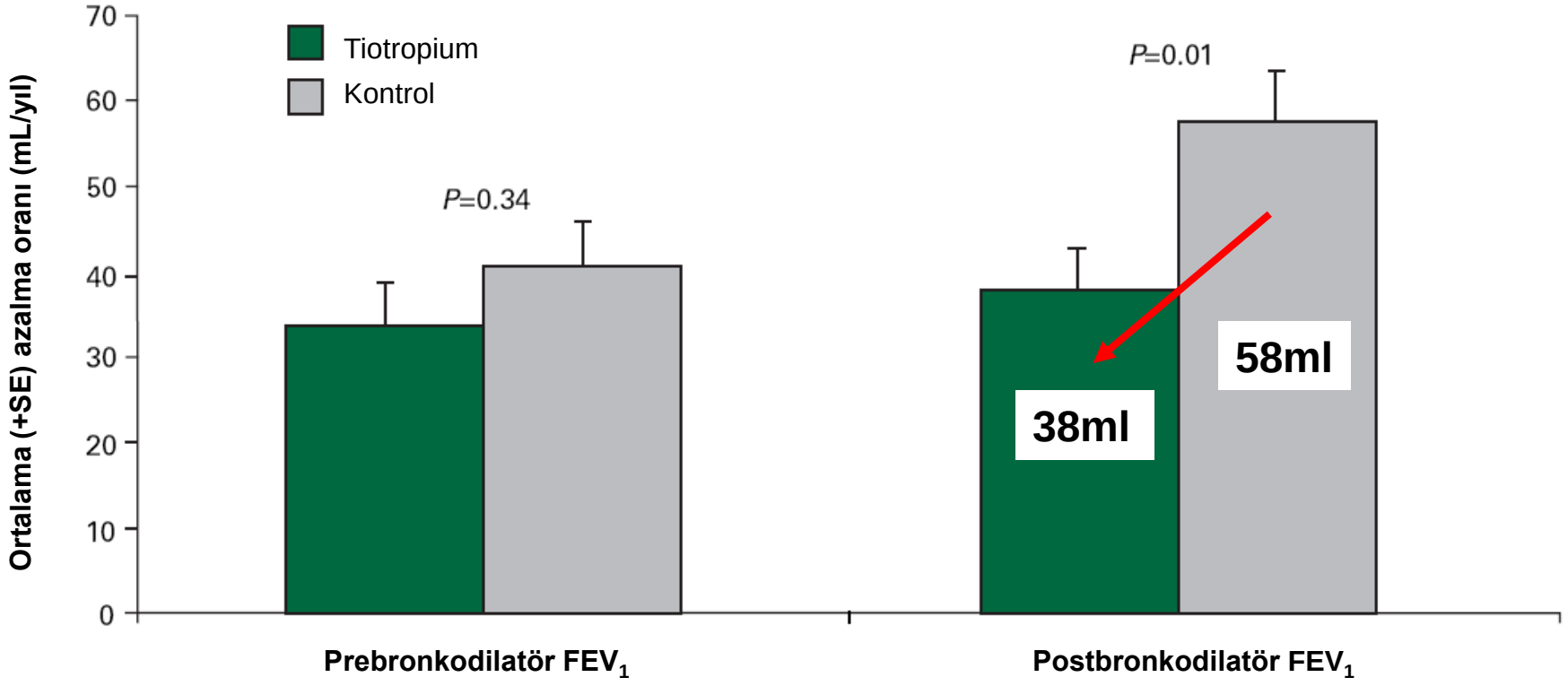


Troosters et al. Am J Respir Crit Care Med 2009;179:A2467

≤50 yaşındaki hastalarda 4 yıl sonunda FEV1 değişimi



≤50 yaşındaki hastalarda yıllık FEV_1 azalma oranları (ortalama±SE)



FEV_1, 1 saniyede zorlu ekspiratuar volümü

Respiratory Research

BioMed Central

Research

Open Access

Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study

Christine R Jenkins*[†1], Paul W Jones[†2], Peter MA Calverley[†3], Bartolome Celli[†4], Julie A Anderson[†5], Gary T Ferguson[†6], Julie C Yates[†7], Lisa R Willits[†5] and Jörgen Vestbo[†8,9]

Respiratory Research 2009, **10**:59 doi:10.1186/1465-9921-10-59

The reduction in the rate of decline in FEV_1 with SFC versus placebo was 16 ml/year (95% CI: 0, 32) in GOLD stage II patients, 16 ml/year (95% CI: 5, 28) in GOLD stage III patients and 11 ml/year (95% CI: -8, 30) in GOLD stage IV patients (Figure 5).

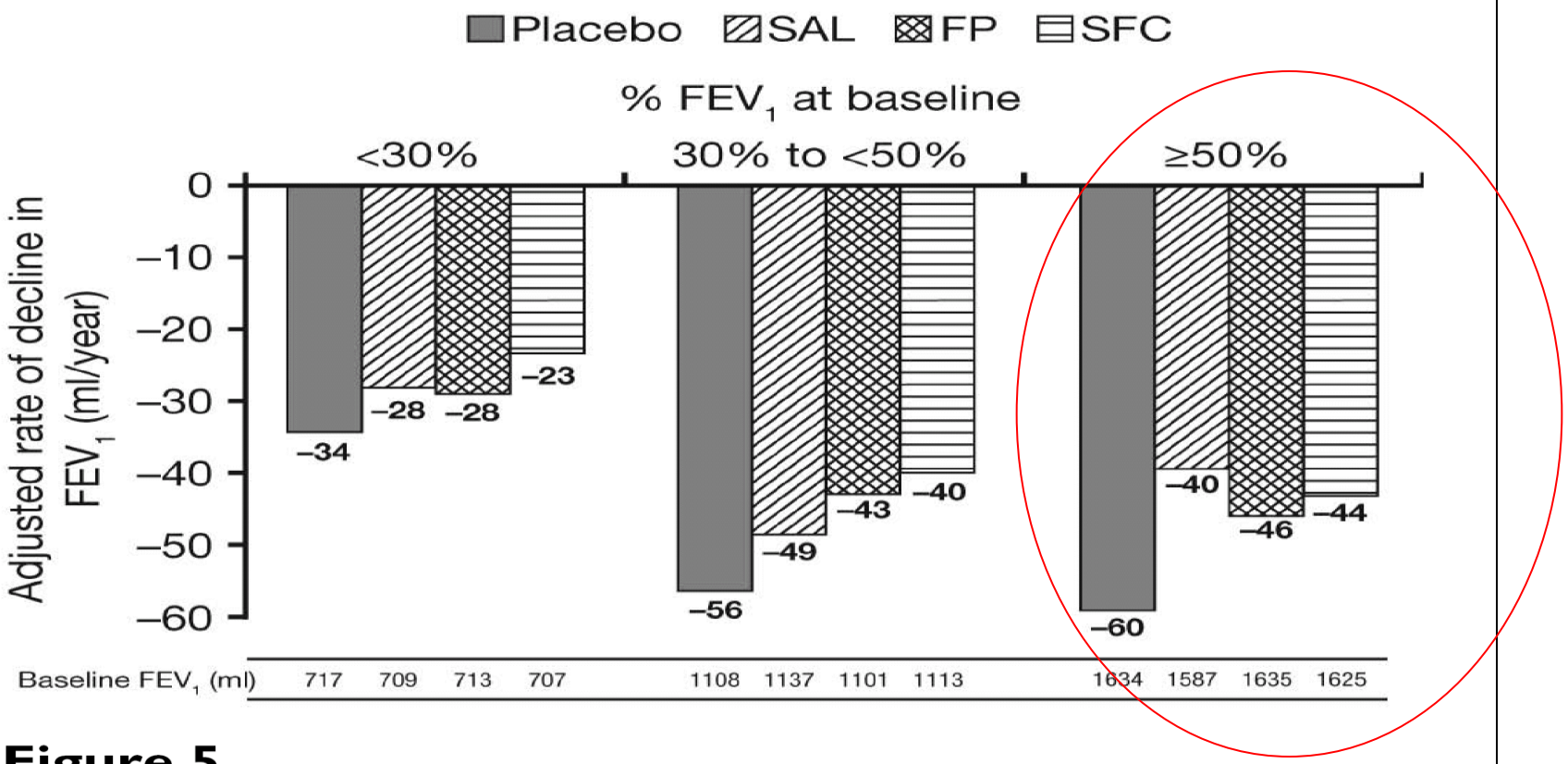


Figure 5
Rate of decline in FEV_1 by baseline post-bronchodilator FEV_1 % predicted.

Klinik Önemi Olan Kötüleşme

Clinicaly Important Deteretion

The concept of clinically important deterioration (CID) in COPD

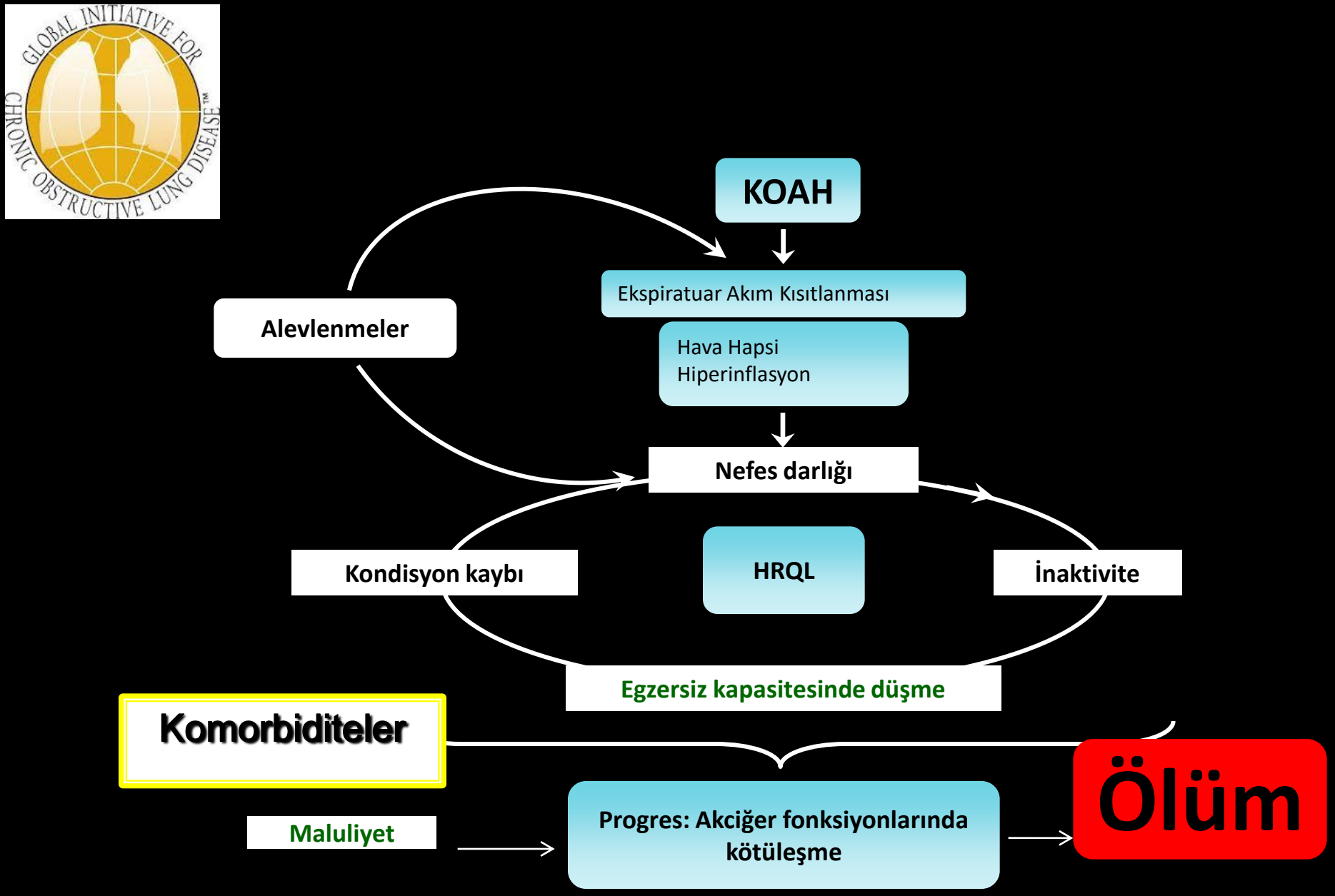
Definition

Comparators	Umeclidinium / vilanterol vs monocomponents and placebo[1]	Aclidinium / formoterol vs monocomponents and placebo[2]	Indacaterol / glycopyrronium vs tiotropium or salmeterol / fluticasone[3]
Included parameters	• Moderate / severe exacerbations, or • ↓ ≥100 mL FEV_1 or • ↑ ≥4-unit SGRQ	• Moderate / severe exacerbations, or • Worsening from baseline in ≥1 of: – Trough FEV_1 ≥100 mL), – TDI ≥1, or – SGRQ ≥4 units	• Moderate / severe exacerbations, and • ↓ ≥100 mL FEV_1/ ↓ ≥1-unit TDI, and • ↑ ≥4-unit SGRQ

1. Singh et al. Int J Chron Obstruct Pulmon Dis 2016;11:1413-24
2. Singh et al. Respir Res 2017;18:106
3. Anzueto et al. Int J Chron Obstruct Pulmon Dis 2017;12:1325-37

CID

- Bazal trough FEV1 >100 ml kötüleşme ve /veya
- SGRQ total skorunda > 4 ünite ve/veya
- Tedavi sırasında orta-ağır alevlenme
- TDI >1 Ünite

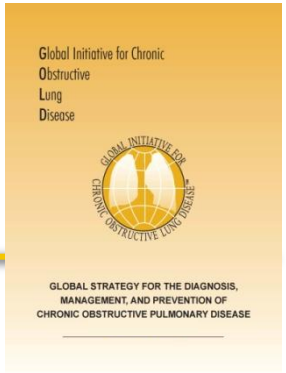


HRQL = Sağlıkla İlişkili Yaşam Kalitesinde Bozulma

Ferro T. Clinical Pulmonary Medicine 2005; Decramer M. Eur Respir Rev 2006

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Tedavinin Amaçları



- Semptomları iyileştir
- Egzersiz toleransınını iyileştir
- Yaşam kalitesini iyileştir

Semptomları azalt

- Hastalığın progresyonunu engelle
- Alevlenmeleri önle ve tedavi et
- **Mortaliteyi azalt**

Riskleri azalt

GOLD 2018

Mortalitenin Azaltılmasında Bronkodilatörler

Mortalite önhabercileri nelerdir?

