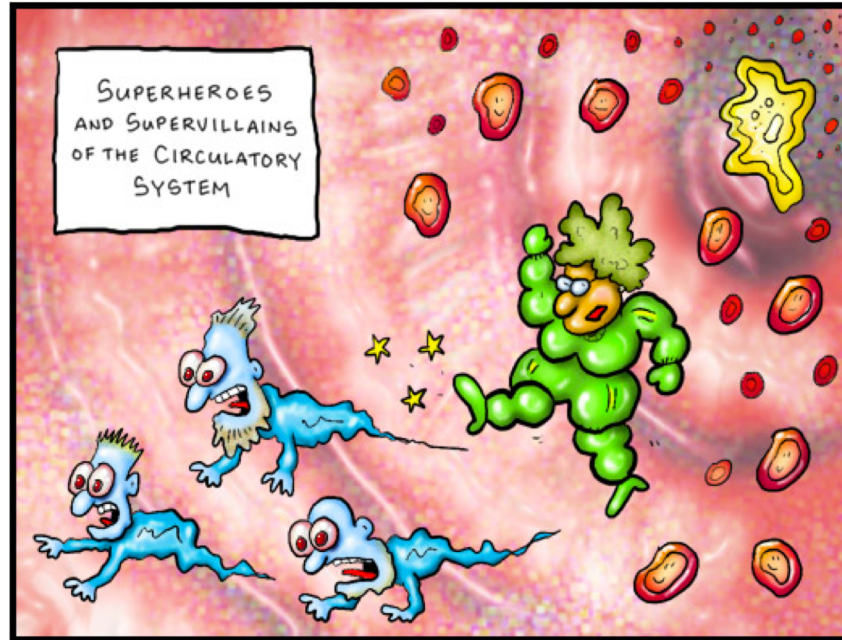


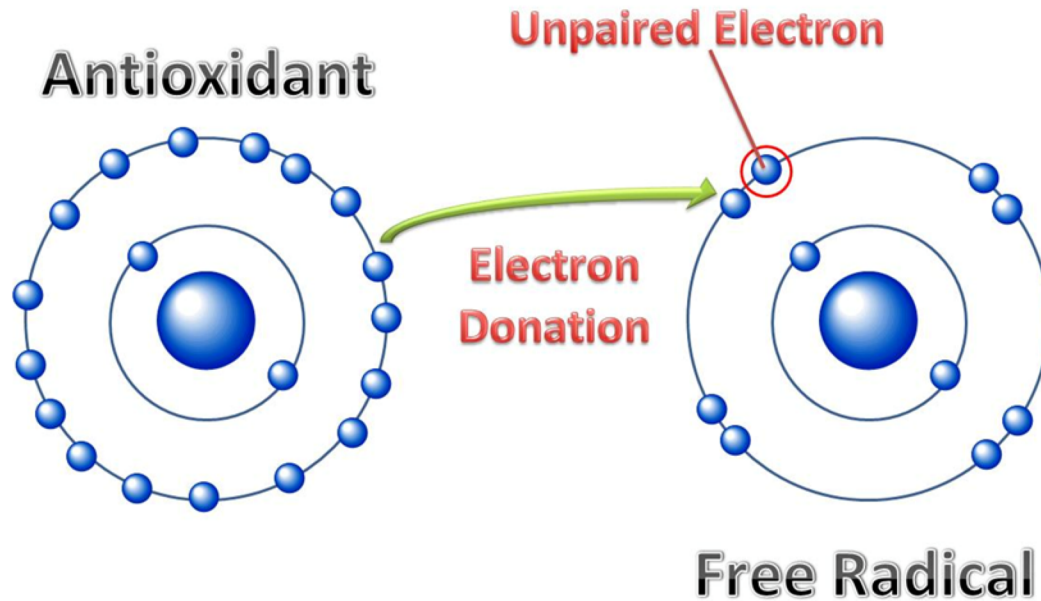
Oksidatif stres ve akciğerler

Erdosteine bunun neresinde

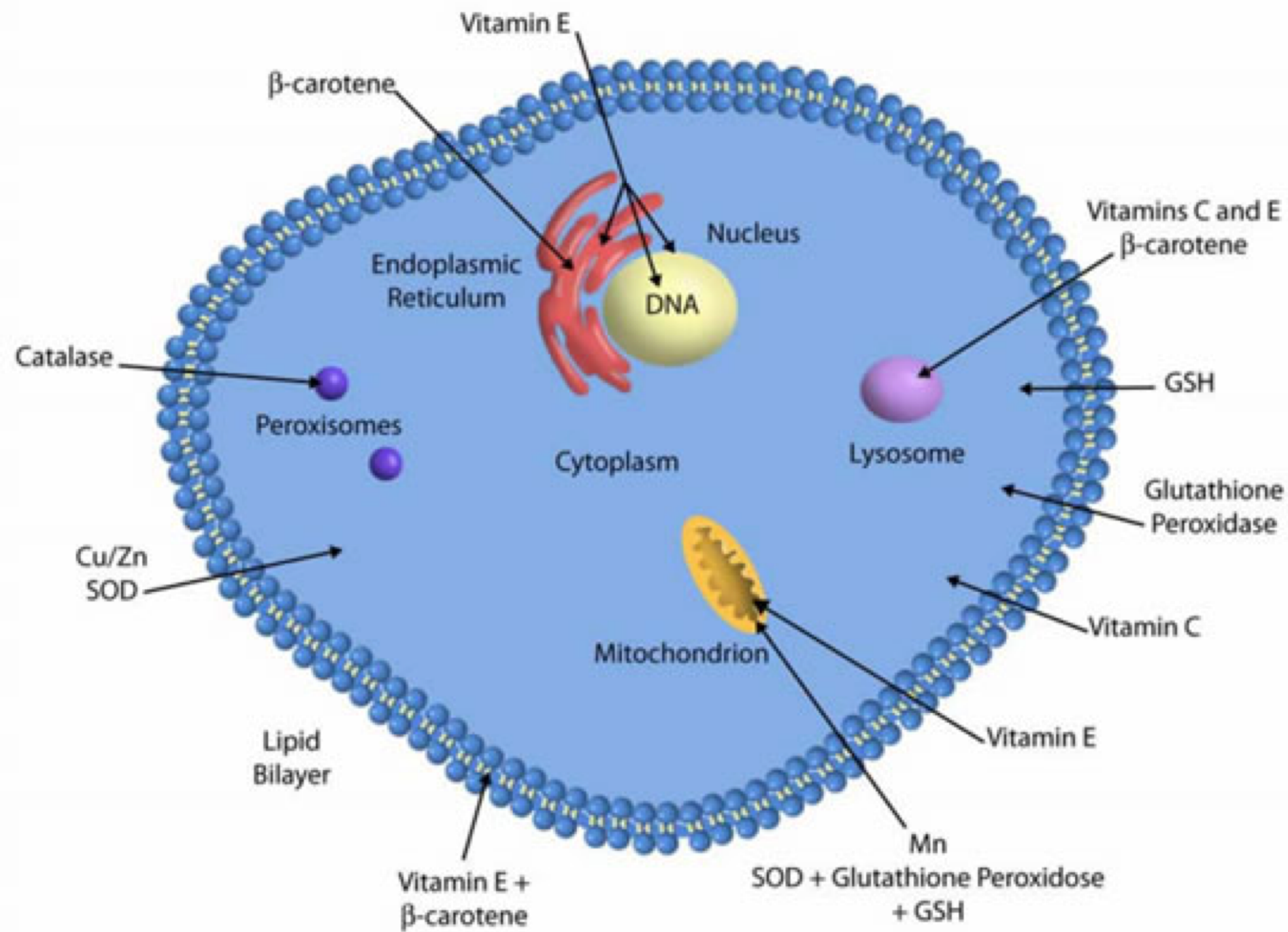


Prof.Dr.Kürşat Uzun
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Konya

Serbest Oksijen Radikalleri







MALİGN PLEVRAL EFÜZYONLARDA MALONDİALDEHİT (MDA) DÜZEYİ'NİN TANISAL DEĞERİ

Dr.Kürşat UZUN⁽¹⁾, Dr. Faruk ÖZER⁽²⁾, Dr. Osman ÇAĞLAYAN⁽³⁾,
Dr. Sadinaz KALAK⁽⁴⁾, Dr. Oktay İMECİK⁽²⁾