- FEV 1
- PEF
- PaO2
- Dispne
- Vücut Kitle İndeksi (VKİ)
- İleri yaş

- Sigara paket yılı
- Alevlenme nedeni ile hastaneye yatış
- Yaşam kalitesi
- Depresyon ve disabilite
- Kronik bronşit

Sağkalım Belirteçleri Nelerdir?

Journal of Respiratory Medicine (2008) 102 (Supplement 1), S27–S35

ELSEVIER

respiratoryMEDICINE

Predictors of Survival in COPD: More than Just the FEV_1

Bartolome R. Celli [1], Claudia G. Cote [2], Suzanne C. Lareau [3,*] and Paula M. Meek [4]

Sağkalım İzlem Belirteçleri Nelerdir?

- **FEV 1**
- **Hiperinflasyon**
- **Dispne**
- **Egzersiz Kapasitesi**
- Anemi
- **Yaşam Kalitesi**

COPD: maximization of bronchodilation

Stefano Nardini[1*], Gianna Camiciottoli[2], Salvatore Locicero[3], Rosario Maselli[4], Franco Pasqua[5], Giovanni Passalacqua[6], Riccardo Pela[7], Alberto Pesci[8], Alfredo Sebastiani[9] and Alessandro Vatrella[10]

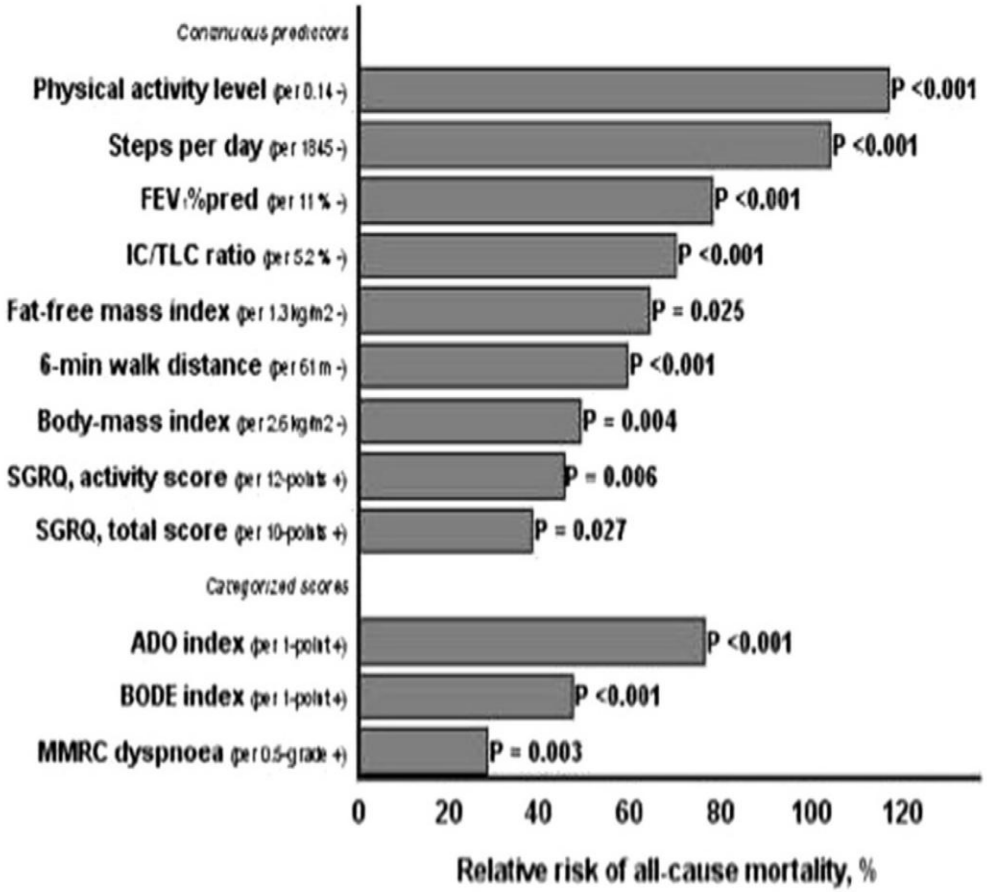


Figure 1 Comparison between relative risk of death associated with physical activity and established predictors of mortality.

Physical activity is the strongest predictor of all-cause mortality in patients with chronic obstructive pulmonary disease: a prospective cohort study

Benjamin Waschki, Anne Kirsten, Olaf Holz, Kai-Christian Müller, Thorsten Meyer, Henrik Watz and Helgo Magnussen

Chest; Prepublished online January 27, 2011;
DOI 10.1378/chest.10-2521

		Survivors	[redacted]	P value
Description	Patient number (%)	143 (84.6)		
	Age (yr), mean (SD)	63.6 (6.6)		0.083
	Men, n (%)	107 (74.8)		0.82
	Current smokers, n (%)	62 (43.4)		0.41
	Pack-years, mean (SD)	52 (26)		0.98
Lung Function	FEV_1 (% of predicted), mean (SD)	58.8 (21.1)		<0.001
	IC/TLC, mean (SD)	34.5 (9.6)		<0.001
Physical Activity	Physical activity level, mean (SD)	1.55 (0.27)		<0.001
	Steps per day, mean (SD)	6424 (3679)		<0.001
Exercise Capacity	6-min walk distance (m), mean (SD)	450 (107)		<0.001
Nutritional Status	Body mass index (kg/m^2), mean (SD)	26.7 (5.1)		0.004
Muscular Status	Fat-free mass index (kg/m^2), mean (SD)	18.9 (2.6)		0.023
	Muscle depletion*, n (%)	13 (9.5)		0.013
Cardiovascular Status	Left ventr. ejection fraction ≤50%, n (%)	4 (3)		0.79
	E wave / A wave, mean (SD)	0.93 (0.21)		0.32
	Tei index, mean (SD)	0.41 (0.11)		0.033
	NT-pro-BNP (pg/mL), median (IQR)	64 (38 - 106)		0.038

COPD: maximization of bronchodilation

Stefano Nardini[1*], Gianna Camiciottoli[2], Salvatore Locicero[3], Rosario Maselli[4], Franco Pasqua[5], Giovanni Passalacqua[6], Riccardo Pela[7], Alberto Pesci[8], Alfredo Sebastiani[9] and Alessandro Vatrella[10]

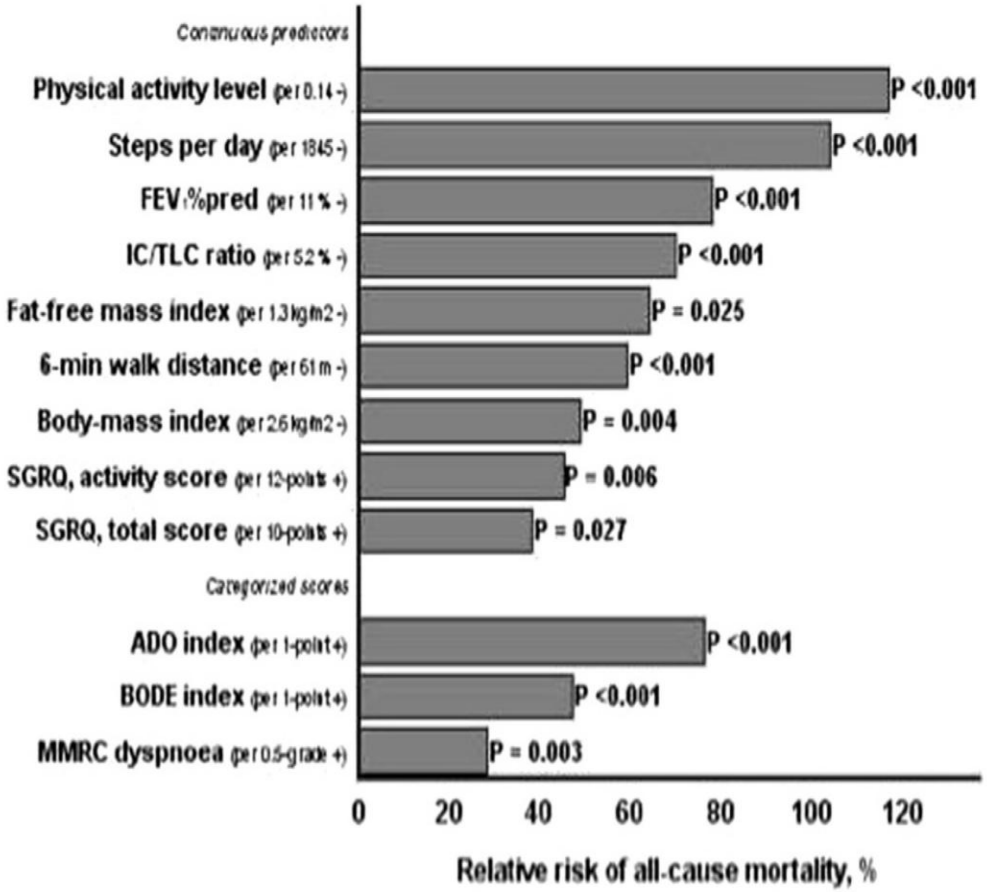
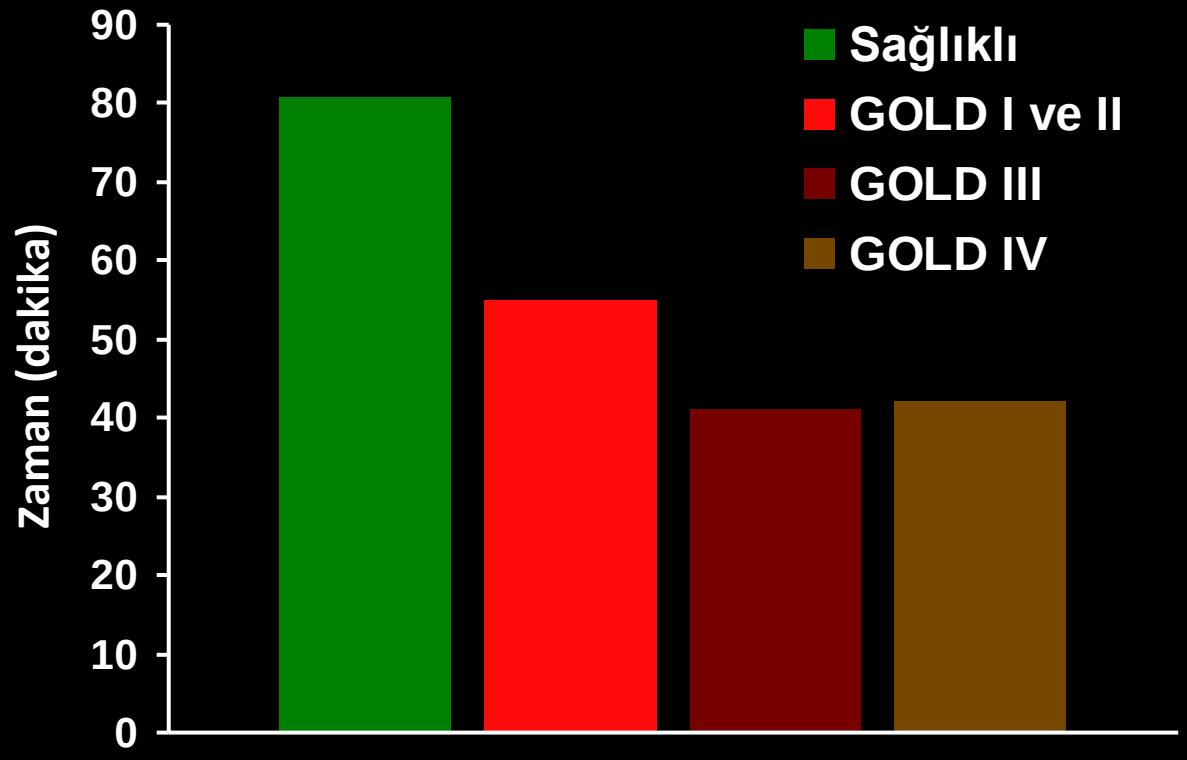


Figure 1 Comparison between relative risk of death associated with physical activity and established predictors of mortality.

Characteristics of Physical Activities in Daily Life in Chronic Obstructive Pulmonary Disease

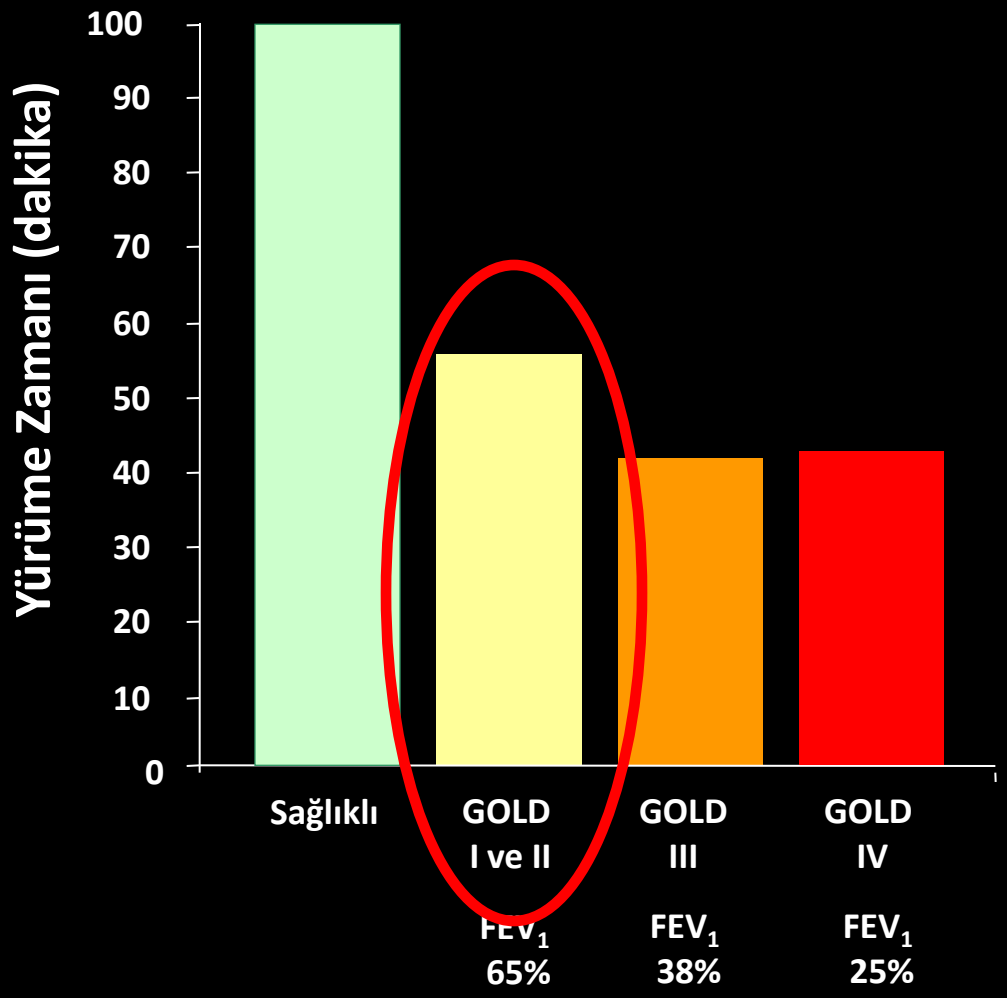
Fabio Pitta, Thierry Troosters, Martijn A. Spruit, Vanessa S. Probst, Marc Decramer, and Rik Gosselink



KOAH İLERLERKEN FİZİK AKTİVİDE DÜŞER

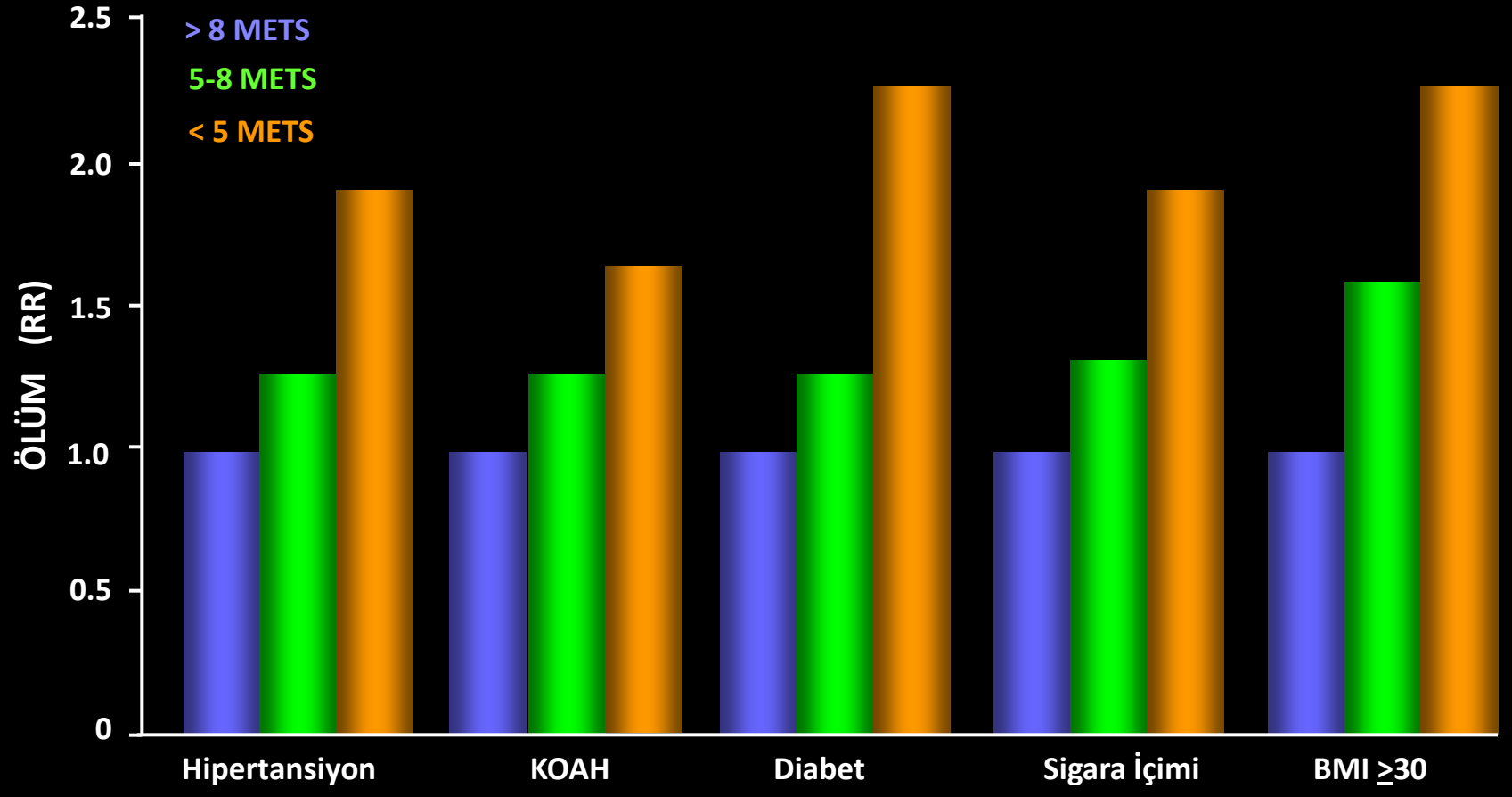
Pitta et al. *Am J Respir Crit Care Med* 2005;171:972-977

Erken Evre KOAH'da bile inaktivite vardır



Pitta et al. *AJRCCM* 2005; 171: 972-977

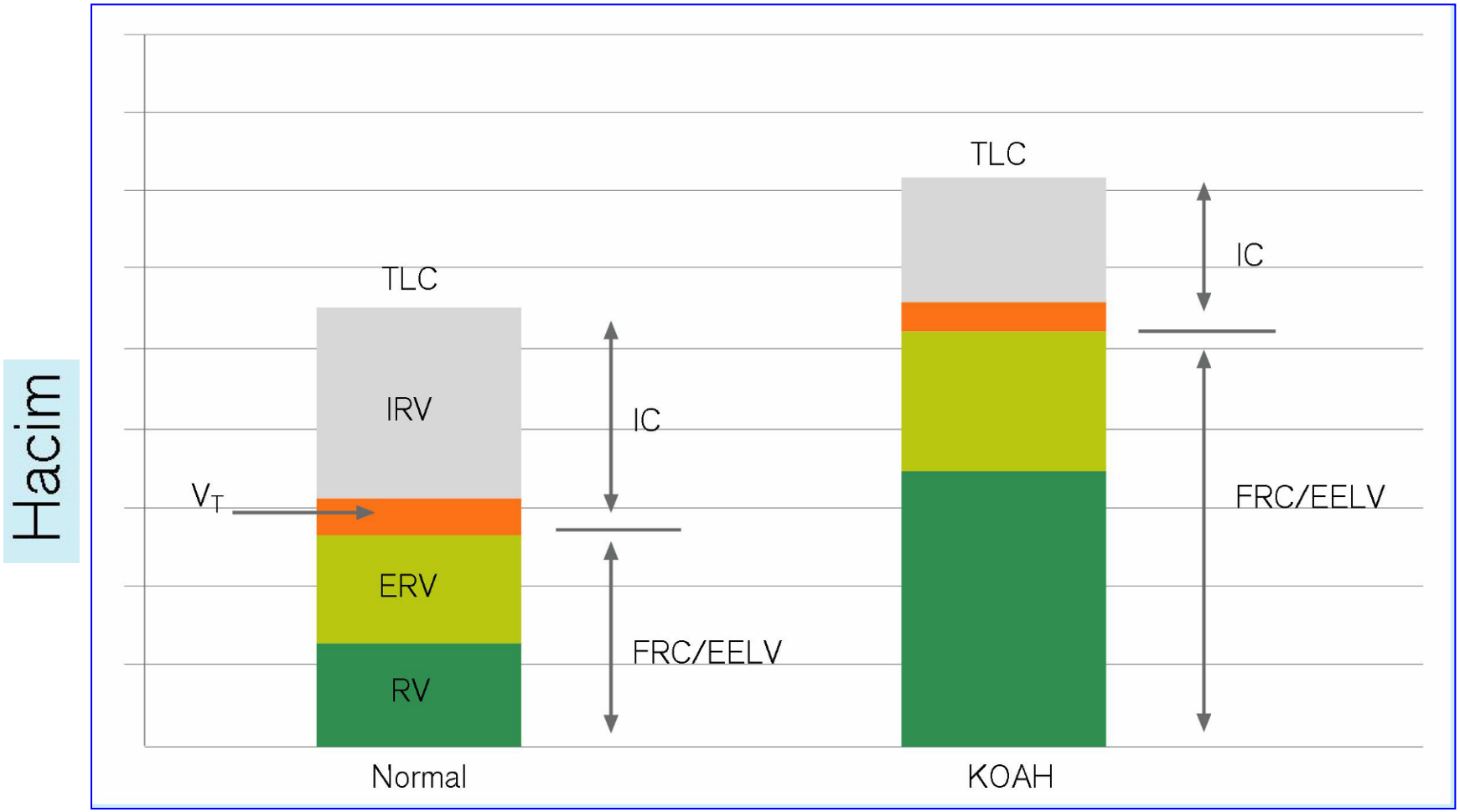
Düşen Egzersiz Kapasitesinin Kronik Hastalıklar Üzerine Etkisi