ÖZET

Bu çalışmada 74 plörezi olgunun plevra sıvısı ve serumunda lipid peroksidasyonun son ürünü olan malondialdehit (MDA) ile kontrol grubu olarak seçilen sağlıklı 29 kişinin serum MDA düzeyleri araştırıldı. Olgularımızın 31'inde (%42) plörezinin malignite kaynaklı olduğu 43'ünde ise (%58) malignite dışı hastalıklara bağlı olduğu saptandı. Ortalama serum MDA düzeyi maligniteli grupta 4.42 ± 0.59 nmol/ml olup malignite dışı olgulardan ve kontrol grubundan anlamlı derecede yüksekti ($p < 0.05$, $p < 0.001$). Çalışmamızda elde edilen ortalama plevra sıvısı MDA düzeyi ise maligniteli olgularda 4.35 ± 0.57 nmol/ml olup aralarında istatistiksel anlamlılık mevcuttu ($p < 0.01$). Her iki grupta sigara içenler ile içmeyenler arasında anlamlı fark yoktu. Sınır değer 4 nmol/ml alınarak plevra sıvısı MDA ölçümünün spesifitesi % 81, sensitivitesi ise % 39 olarak bulunmuştur. Bu bulgular bize malign olgularda oksidatif stresin diğer gruba oranla daha fazla arttığını ve plevra sıvısında MDA düzeyinin ölçülmesi malignite kaynaklı sıvılarda tanısasal değeri olabileceğini göstermektedir.

Anahtar Sözcükler: Plevra efüzyonu, malondialdehit, lipid peroksidasyonu

MALİGN PLEVRA SIVILARINDA SÜPEROKSİD DİSMUTAZ VE KATALAZ DÜZEYLERİNİN TANISAL DEĞERİ

**DIAGNOSTIC VALUE OF SUPEROXIDE DISMUTASE AND CATALASE IN MALIGNANT
PLEURAL EFFUSIONS**

Kürşat Uzun*, Faruk Özer, Osman Çağlayan***, Oktay İmecik****, Hüseyin Vural*******

Plevra sıvılarının transuda-eksuda ayırımında glutatyon peroksidaz enzim aktivitesinin tanısal değeri

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Amaç: Bu çalışmada plevra sıvısı serumundaki glutatyon peroksidaz (GSH-Px) enzim aktivitesinin transuda-eksuda ayırımındaki değerinin araştırılması amaçlanmıştır. **Yöntem:** Çalışmaya alınan 52 plörezili olgunun (34 erkek ve 18 kadın) Light kriterlerine göre 44'ü eksuda (%85), 8'i transuda (%15) vafındaydı. **Bulgular:** Plevra sıvısında GSH-Px eksudalı olgularda 5109 ± 869 U/L, transudalı olgularda 4766 ± 365 U/L olup aralarında istatistiksel açıdan fark yoktu. Plevra sıvısında GSH-Px'i 5500 U/L sınır değeri aldığımızda spesifite %87, sensitivite %36 olarak saptandı. Plevra sıvısı GSH-Px değerinin serum değerine oranı eksudalı olgularda 0.96 ± 0.04 , transudalı olgularda 0.88 ± 0.07 idi ve aralarında önemli bir fark yoktu. Plevra sıvısı/serum oranının 1.00 olması sınır değeri kabul edilirse spesifite %75, sensitivite %36 idi. **Sonuç:** Bu bulgular eksudalı olgularda oksidatif stresin ve buna bağlı olarak GSH-Px'in arttığını göstermektedir. GSH-Px değerinin 5500 U/L'den, plevra sıvısı/serum oranının 1.00'den fazla olması plörezinin eksuda olabileceğini ifade edebilir. Transuda-eksuda ayırımında GSH-Px enzim aktivite tayininin faydalı bir yöntem olamayacağı kanısına varıldı.

Anahtar kelimeler: Plevra sıvısı, antioksidan sistem, glutatyon peroksidaz

Tüberküloz Plörezilerde Plevra Sıvısı Reaktif Oksijen Metabolitlerinin Tanısal Değeri

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ÖZET

Tüberküloz plörezi de tanı, plevra sıvısında aside dirençli basil (ARB) aranması, kültür ve plevra biyopsisi yöntemleriyle konulmaktadır. Plevra hastalıklarında serbest radikallerin rolü tam olarak bilinmemektedir. Serbest radikaller normal metabolizmanın yan ürünü olarak oluşabildiği gibi infeksiyon, inflamasyon, karsinogenezis, ilaç ve diğer zararlı kimyasal maddelerin etkisiyle de oluşabilmektedir. Bu çalışmada tüberküloz plörezili olgularda reaktif oksijen metabolitlerinin (ROM) ayırıcı tanıdaki yeri araştırıldı.

Serum ROM düzeyleri değerlendirildiğinde, tüberküloz plörezilerde elde edilen değerler malign plörezi, parapnömonik plörezi ve sağlıklı bireylerin oluşturduğu kontrol grubunun serum ROM değerlerinden yüksek olup, bu farklılık istatistiksel olarak anlamlı düzeydeydi ($p<0.0001$, $p<0.05$, $p<0.0001$).

Plevra sıvısı ROM düzeyleri değerlendirildiğinde, tüberküloz plevra sıvısı ROM değerleri ile malign, parapnömonik plörezili gruplar arasında istatistiksel olarak anlamlı bir fark vardı ($p<0.0001$, $p<0.0001$).

Sonuç olarak, tüberküloz plörezili olguların plevra sıvılarında oksidatif stresin varlığını gösteren serbest oksijen radikallerinin, diğer plörezi nedenlerine göre daha fazla arttığı gözlenmiştir. Buna göre tüberküloz plörezi ayırıcı tanısında ROM'un tanısal değeri olabileceği sonucuna vardık.

Anahtar sözcükler: tüberküloz plörezi, reaktif oksijen metabolitleri

OXIDATIVE STRESS AND ANTIOXIDANT STATUS IN BRONCHOALVEOLAR LAVAGE FLUID, PLASMA AND ERYTHROCYTE OF CRITICALLY MIXED ILL WITH RESPIRATORY FAILURE

Sadık Büyükbaş¹, Kürşat Uzun², Elif Demirkapı¹, Kemal Başaralı¹

Table 3. The mean levels of oxidants and antioxidants parameters in exitus and survivor patients.