MET: metabolic equivalents

Myers J. *N Engl J Med* 2002;346:793–801

Akciğer Volüm Parametreleri

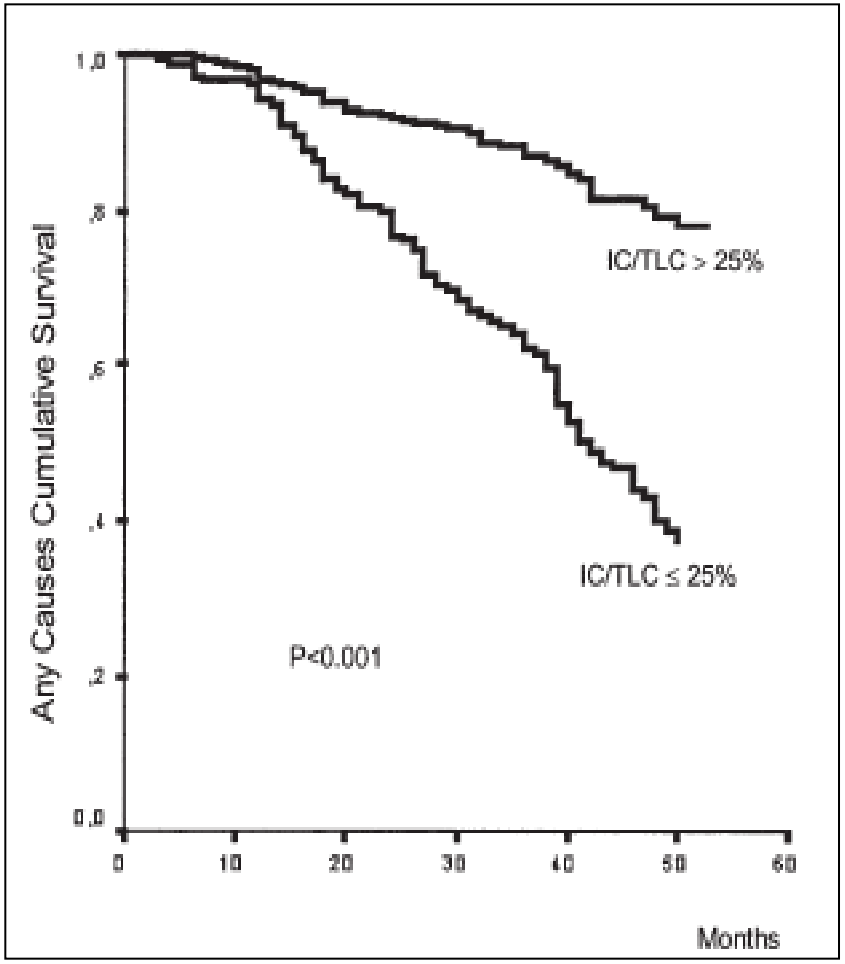


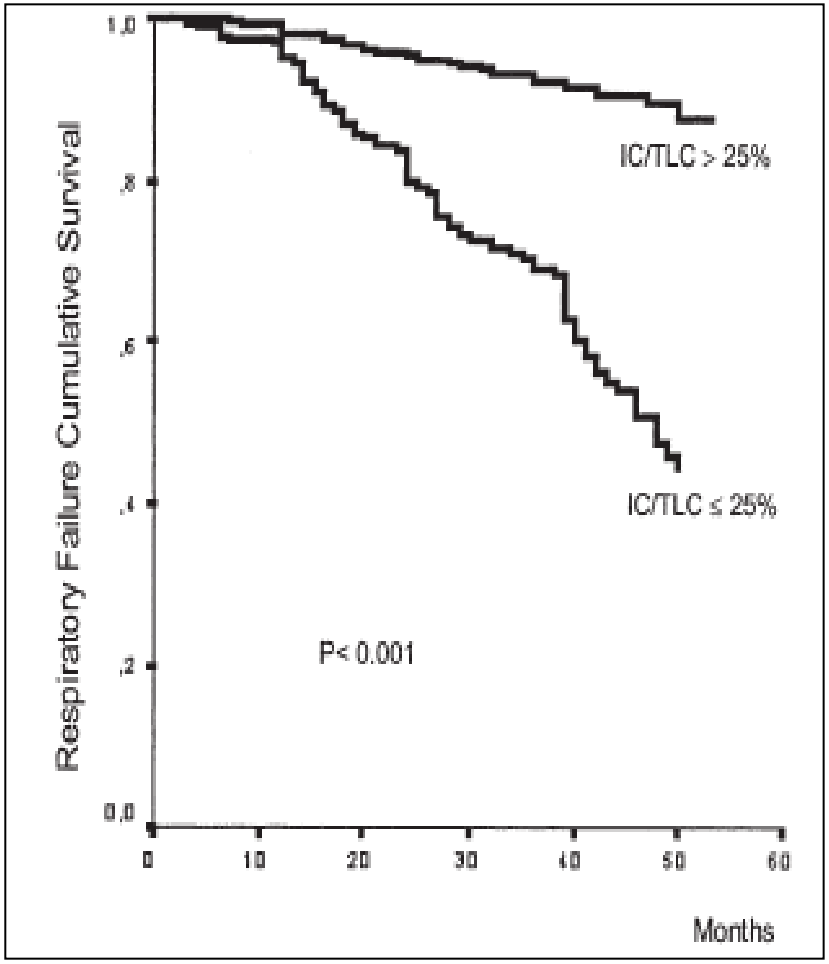
Hiperinflasyon

- Inspiratuvar kapasitenin (IC) total akciğer kapasitesine (TLC) oranı
- IC/ TLC oranının % 25’ in altına inmesi mortalitede belirgin artışa neden olur

Inspiratory-to-Total Lung Capacity Ratio Predicts Mortality in Patients with Chronic Obstructive Pulmonary Disease

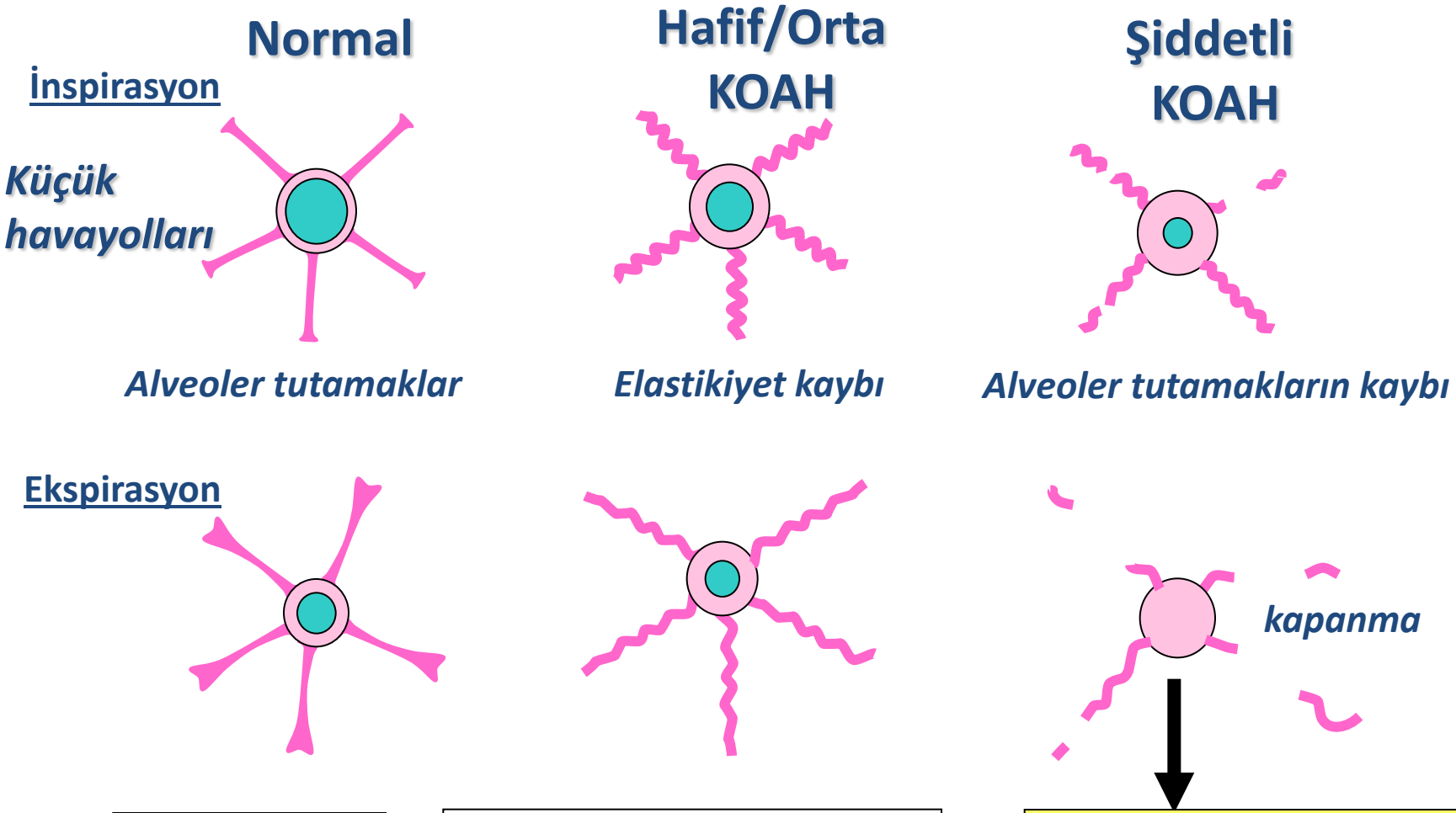
Ciro Casanova, Claudia Cote, Juan P. de Torres, Armando Aguirre-Jaime, Jose M. Marin, Victor Pinto-Plata, and Bartolome R. Celli





Casanova C, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005 ; 15;171:591-7

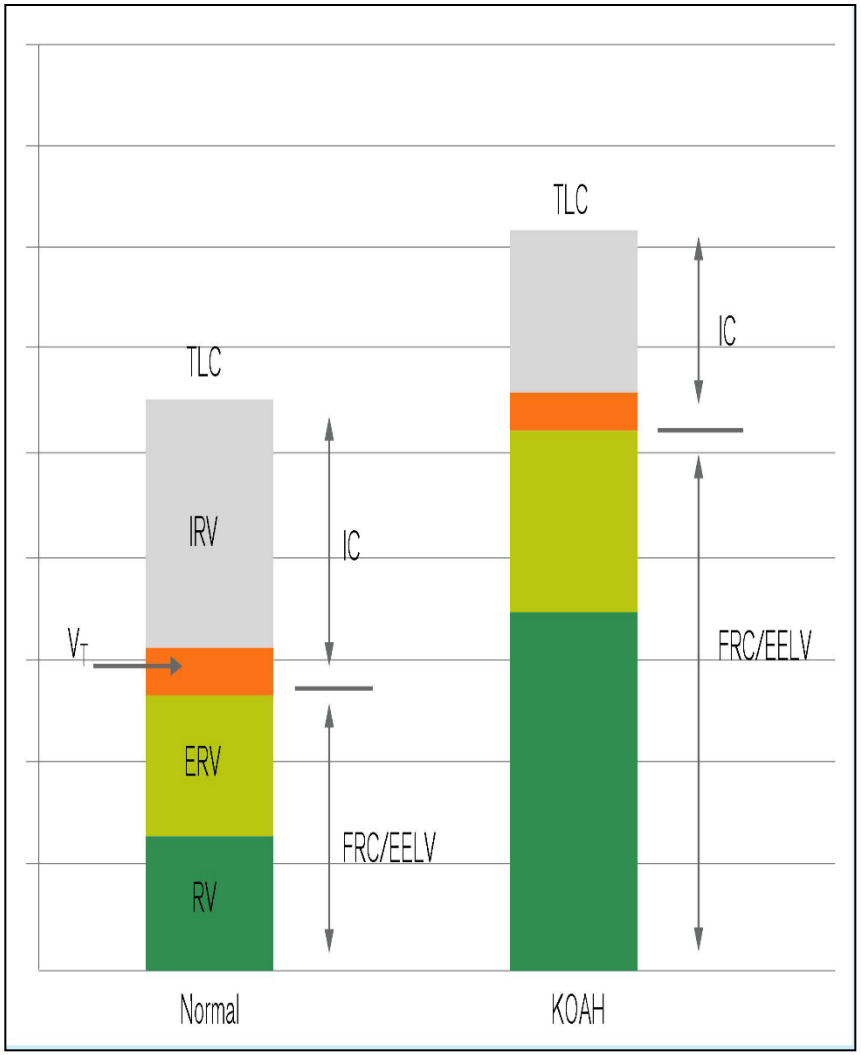
KOAH'ta hava hapsi

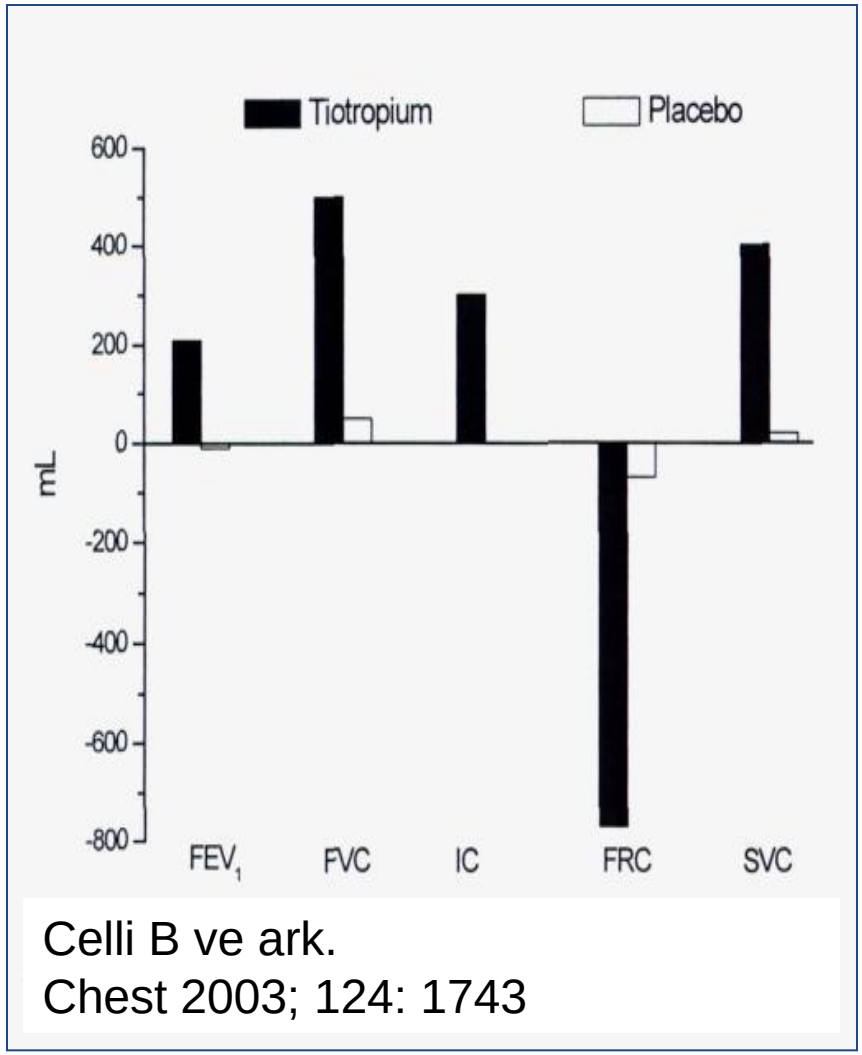


Peter J. Barnes

İnspirasyon kapasitesindeki artış, hastaların solunum volümlerini daha rahat arttırabilmelerine ve egzersiz kapasitelerinin artmasına olanak vermektedir