	Exitus	Survivor
MDAp, $\mu\text{mol/L}$	1.62 $\pm$ 0.37	1.59 $\pm$ 0.39
NOp, $\mu\text{M/L}$	53.7 $\pm$ 10.9	58.5 $\pm$ 9.9
SODp, U/ml	7.46 $\pm$ 0.73	6.28 $\pm$ 1.38
C vitp, mg/dl	0.39 $\pm$ 0.16	0.42 $\pm$ 0.2
Evitp, $\mu\text{g/dl}$	0.58 $\pm$ 0.17	0.65 $\pm$ 0.19
UAp, mg/dl	4.6 $\pm$ 1.5	5.8 $\pm$ 1.1
MDAe, nmol/gr Hgb	24.2 $\pm$ 6.5	27.7 $\pm$ 9.0
SODE, U/mg Hgb	3.39 $\pm$ 1.3	2.7 $\pm$ 0.4
GSH-Pxe, U/gr Hgb	88.5 $\pm$ 24.7	85.2 $\pm$ 9.4
MDAlv, $\mu\text{mol/L}$	1.29 $\pm$ 0.3	1.29 $\pm$ 0.2
NOlv, $\mu\text{M/L}$	44.5 $\pm$ 8.0	44.2 $\pm$ 9.7
SODlv, U/ml	6.8 $\pm$ 1.7	7.1 $\pm$ 2.4

p; plasma, e; erythrocyte, lv; lavage

Mekanik ventilasyona baęlı olarak gelişen diafragma disfonksiyonunda serum ve doku düzeyindeki oksidatif strese teofilinin etkisi

[The effect of theophylline on oxidative stress in serum and tissues in mechanical ventilation-induced diaphragm dysfunction]

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Nihal Bakırkalay Aydın¹,
Turgut Teke¹,
Sadık Büyükbaş²,
Kemal Başaralı²

Selçuk Üniversitesi, Meram Tıp Fakültesi, Göğüs Hastalıkları¹ ve Biyokimya² Anabilim Dalları, Konya

ÖZET

Amaç: Mekanik ventilasyona baęlı diafragma disfonksiyonunda (VBDD) oksidatif stresin rolü olduęu çeşitli çalışmalar ile gösterilmiştir. Bu çalışmada hayvan modelinde VBDD’unda diafragmatik ve sistemik oksidatif stresin rolünün ve teofilin uygulanmasının oksidatif stres üzerindeki etkisinin araştırılması planlanmıştır.

Gereç ve Yöntemler: Çalışmamızda 30 adet, sağlıklı erkek Sprague-Dawley cinsi sıçanlar kullanıldı. Sıçanlar 3 eşit gruba ayrıldı. Grup 1, Mekanik Ventilasyon (MV) uygulanmayan kontrol grubu; Grup 2, 24 saat süreyle MV uygulanan plasebo grubu; Grup 3, 24 saat süreyle MV ve teofilin uygulanan teofilin grubu olarak adlandırıldı. Her üç grupta diafragma, akciğer dokusu ve plazmada oksidatif stresi değerlendirmek için malondialdehit (MDA) ve nitrik oksit (NO) seviyeleri ile ksantin oksidaz (XO) ve superoksit dismutaz (SOD) aktiviteleri ölçüldü.

Bulgular: Kontrol grubuyla karşılaştırıldığında plasebo grubunda diafragmada SOD (0,01–0,07 U/mg) ve XO (0,61–1,76 U/g) aktiviteleri ile NO (0,05–0,14 µmol/g) seviyesinde; akciğerde XO (0,36–2,26 U/g) aktivitesinde; plazmada SOD (2,06–5,24 U/mL) ve XO (7,76–14,04 U/mL) aktiviteleri ile MDA (0,35–1,09 nmol/L) seviyesinde istatistiksel olarak anlamlılık gösteren artışlar mevcuttu ($p<0,05$). Plasebo grubuyla karşılaştırıldığında teofilin alan grupta diafragmada sadece SOD (0,096 U/mg) aktivitesindeki artış ($p<0,05$); akciğerde sadece XO (0,39 U/g) aktivitesindeki azalma ($p<0,001$); plazmada ise MDA (0,36 nmol/L) seviyesindeki azalma ($p<0,001$) ve NO (22,3–29,7 µmol/L) seviyelerindeki artış ($p<0,05$) anlamlılık gösteriyordu.

Sonuçlar: Bu çalışmada sıçanlarda MV uygulanmasına baęlı diafragmatik oksidatif strese akciğer ve sistemik oksidatif streslerinin de eşlik ettięi ve bu oksidatif hasarın baskın olarak XO yolaęı ile oluştugu gösterilmiştir. Ayrıca teofilin tedavisinin, oluşan bu oksidatif stresi SOD aktivitesini arttırıp, XO aktivitesini baskılayarak hafiflettięi ortaya konulmuştur. Ancak bu konuyla ilgili daha çok sayıda ve moleküler düzeyde hayvan ve insan çalışmalarına ihtiyaç vardır.

Çıkar Çatışması: Yazarların çıkar çatışması bulunmamaktadır.

Anahtar Kelimeler: Mekanik ventilasyon, solunum kasları, kas hasarı, oksidatif stres, teofilin

Kronik Obstrüktif Akciğer Hastalığında Hipoksi Göstergesi Olarak Serum Ürik Asit Düzeyi

Haluk Dülger ¹, Kürşat Uzun ², Bülent Özbay ², Reha Erkoç ³
Ahmet Durmuş ³

*Yüzüncü Yıl Üniversitesi Tıp Fakültesi Biyokimya ¹,
Göğüs Hastalıkları ² Anabilim Dalları ve Nefroloji ³ Bilim Dalı Van*

Tablo 1. KOAH tedavi öncesi-sonrası değerler (ort± SD).

	Tedavi öncesi	Tedavi sonrası	p değeri
Ürik asit (mg/dl)	8.69±2.94	6.82±2.88	0.015
FEV ₁ (L)	1.28±0.73	1.76±0.78	0.001
FEV ₁ /FVC (%)	62.5±24.5	63.12±24.2	0.972
PO ₂ (mmHg)	49.7±16.8	53.06±15.8	0.045
PCO ₂ (mmHg)	47.52±12	45.6±7.9	0.047
O ₂ Sat (%)	78.01±19.58	82.66±14.05	0.040

Oxidative Stress in Smokers and COPD

KOAH VE SİGARA İÇENLERDE OKSİDATİF STRES

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Summary

There are numerous reports of increased oxidative stress in smokers and in patients with COPD. Cigarette smoke contains abundant amounts of oxygen-based free radicals. In addition, many studies suggest that phagocytes in smokers release increased amounts of reactive oxygen species under certain conditions. The levels of lipid peroxidation products are increased in plasma of patients with acute exacerbations of COPD compared to healthy subjects. There is limited information on the lung antioxidant defences in smokers and COPD. Studies have shown that some antioxidants are decreased in COPD. Thus, in general, it appears that an imbalance between oxidants and antioxidants occurs in cigarette smokers that favours an excess oxidant stress and may play an important role in the pathogenesis of COPD.

Key Words: Oxidative stress, Smokers, COPD

T Klin J Med Sci 1999, 19:123-129

Özet

KOAH ve sigara içenlerde oksidatif stresin arttığını bildiren birçok çalışmalar vardır. Sigara dumanı sayısız oksijen kaynaklı radikaller içerir. Bununla beraber çoğu çalışmalar belirli durumlarda sigara içenlerin fagosit hücrelerinde serbest radikal üretiminde artma meydana geldiğini göstermişlerdir. Sağlıklı insanlar ile karşılaştırıldığında akut ataklı KOAH hastalarında lipid peroksidasyon ürün düzeyleri artmıştır. Sigara içen ve KOAH'lılarda akciğerlerdeki antioksidan savunma sisitemi hakkındaki bilgiler kısıtlıdır. Çalışmalar KOAH'da birkısım antioksidanların azaldığını göstermişlerdir. Böylece sigara içenlerde aşırı oksidan strese yol açan bir oksidan-antioksidan dengesizliği olduğu ve bunun da KOAH patogeneğinde önemli bir rol oynayabileceği düşünülebilir.