Egzersiz kapasitesi FEV1 düzeyiyle değil, inspirasyon kapasitesiyle ilişkilidir





Celli B ve ark.
Chest 2003; 124: 1743

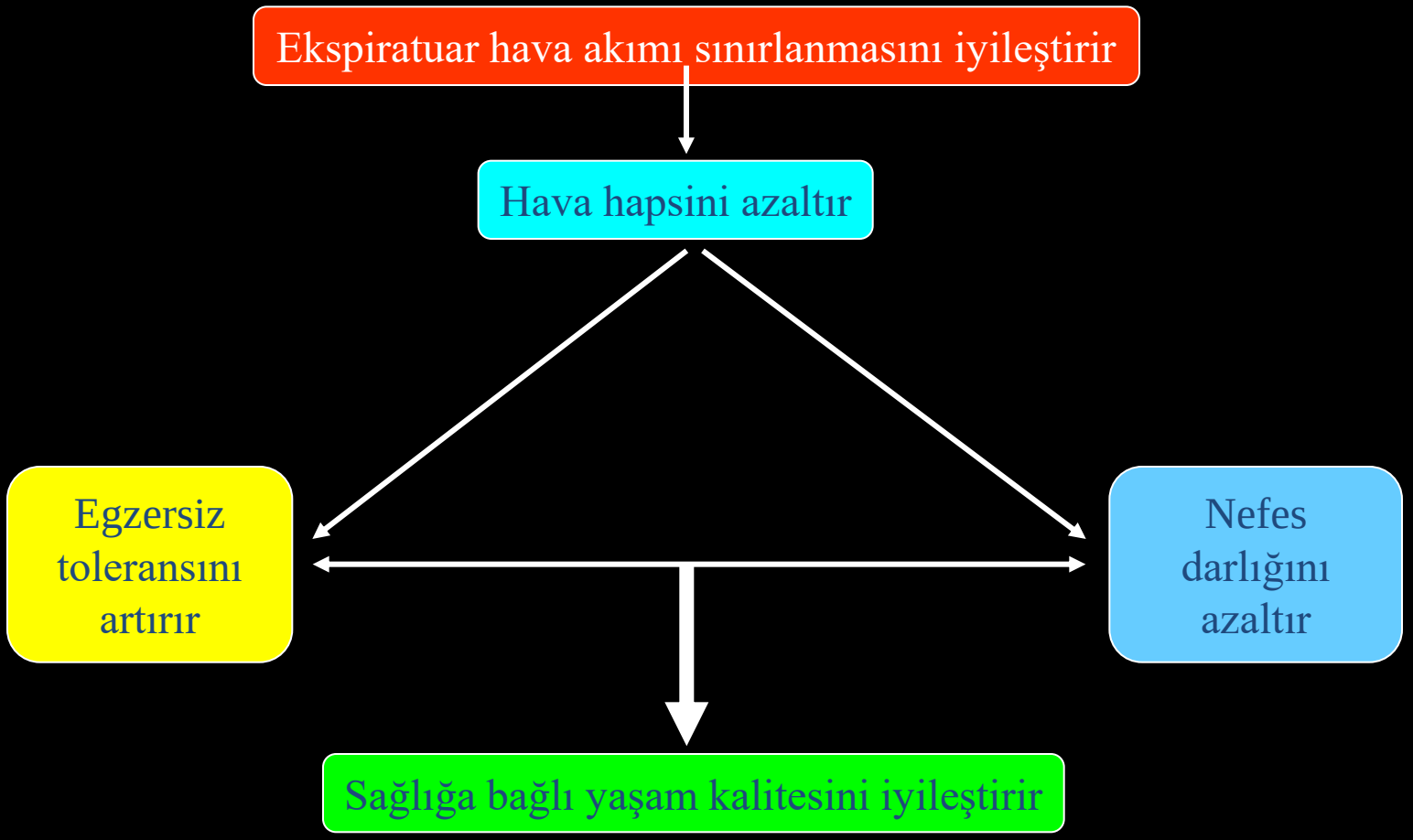
UZUN ETKİLİLER

	Tiotropium*	Salmeterol**
FEV_1 (L)	+0.22	+0.21
FVC (L)	+0.43	+0.54
RV (L)	-0.56	-0.23
TLC (L)	-0.19	-0.11
RV/TLC (%)	-6.0	-2.6

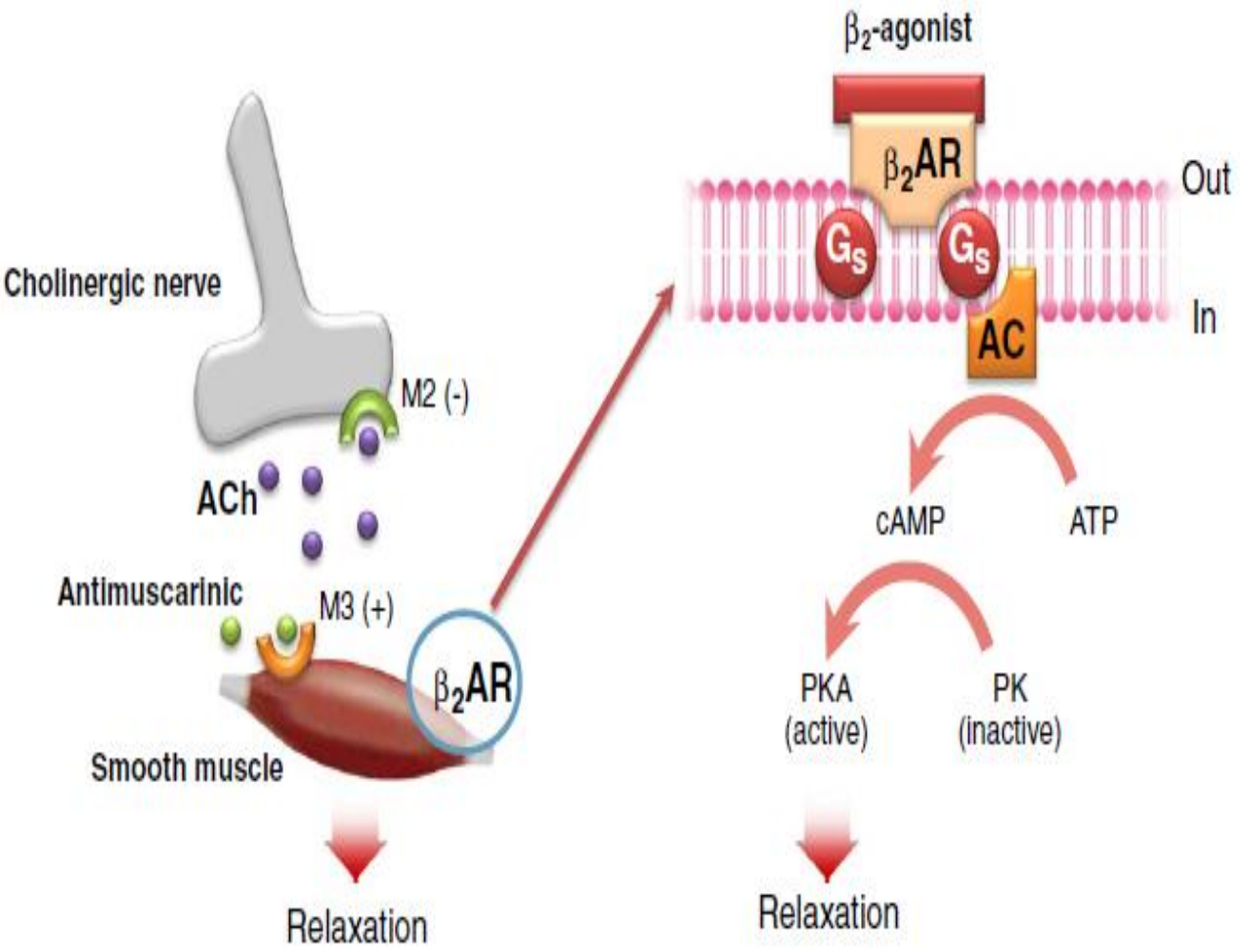
*Mean treatment difference versus placebo at peak after 42 days of treatment
**Mean treatment difference versus placebo

Man WD, et al. *Thorax.* 2004;59:471-476.
O'Donnell DE, et al. *Eur Resp J.* 2004;23:832-840.

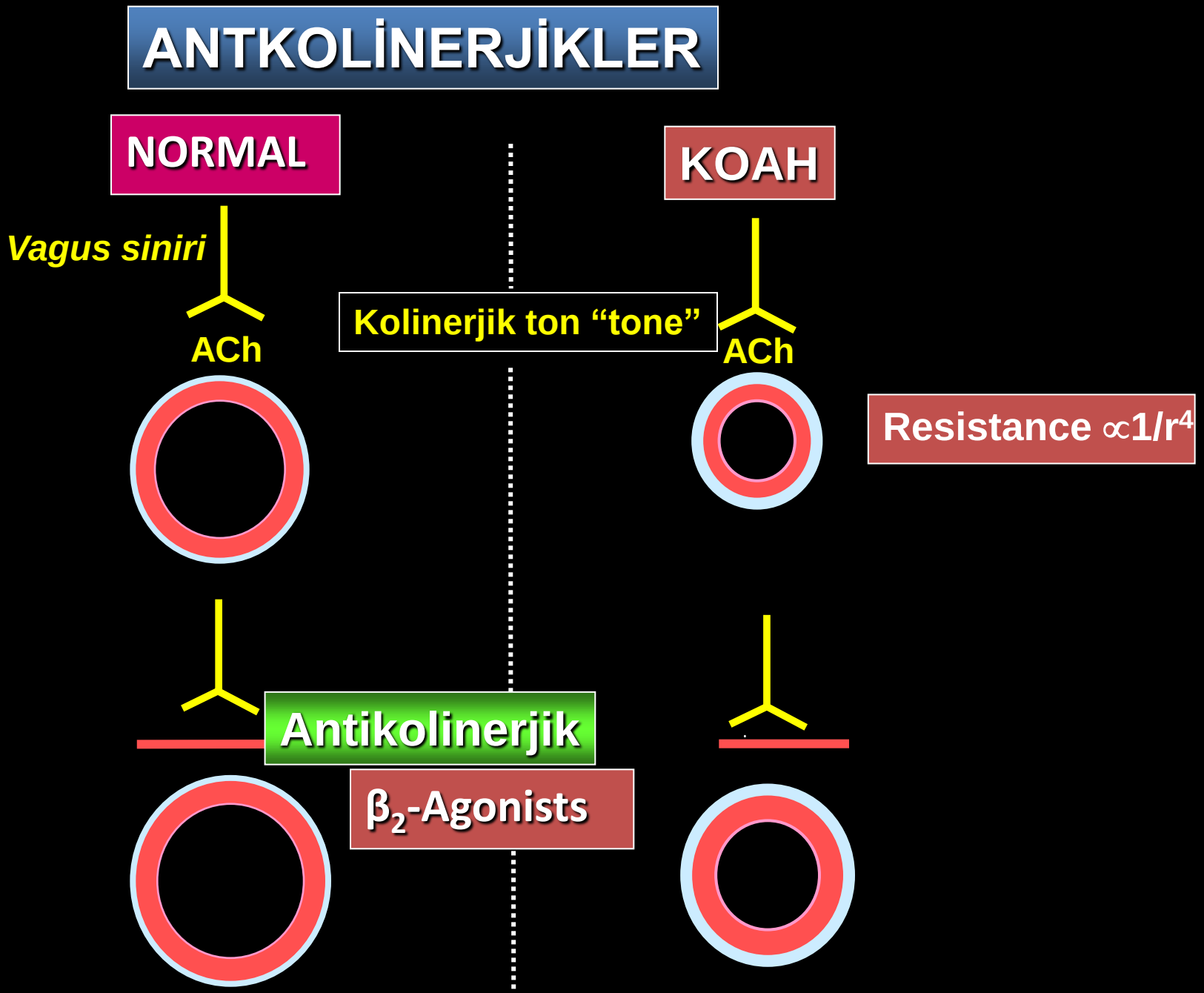
Uzun Etkili Bronkodilatörlerin Etkisi



Bronkodilatasyon



Nardini *et al. Multidisciplinary Respiratory Medicine* 2014, **9**:50


ANTKOLİNERJİKLER
NORMAL
KOAH
Vagus siniri
ACh
Kolinerjik ton "tone"
ACh
Resistance ∝1/r4
Antikolinerjik
β2-Agonists