Anahtar Kelimeler: Oksidatif stres, Sigara içenler, KOAH

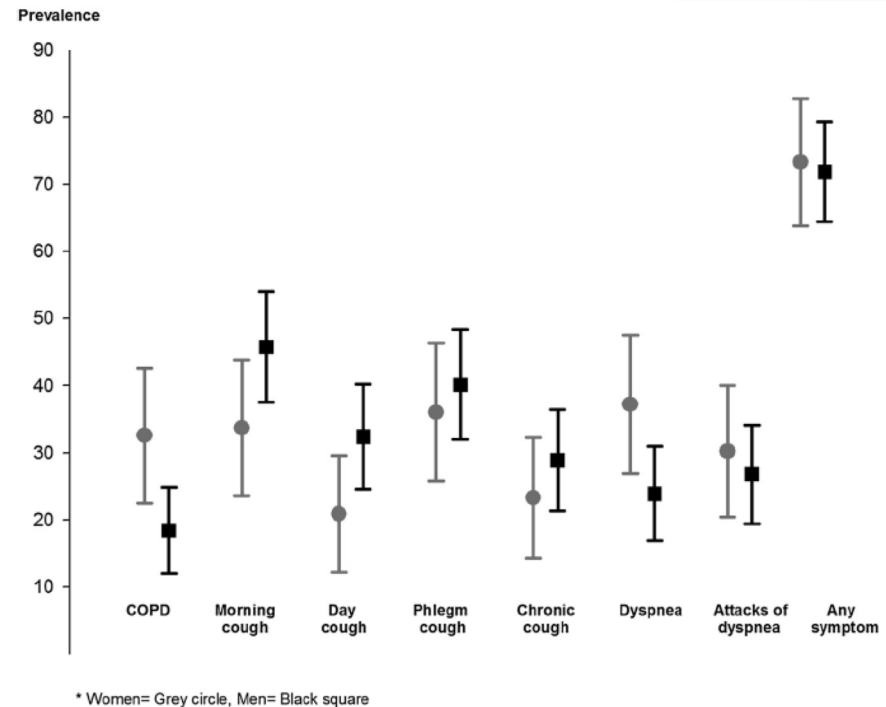
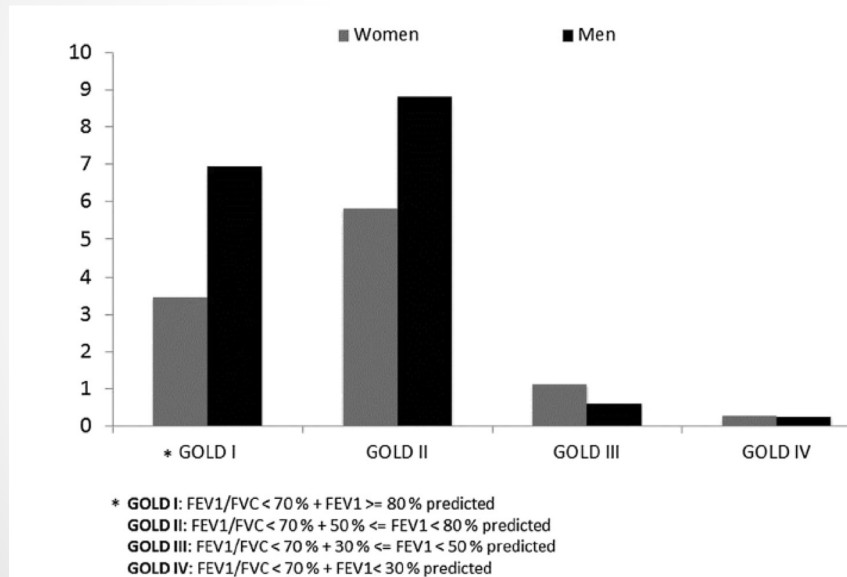
T Klin Tıp Bilimleri 1999, 19:123-129

KOAH

2002	2030
1. Ischaemic heart disease	1. Ischaemic heart disease
2. Cerebrovascular disease	2. Cerebrovascular disease
3. Lower respiratory infections	3. HIV/AIDS
4. HIV/AIDS	4. Chronic obstructive pulmonary disease
5. Chronic obstructive pulmonary disease	5. Lower respiratory infections
6. Perinatal conditions	6. Diabetes mellitus
7. Diarrhoeal disease	7. Trachea, bronchus, lung cancer
8. Tuberculosis	8. Road traffic accidents
9. Trachea, bronchus, lung cancer	9. Tuberculosis
10. Road traffic accidents	10. Perinatal conditions

Increased prevalence of chronic obstructive pulmonary disease in a general population

Marie Waatevik^{a,*}, Trude Duelien Skorge^b, Ernst Omenaas^{a,c},
Per Sigvald Bakke^{c,d}, Amund Gulsvik^{c,d}, Ane Johannessen^a



Ort.yaş 55 (K), 54 (E)

1996/97 2003/05

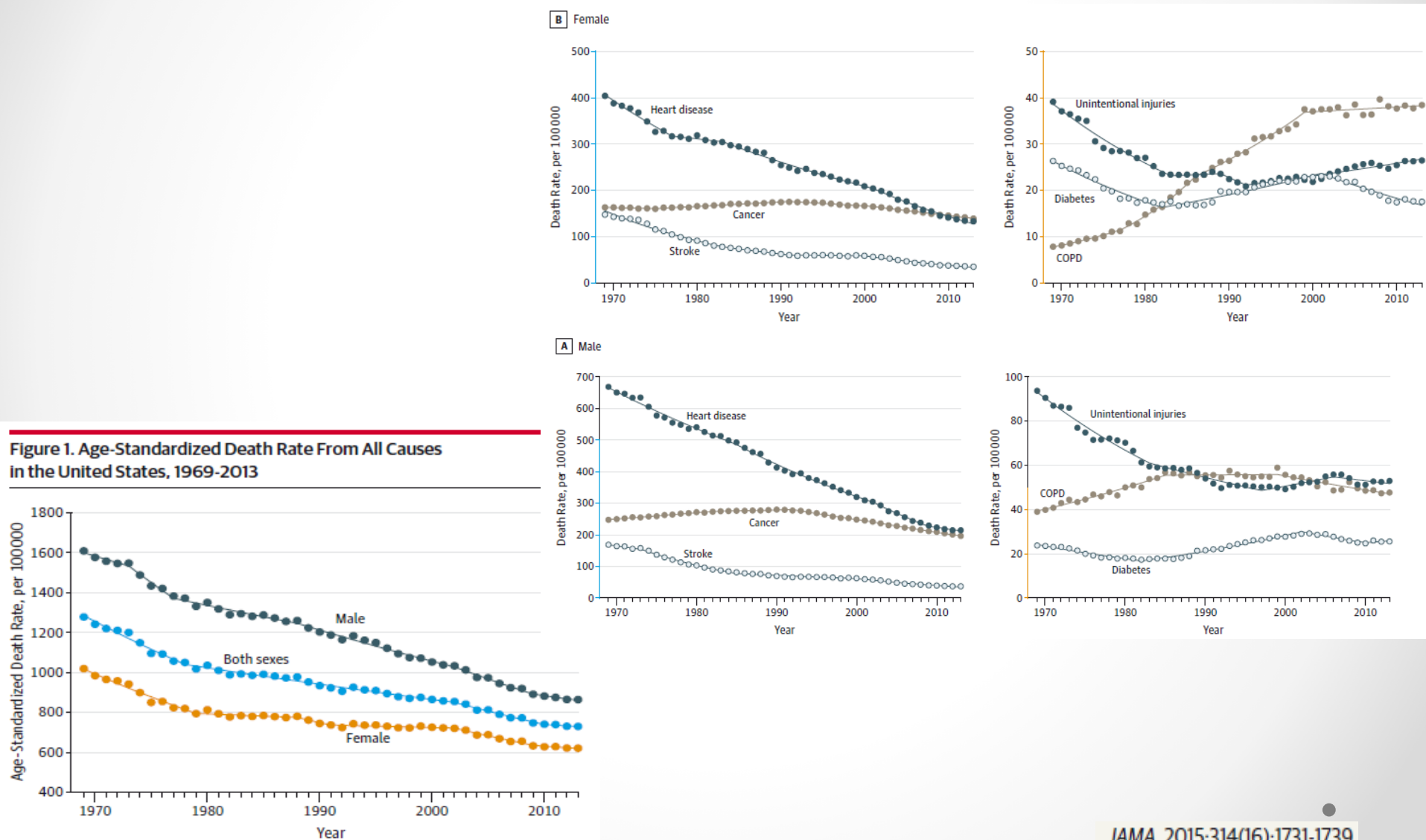
E: %17, K: %11

Kadınlarda %175 artış

Genelde %7 den %14 artış

Temporal Trends in Mortality in the United States, 1969-2013

Jiemin Ma, PhD, MHS; Elizabeth M. Ward, PhD; Rebecca L. Siegel, MPH; Ahmedin Jemal, DVM, PhD





Global Strategy for Diagnosis, Management and Prevention of COPD

KOAH Tanım

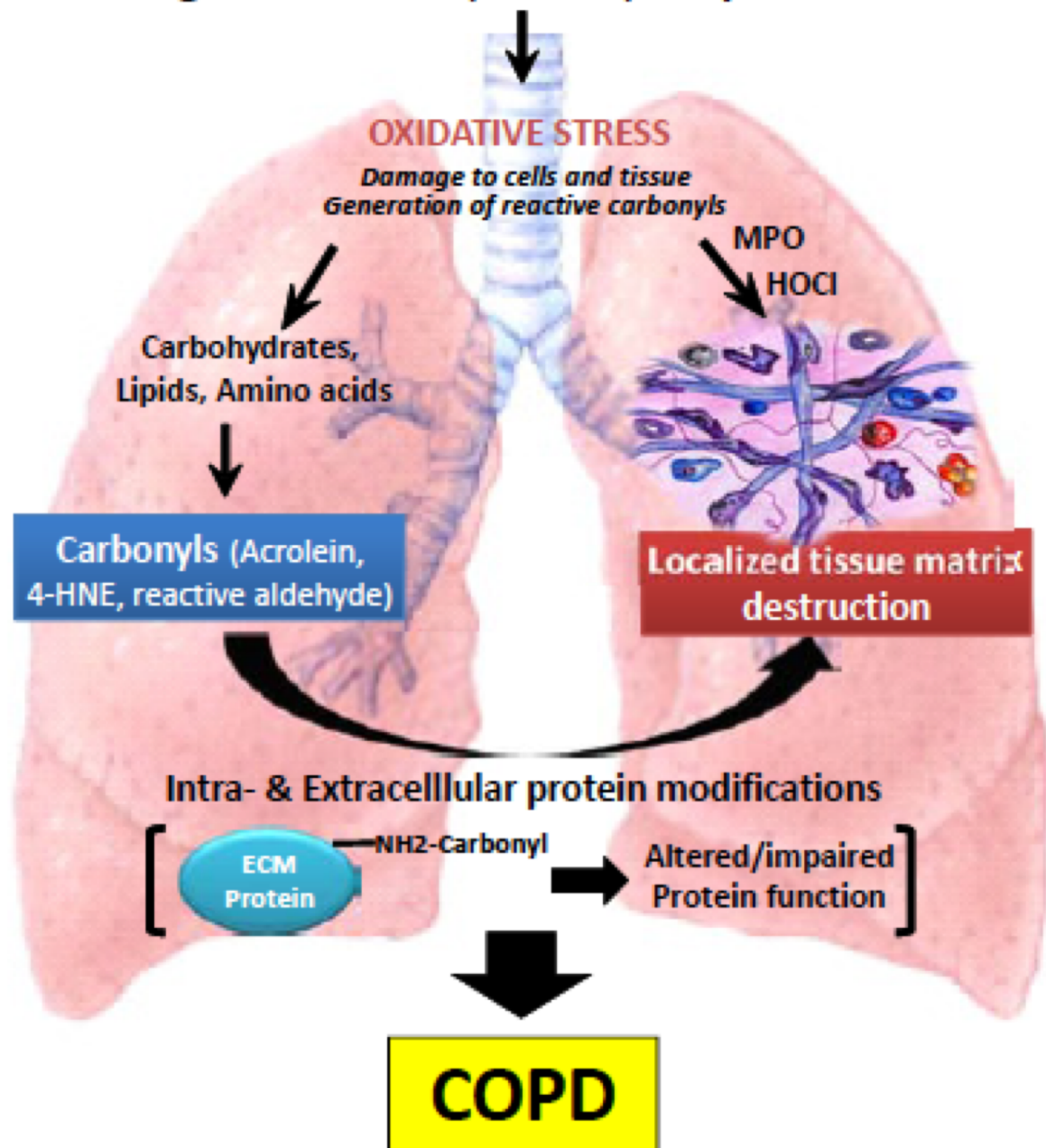
- KOAH önlenabilir ve tedavi edilebilir yaygın bir hastalıktır
- Kalıcı havayolu kısıtlaması
 - Progresiv
 - Zararlı partikül ve gazlara akciğerlerdeki havayollarındaki kronik inflamasyon
- Atak ve ek hastalıklar ile