Uzun etkili antikolinerjik

- **FEV 1**
- **Hiperinflasyon**
- **Dispne**
- **Egzersiz Kapasitesi**
- Anemi
- **Yaşam Kalitesi**

The NEW ENGLAND JOURNAL of MEDICINE

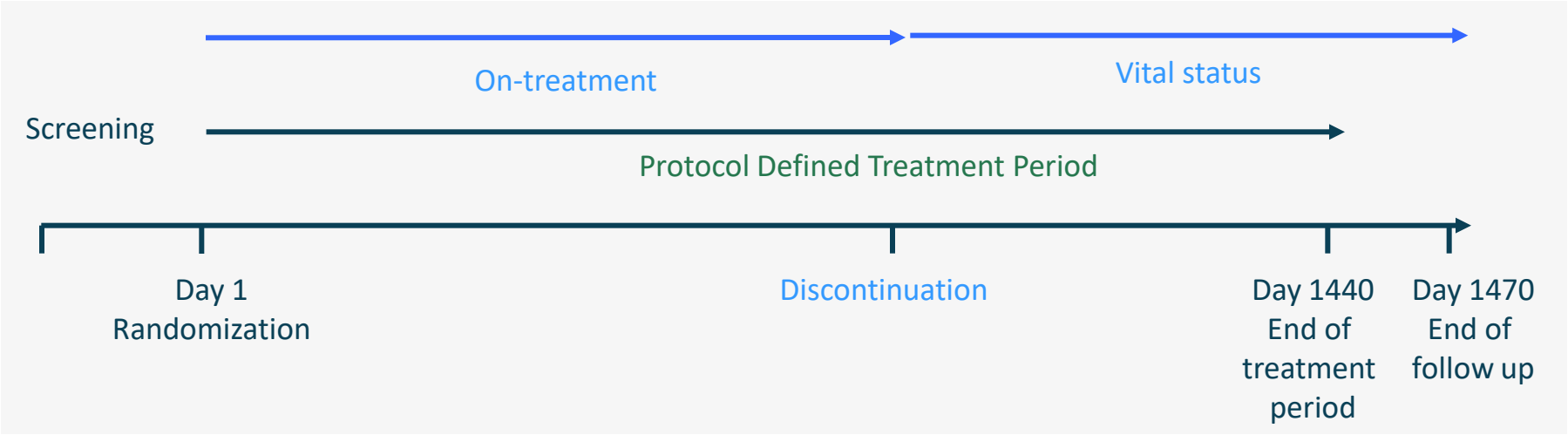
ESTABLISHED IN 1812 OCTOBER 9, 2008 VOL. 359 NO. 15

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*

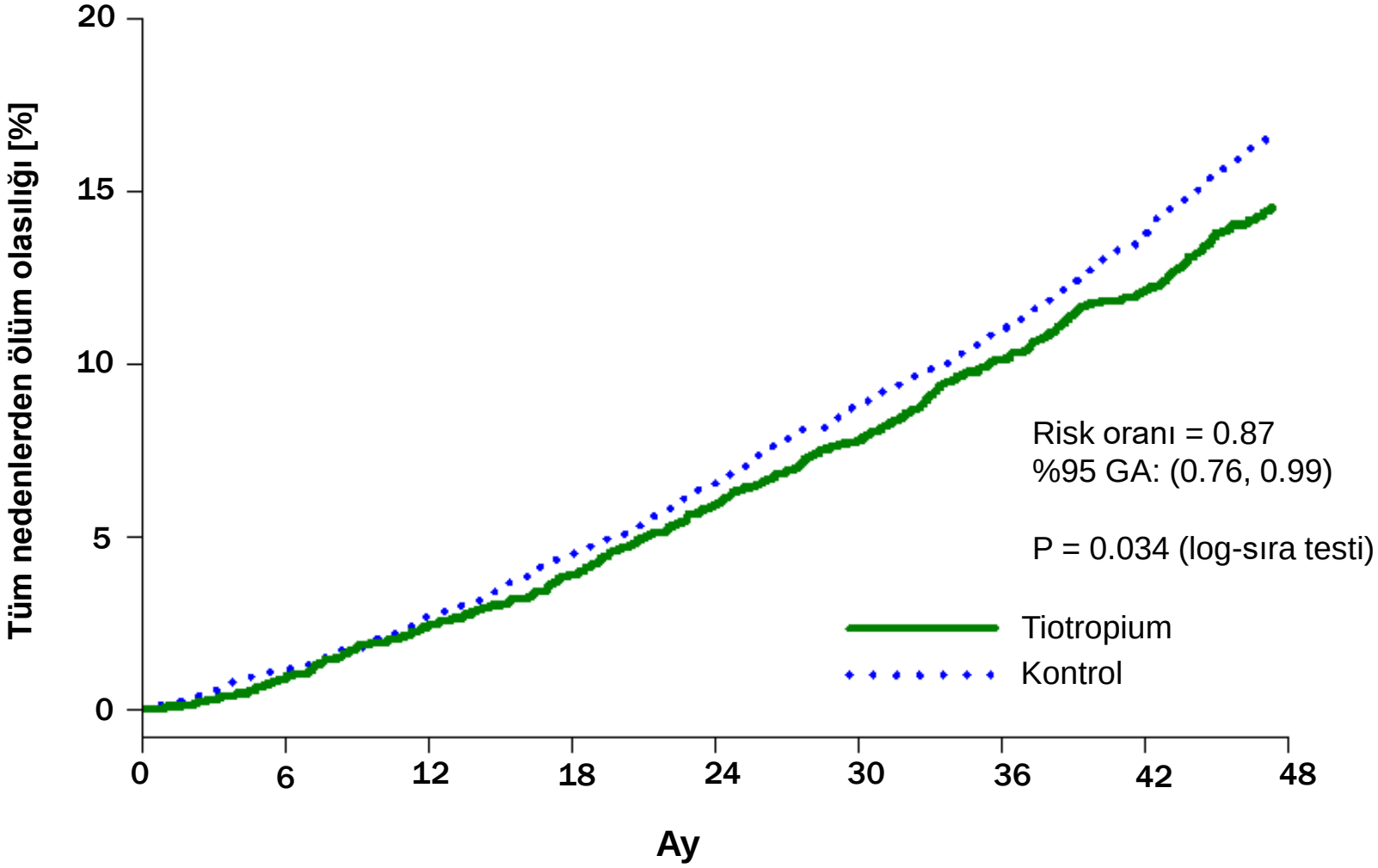
MORTALİTE

- Tedavide
  - 1.günden tedavi aldığı son gün
- Vital durum
  - 4 yıl (1440 gün)
  - 4 yıl + 30 gün izlem (1470 gün)



Tüm Nedenlerden Ölüm Olasılığı

Tedavi Sırasında + Vital Durum – 1440. Gün



Kardiyovasküler Olaylar

	Plasebo		Tiotropium		Risk Oranı[1] (%95 GA)
	n	Hız[2]	n	Hız[2]	
UPLIFT					
Bileşik sonlanım noktası	246	2.89	208	2.25	0.78 (0.65, 0.94)
Ölümcül bileşik sonlanım noktası	124	1.42	98	1.04	0.73 (0.56, 0.95)

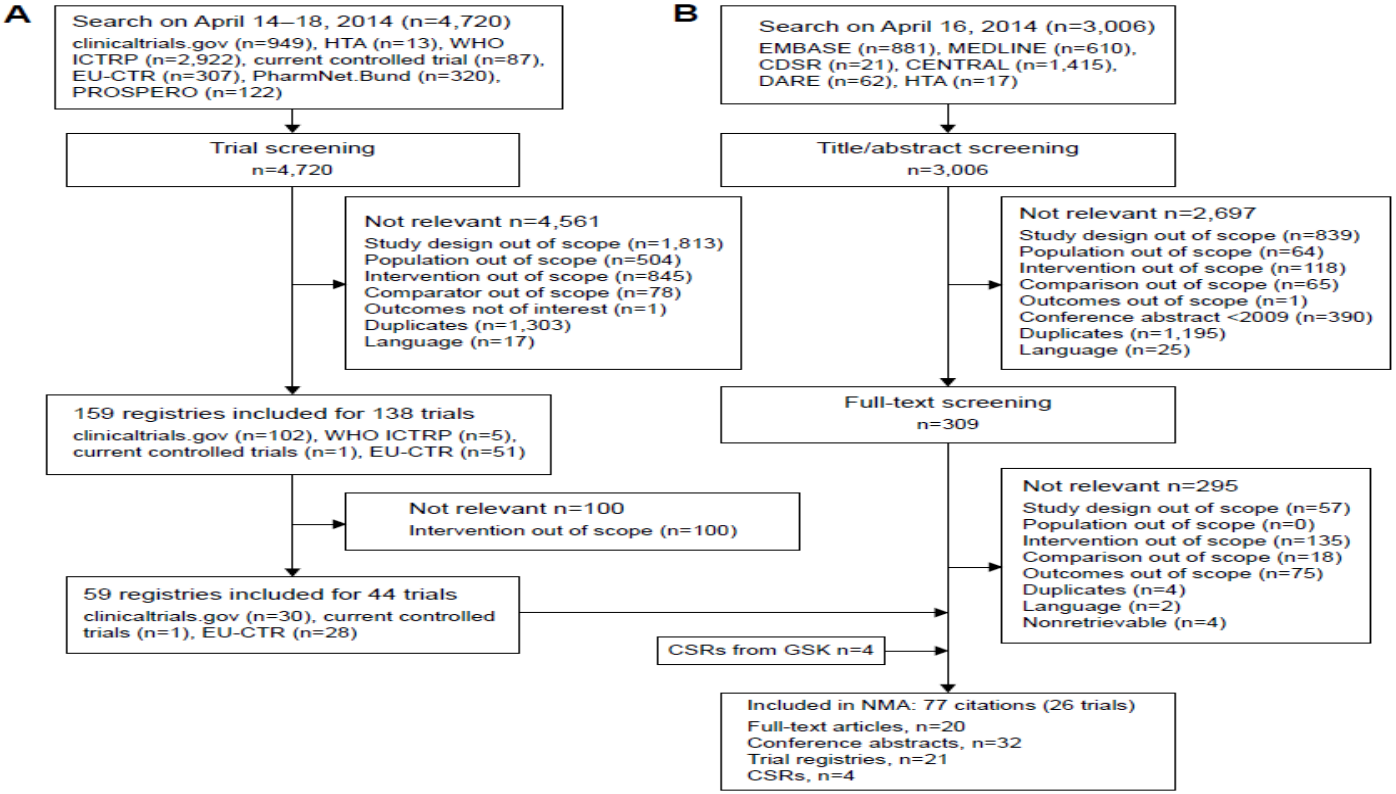
[1] risk oranına karşı plasebo; [2] risk altındaki 100 kişi yılı başına tiotropium ya da plasebo

*SOC kardiyak (ölümcü), SOC vasküler (ölümcül), MI (ölümcül+ölümcül-olmayan), inme (ölümcül+ölümcül-olmayan), ani ölüm, ani kardiyak ölüm

Ne kadar?

Bronkodilatör ve bronkodilatör kombinasyonları plasebodan yani tedavi edememekten daha iyi…….