Sigara

Sigarada 4000 adet zehirli madde vardır



Cigarette smoke, Ozone, Air pollution

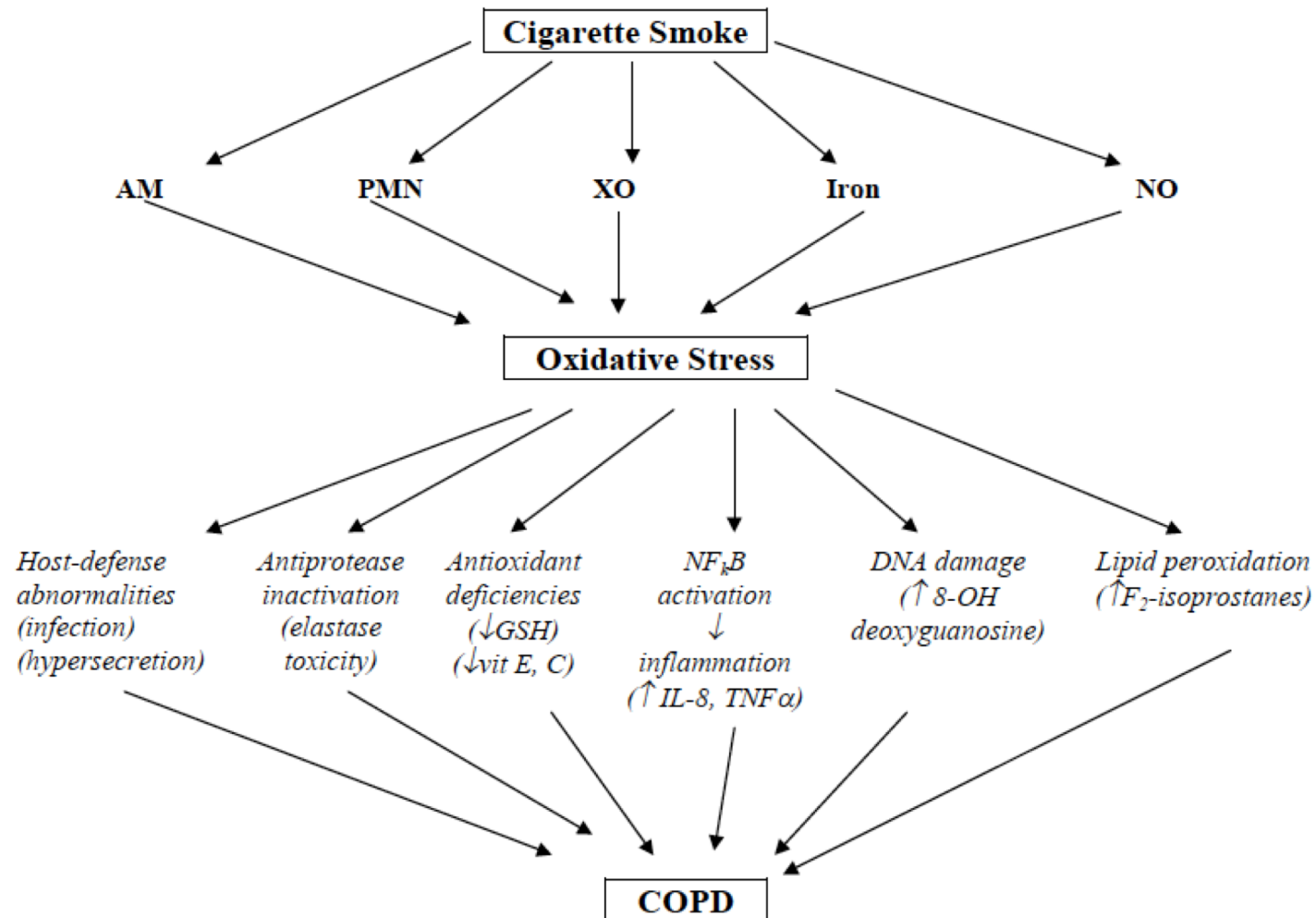


Oxidative Stress in Smokers and COPD

KOAH VE SİGARA İÇENLERDE OKSİDATİF STRES

Kürşat UZUN*

*Dept. of Chest Diseases and Tuberculosis, Medical School of Yüzüncü Yıl University, Van, TURKEY



KOAH GELİŞİMİ

**İnhale edilen
Zararlı etkenler**



İnflamasyon



Koruyucu
mekanizmalar



Tamir mekanizmaları

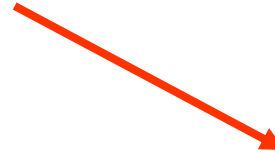
Akciğerde zedelenme



**Hava yolu daralması ve
peribronşiyal fibrozis
(Küçük hava yolu
hastalığı)**

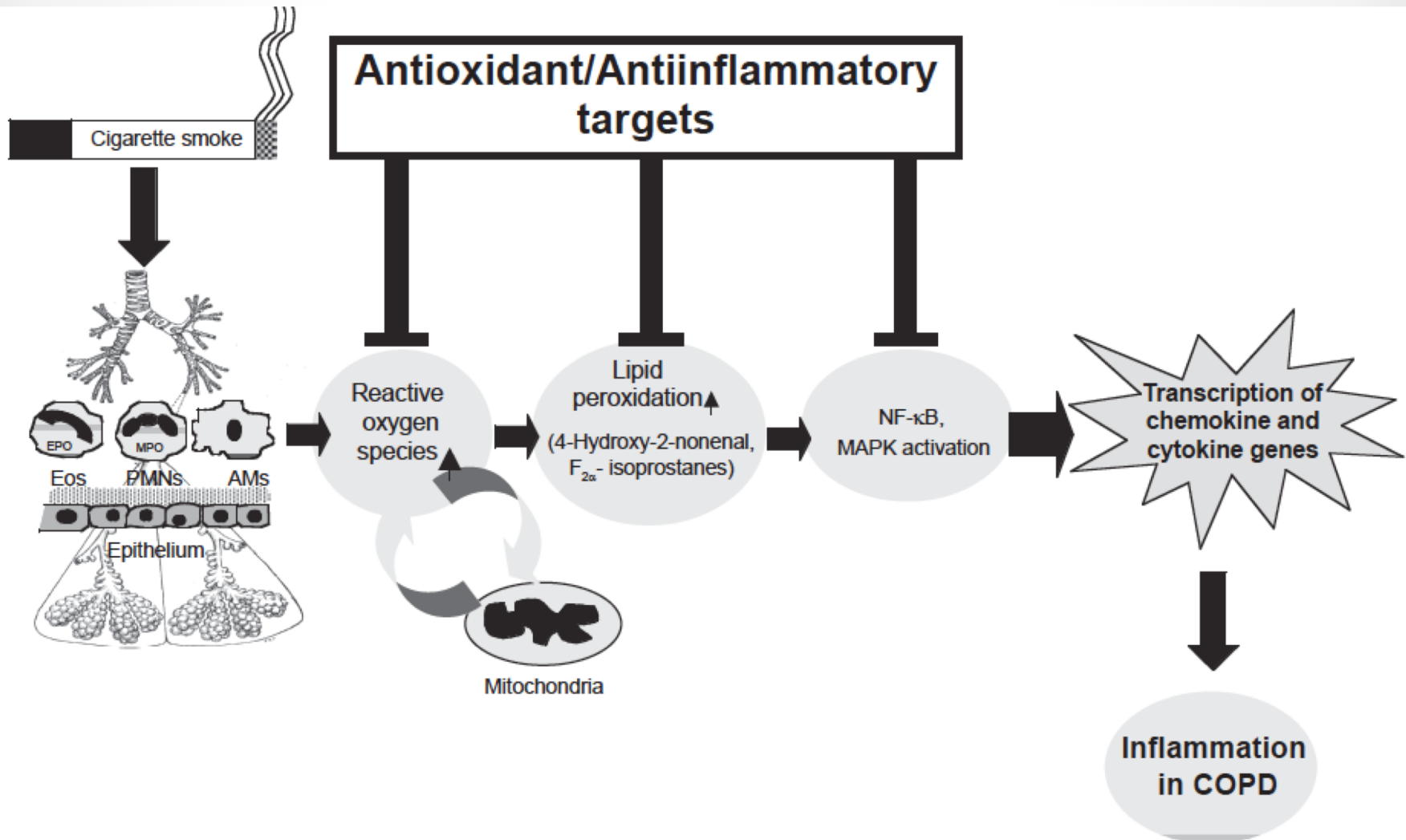


**Parankim yıkımı
(Amfizem)**



**Mukus
hipersekresyonu
(Kronik bronşit)**

Antioxidant therapies in COPD



Antioksidanlar

Enzimatik ve Non-enzimatik

- SOD
- GSH-peroksidaz
- Katalaz

- Albumin
- Bilirubin
- Ceruloplasmin
- Haptoglobulin
- Hemopexin
- Pyruvate
- Sulphydryl groups
- Transferrin
- Uric acid

Sentetik

- Thiol içerenler
 - N-acetyl-L-cysteine, N-acetylcystein, glutathione esters, thioredoxin, procysteine, carbocysteine, erdosteine, N-isobutyrylcysteine
- Antioxidant vitaminler
 - vitamin A, E, C, β -carotene, CoQ10
- Polifenoller
 - curcumin, resveratrol, quercetin, and green tea catechins)



Therapeutic Options: Other Pharmacologic Treatments

Alpha-1 antitrypsin augmentation therapy: not recommended for patients with COPD that is unrelated to the genetic deficiency.

Mucolytics: Patients with viscous sputum may benefit from mucolytics; overall benefits are very small.

Antitussives: Not recommended.

Vasodilators: Nitric oxide is contraindicated in stable COPD. The use of endothelium-modulating agents for the treatment of pulmonary hypertension associated with COPD is not recommended.

Diagnosis and Management of Cough

Executive Summary

ACCP Evidence-Based Clinical Practice Guidelines

*Cough Suppressant and Pharmacologic Protussive Therapy*³²

13. In patients with bronchitis, hypertonic saline solution and erdosteine are recommended on a short-term basis to increase cough clearance. Level of evidence, good; benefit, substantial; grade of recommendation, A

Antioxidant therapies in COPD

Irfan Rahman

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Medical Center, Rochester, NY, USA

Abstract: Oxidative stress is an important feature in the pathogenesis of COPD. Targeting oxidative stress with antioxidants or boosting the endogenous levels of antioxidants is likely to be beneficial in the treatment of COPD. Antioxidant agents such as thiol molecules (glutathione and mucolytic drugs, such as N-acetyl-L-cysteine and N-acetylcysteine), dietary polyphenols (curcumin, resveratrol, green tea, catechins/quercetin), erdosteine, and carbocysteine lysine salt, all have been reported to control nuclear factor-kappaB (NF- κ B) activation, regulation of glutathione biosynthesis genes, chromatin remodeling, and hence inflammatory gene expression. Specific spin traps such as α -phenyl-N-tert-butyl nitrone, a catalytic antioxidant (ECSOD mimetic), porphyrins (AEOL 10150 and AEOL 10113), and a superoxide dismutase mimetic M40419 have also been reported to inhibit cigarette smoke-induced inflammatory responses in vivo. Since a variety of oxidants, free radicals, and aldehydes are implicated in the pathogenesis of COPD, it is possible that therapeutic administration of multiple antioxidants will be effective in the treatment of COPD. Various approaches to enhance lung antioxidant capacity and clinical trials of antioxidant compounds in COPD are discussed.

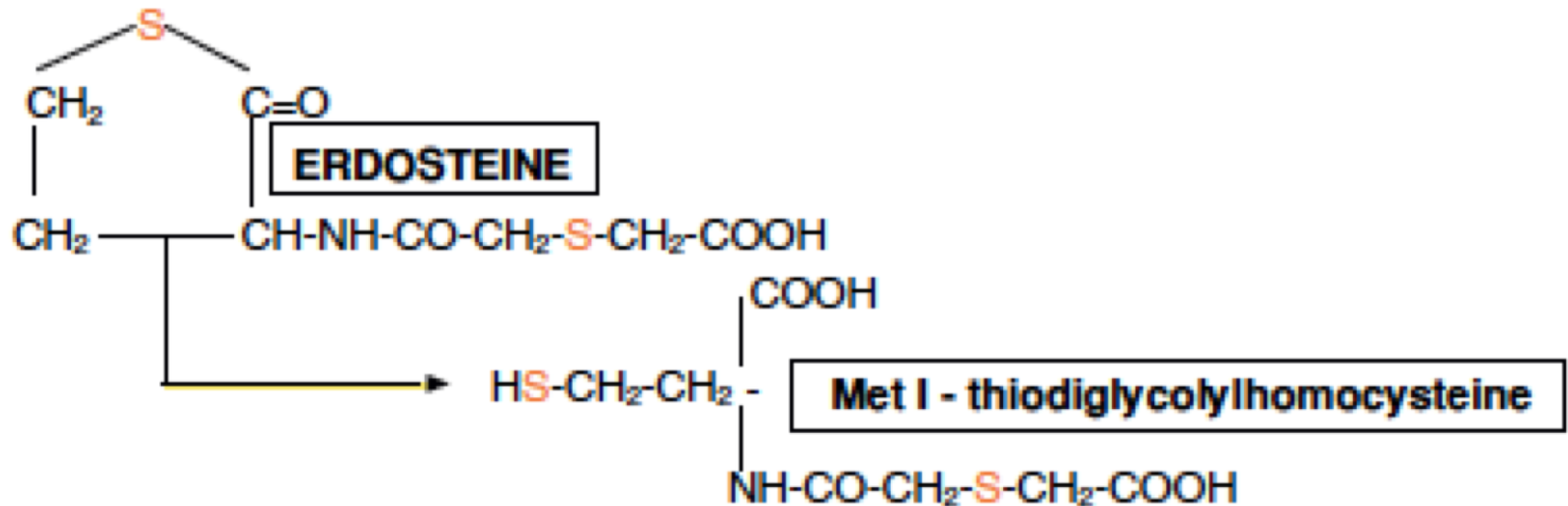
Keywords: reactive oxygen species, lipid peroxides, polyphenols, glutathione, antioxidants, NF- κ B, corticosteroids, chronic obstructive pulmonary disease, lungs

TABLE 1 Clinical trials conducted for the efficacy of antioxidants in smokers and chronic obstructive pulmonary disease (COPD)

Trial name	Antioxidant used	Aim of study	Disease	Outcome	First author [ref.]
BRONCUS	NAC	Effect of NAC on FEV ₁	COPD	No effect on decline in FEV ₁ . A reduction in lung over inflation was observed in patients with severe COPD and exacerbation rate in patients who are not treated with inhaled glucocorticoids	DECRAMER [174], DECRAMER [175]
Systematic Cochrane review of 23 randomised controlled trials	2 months of oral NAC therapy	Effect of NAC and antibiotics on number of days of disability	COPD	Significant reduction in days of disability (0.65 day·patient ⁻¹ ·month ⁻¹) and 29% reduction in exacerbations. No difference in lung function	POOLE [176], POOLE [177]
Systematic Cochrane review of randomised, controlled trials of 11 out of 39 retrieved trials	NAC	Used a validated score to evaluate the quality of each study	COPD	Nine trials showed prevention of exacerbation and five addressed improvement of symptoms compared with 34.6% of patients receiving placebo	STEY [178]
A meta-analysis of published trials	NAC	To assess the possible prophylactic benefit of prolonged treatment	COPD	23% decrease in number of acute exacerbations	GRANDJEAN [172]
	NAC, 600 mg <i>b.i.d.</i> for 12 months	Effect of NAC on H ₂ O ₂ and TBARS in EBC	COPD	No change in TBARS reduce H ₂ O ₂ levels	KASIELSKI [179], DE BENEDETTO [180]
MORGEN study	Diet rich in polyphenols/bioflavonoids <i>i.e.</i> catechin, flavonol and flavone 58 mg·day ⁻¹	Effect on FEV ₁ , chronic cough, breathlessness and chronic phlegm	COPD	Positively associated with decline in FEV ₁ and inversely associated with chronic cough and breathlessness, but not chronic phlegm	TABAK [181]
European countries*	Diet rich in fruits, vegetables and fish	Effect on 20-yr COPD mortality	COPD	A 24% lower COPD mortality risk	WALDA [182]
EQUALIFE Study	Vectrine-erdosteine, thiol compound, 300 mg <i>b.i.d.</i> for 8 months	Effect exacerbation rate, hospitalisation, lung function and quality of life in 124 patients	COPD	Fewer exacerbations and fewer days spent in hospital. No loss of lung function and significant improvement in health-related quality of life	MORETTI [183]

Kimyasal yapısı

- Erdosteine



Review

An overview of erdosteine antioxidant activity in experimental research

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Accepted 11 December 2006

Abstract

Erdosteine was introduced in the market as a mucolytic agent for chronic pulmonary diseases more than 10 years ago. The drug contains two blocked sulphhydryl groups one of which, after hepatic metabolization and opening of the thiolactone ring, becomes available both for the mucolytic and free radical scavenging and antioxidant activity too.