Comparative efficacy of combination bronchodilator therapies in COPD: a network meta-analysis



Huisman E.L. et. al. International Journal of COPD 2015:10 1863–1881

Comparative efficacy of combination bronchodilator therapies in COPD: a network meta-analysis

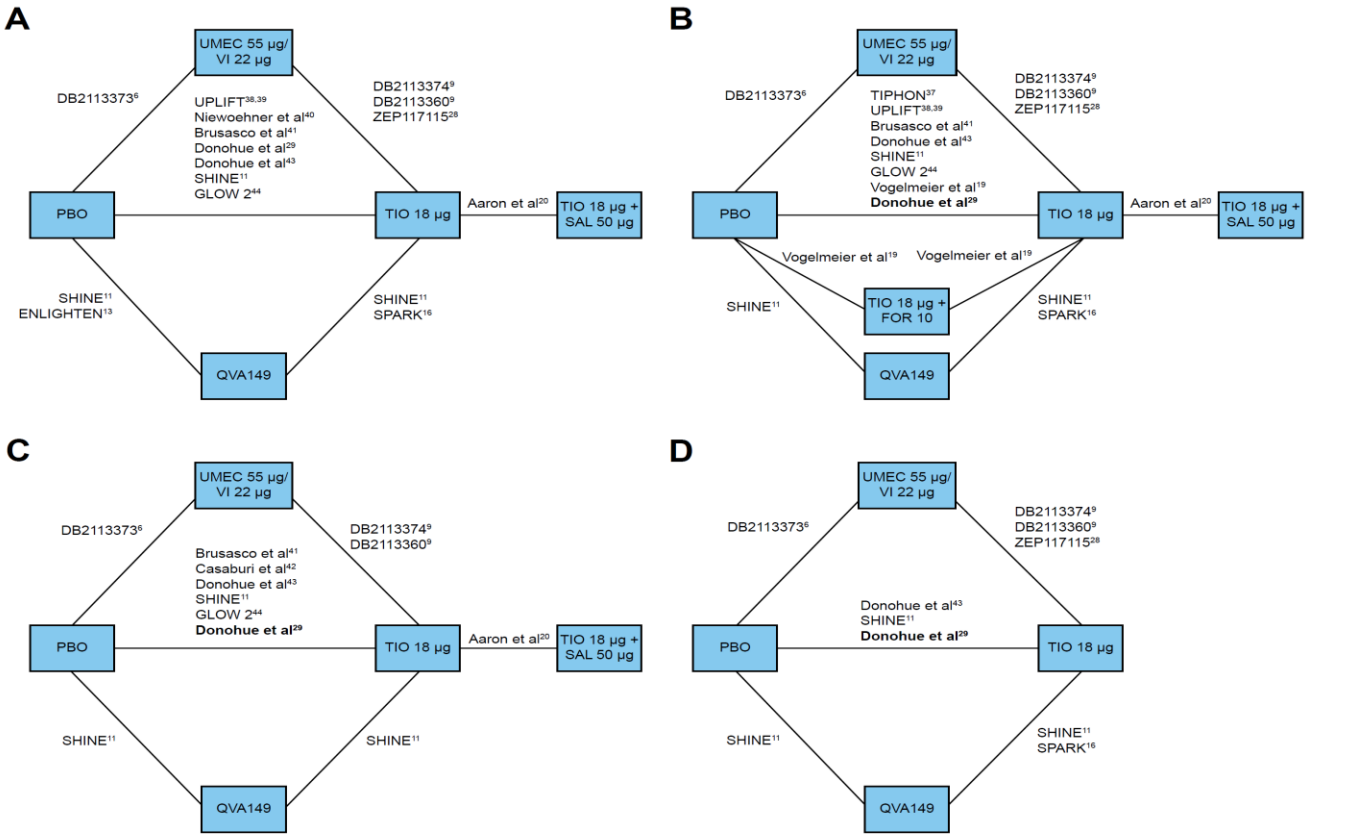
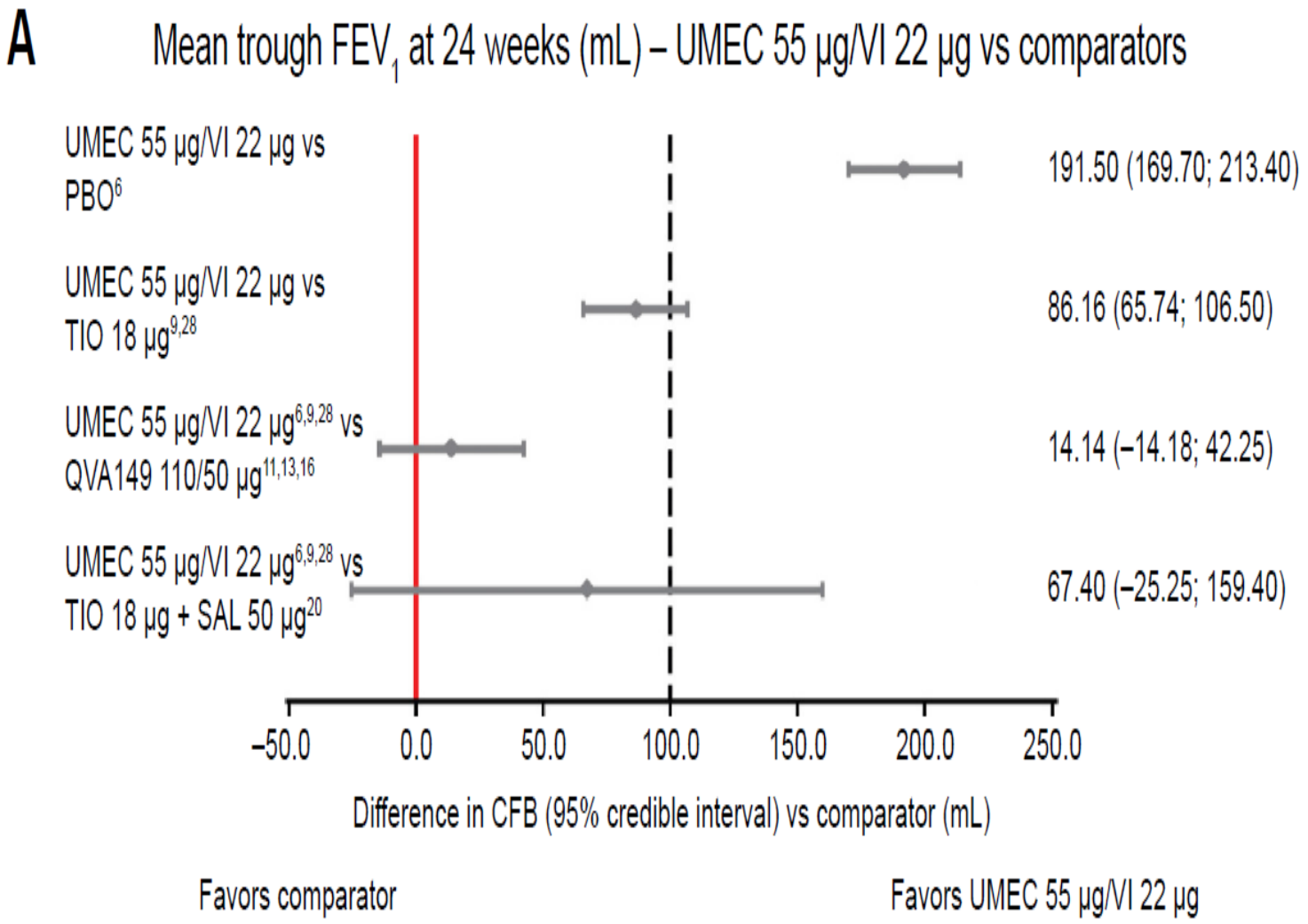
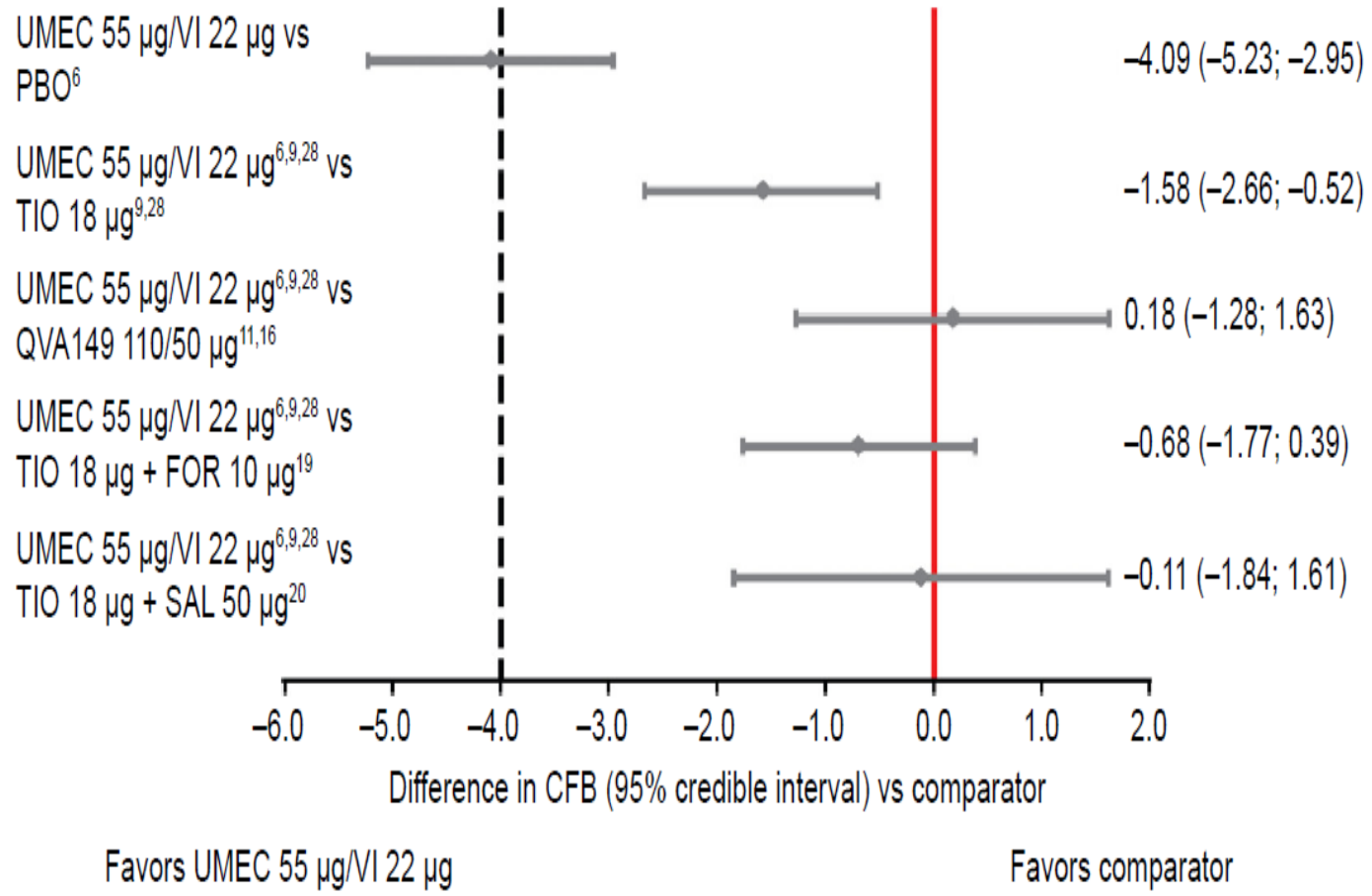


Figure 2 Overall network of studies in the NMA analysis of UMEC/VI versus LABA/LAMA combination therapies evaluated at 24 weeks for (**A**) trough FEV_1, (**B**) SGRQ total score, (**C**) TDI focal score, and (**D**) rescue medication use.

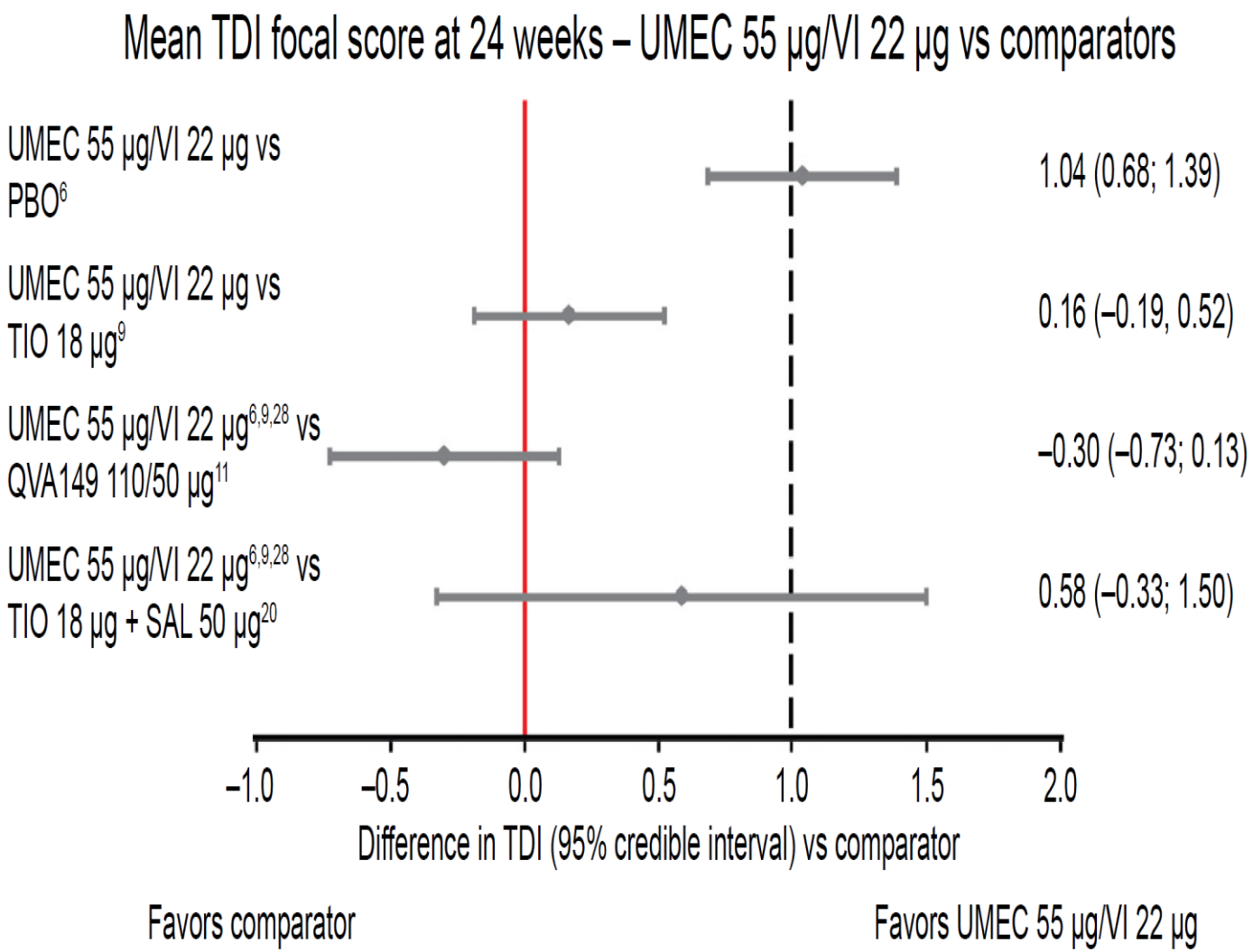
Huisman E.L. et. al. International Journal of COPD 2015:10 1863–1881


A
Mean trough FEV1 at 24 weeks (mL) – UMEC 55 µg/VI 22 µg vs comparators
UMEC 55 µg/VI 22 µg vs PBO6
UMEC 55 µg/VI 22 µg vs TIO 18 µg9,28
UMEC 55 µg/VI 22 µg6,9,28 vs QVA149 110/50 µg11,13,16
UMEC 55 µg/VI 22 µg6,9,28 vs TIO 18 µg + SAL 50 µg20
191.50 (169.70; 213.40)
86.16 (65.74; 106.50)
14.14 (–14.18; 42.25)
67.40 (–25.25; 159.40)
–50.0
0.0
50.0
100.0
150.0
200.0
250.0
Difference in CFB (95% credible interval) vs comparator (mL)
Favors comparator
Favors UMEC 55 µg/VI 22 µg

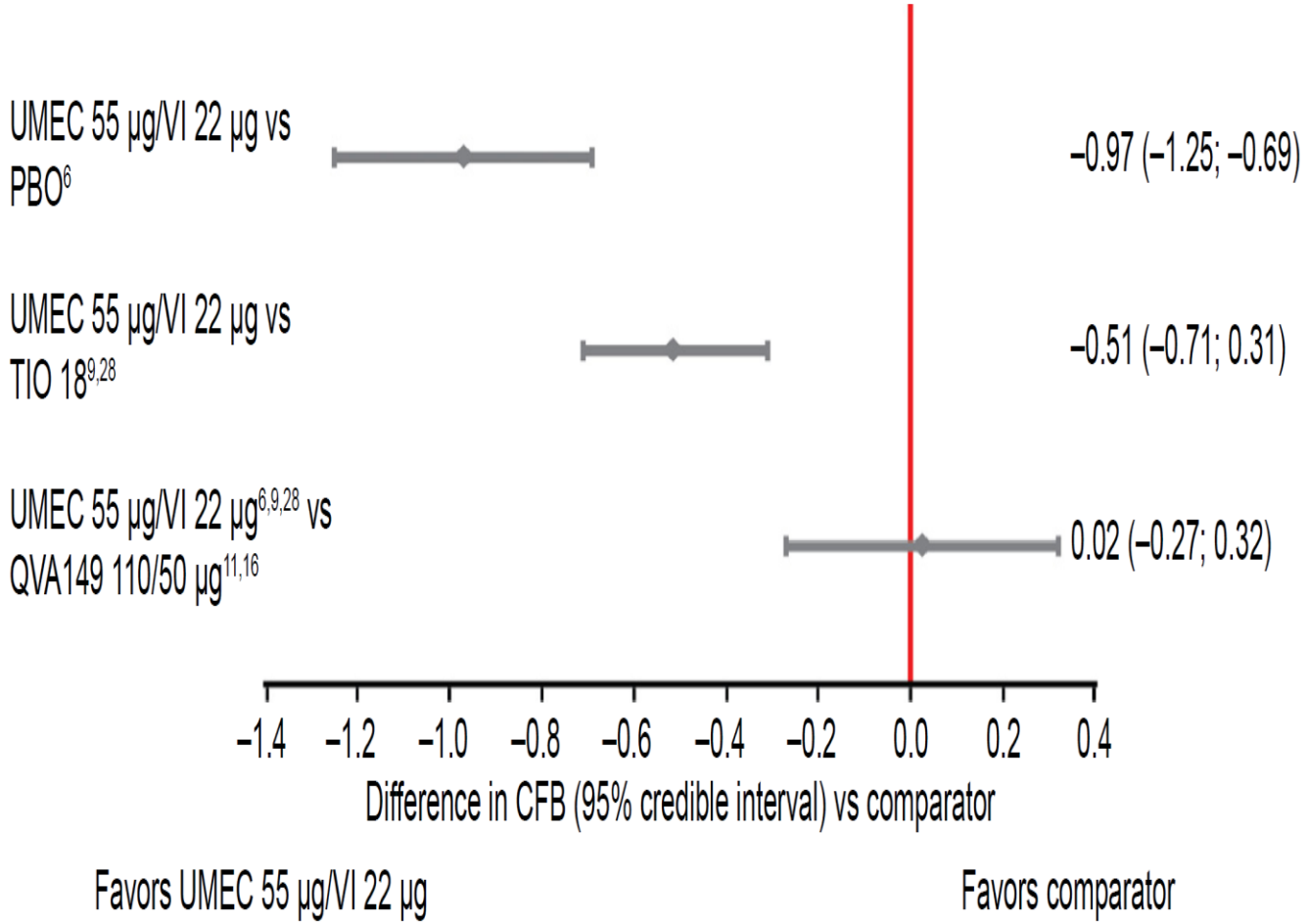
B Mean SGRQ total score at 24 weeks – UMEC 55 µg/VI 22 µg vs comparators



C

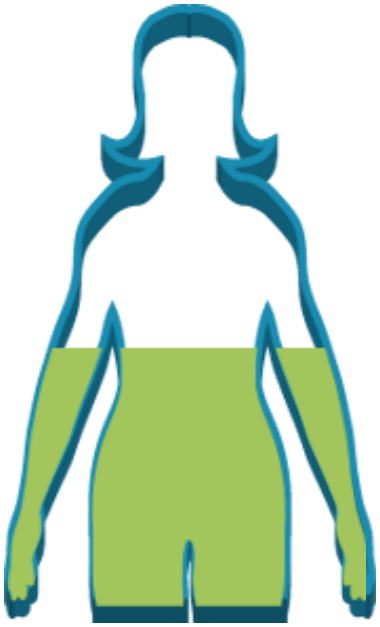

Mean TDI focal score at 24 weeks – UMEC 55 µg/VI 22 µg vs comparators
UMEC 55 µg/VI 22 µg vs PBO[6]
1.04 (0.68; 1.39)
UMEC 55 µg/VI 22 µg vs TIO 18 µg[9]
0.16 (–0.19, 0.52)
UMEC 55 µg/VI 22 µg[6,9,28] vs QVA149 110/50 µg[11]
–0.30 (–0.73; 0.13)
UMEC 55 µg/VI 22 µg[6,9,28] vs TIO 18 µg + SAL 50 µg[20]
0.58 (–0.33; 1.50)
–1.0
–0.5
0.0
0.5
1.0
1.5
2.0
Difference in TDI (95% credible interval) vs comparator
Favors comparator
Favors UMEC 55 µg/VI 22 µg

D Rescue medication use (puffs/day) at 24 weeks – UMEC/VI 55/22 µg vs comparators



Doğru Tanı Oranı

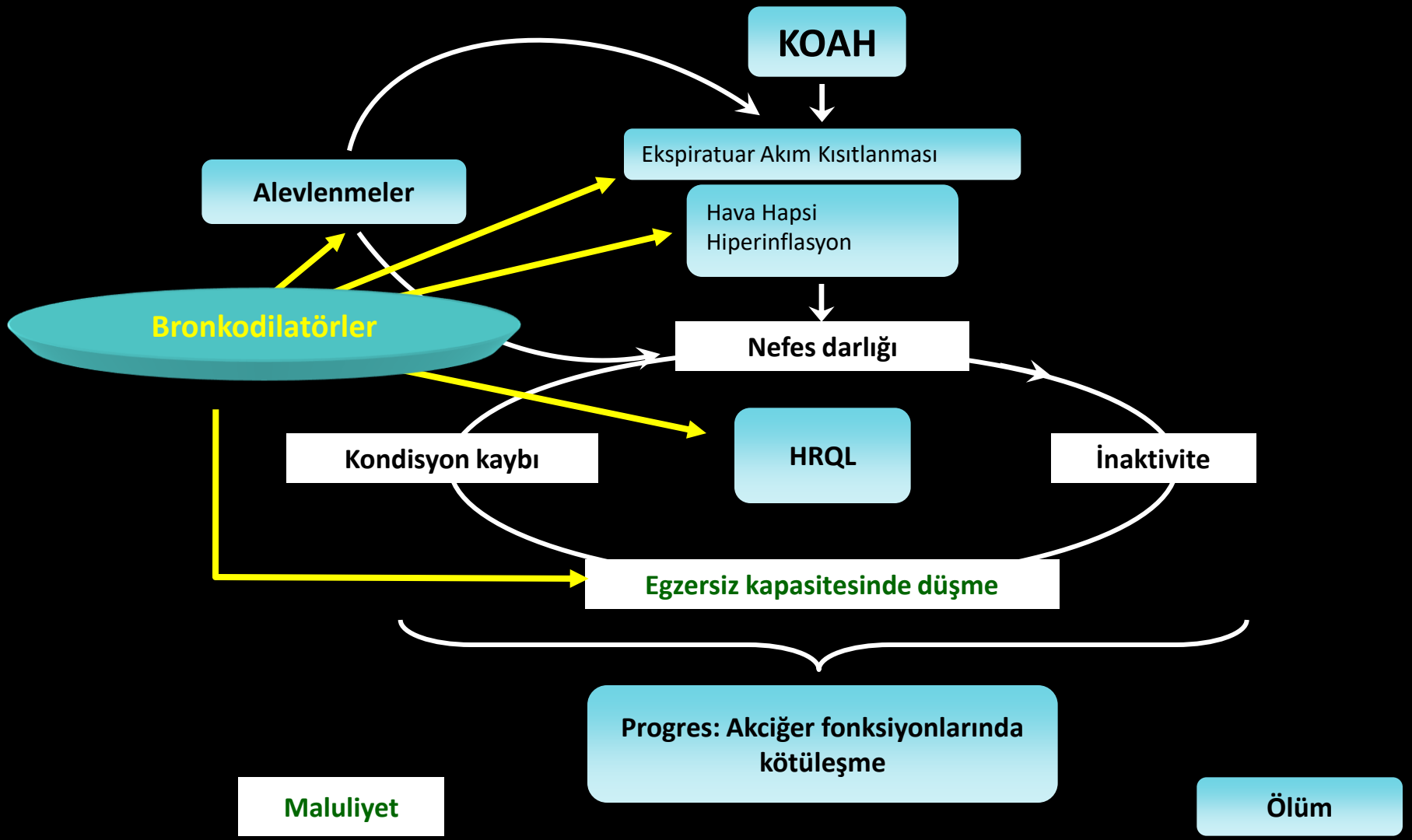
% 65



% 49

Chapman, et al. Chest 2001.

Ne kadar?



HRQL = Sağlıkla İlişkili Yaşam Kalitesinde Bozulma

Ferro T. Clinical Pulmonary Medicine 2005; Decramer M. Eur Respir Rev 2006

Yerin seni çektiği kadar ağırsın
Kanatların çırpındığı kadar hafif
Kalbinin attığı kadar canlısın
Gözlerinin uzağı gördüğü kadar genç…
Sevdiklerin kadar iyisin
Sevdiğin kadar sevileceksin.
Güneşin doğuşundadır doğanın sana verdiği değer
Ve karşındakine değer verdiğin kadar insansın

Teşekkür ederim