There are several experimental evidences which support the protective effect of erdosteine in acute injury induced by a variety of pharmacological or noxious agents, mediated by products of oxidative stress. Experimental data in animal assigned to receive the noxious agent evidence that co-treatment with erdosteine increases the tissue antioxidant enzyme activities such as superoxide dismutase, catalase and glutathione peroxidase, compared with the toxic agent alone; meanwhile erdosteine decreases the tissue level of nitric oxide, xanthine oxidase, which catalyze oxygen-free radical production. In summary, erdosteine prevents the accumulation of free oxygen radicals when their production is accelerated and increases antioxidant cellular protective mechanisms. The final result is a protective effect on tissues which reduces lipid peroxidation, neutrophil infiltration or cell apoptosis mediated by noxious agents.

Recent positive clinical trials in humans seem to fulfill the impressive promises that theory and experimental research have put forward.

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Keywords: Erdosteine; Oxidative stress; Antioxidant treatment; Pulmonary disease

Effects of aminoguanidine and antioxidant erdosteine on bleomycin-induced lung fibrosis in rats

Zeki Yildirim^{a,*}, Yusuf Turkoz^b, Mahir Kotuk^a, Ferah Armutcu^c, Ahmet Gurel^c, Mustafa Iraz^d, Suleyman Ozen^e, Ismet Aydogdu^f, Omer Akyol^{b,1}

Abstract

Reactive oxygen and nitrogen species have been implicated in the pathogenesis of bleomycin-induced lung fibrosis. The effects of aminoguanidine and erdosteine on the bleomycin-induced lung fibrosis were evaluated in rats. The animals were placed into five groups: Vehicle + vehicle, vehicle + bleomycin (2.5 U/kg), bleomycin + aminoguanidine (200 mg/kg), bleomycin + erdosteine (10 mg/kg), and bleomycin + erdosteine + aminoguanidine. Bleomycin administration resulted in prominent lung fibrosis as measured by lung hydroxyproline content and lung histology, which is completely prevented by erdosteine and aminoguanidine. A strong staining for nitro tyrosine antibody in lung tissue and increased levels of lung NO were found in bleomycin group, that were significantly reduced by aminoguanidine and erdosteine. Aminoguanidine and erdosteine significantly prevented depletion of superoxide dismutase and glutathione peroxidase and elevated myeloperoxidase activities, malondialdehyde level in lung tissue produced by bleomycin. Data presented here indicate that aminoguanidine and erdosteine prevented bleomycin-induced lung fibrosis and that nitric oxide mediated tyrosine nitration of proteins plays a significant role in the pathogenesis of bleomycin-induced lung fibrosis. Also our data suggest that antifibrotic affect of antioxidants may be due to their inhibitory effect on nitric oxide generation in this model.

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Keywords: Bleomycin; Lung fibrosis; Nitric oxide; Aminoguanidin; Erdosteine

The effects of erdosteine on the activities of some metabolic enzymes during cisplatin-induced nephrotoxicity in rats

H. Ramazan Yilmaz^{a,*}, Mustafa Iraz^b, Sadik Sogut^c, Huseyin Ozyurt^d,
Zeki Yildirim^e, Omer Akyol^f, Serdar Gergerlioglu^g

Abstract

Cisplatin is one of the widely used chemotherapeutic agents. One of the major side effects of the drug is renal toxicity. The aims of the presented study was (1) to investigate the effect of cisplatin on some renal metabolic enzyme activities such as hexokinase (HK), glucose-6-phosphate dehydrogenase (G6PD), lactate dehydrogenase (LDH), and malate dehydrogenase (MDH) in an experimental model of acute renal failure and (2) to examine the protective role of erdosteine, an expectorant agent which has also antioxidant properties on cisplatin-induced nephrotoxicity and the enzyme activities mentioned above. Female Wistar albino rats were divided into three groups: sham operation group ($n = 6$), cisplatin group ($n = 9$), erdosteine + cisplatin group ($n = 8$). All the chemicals used were applied intraperitoneally. Hexokinase, G6PD, LDH, and MDH activities were determined in the kidney supernatant at the end of the surgical procedures. Spectrophotometric methods were used to determine the activities of above-mentioned enzymes in the kidney tissue.

Hexokinase and G6PD activities were found to be increased in cisplatin group compared to control group. G6PD activities were found to be decreased in erdosteine + cisplatin group compared to cisplatin group. There were minimal changes in LDH and MDH activities of the two study groups compared with the control group. The results obtained suggested that the glucose metabolizing metabolic pathways of renal tissue were partially affected from cisplatin toxicity and erdosteine have some protective effects on these enzyme activities.

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Keywords: Erdosteine; Cisplatin; Hexokinase; Glucose-6-phosphate dehydrogenase; Lactate dehydrogenase; Malate dehydrogenase; Kidney

Erdosteine prevents bleomycin-induced pulmonary fibrosis in rats

Sadik Sogut^a, Huseyin Ozyurt^b, Ferah Armutcu^c, Levent Kart^d, Mustafa Iraz^e, Omer Akyol^f,
Suleyman Ozen^g, Suleyman Kaplan^h, Ismail Temel^f, Zeki Yildirim^{i,*}

Abstract

Oxidative stress plays an important role in the pathogenesis of idiopathic pulmonary fibrosis. Therefore, erdosteine, an antioxidant, is expected to have an inhibitor potential against the disease. Rats were given one dose of bleomycin in pulmonary fibrosis groups and saline in controls. The first dose of oral erdosteine (10 mg/kg/day) was given 2 days before the bleomycin injection to achieve the plateau level in blood and continued until killing. At day 14, fibrotic changes were evaluated, using Aschoff's criteria and lung hydroxyproline content. Bleomycin produced a fivefold increase in fibrosis score that was decreased by 87% by erdosteine ($P>0.001$) and almost twofold increases in hydroxyproline content which were completely prevented by erdosteine. Myeloperoxidase activities and MDA levels, which were significantly higher in the bleomycin group, were then significantly attenuated by erdosteine. These results revealed that oral erdosteine may prevent the development of acute pulmonary inflammation caused by bleomycin injection via the repression of neutrophil accumulation and lipid peroxidation, resulting in the inhibition of subsequent lung fibrosis.

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Keywords: Erdosteine; Bleomycin; Lung fibrosis; Myeloperoxidase; Hydroxyproline

Oral erdosteine administration attenuates cisplatin-induced renal tubular damage in rats

Zeki Yildirim^{a,*}, Sadik Sogut^b, Ersan Odaci^c, Mustafa Iraz^d,
Huseyin Ozyurt^b, Mahir Kotuk^a, Omer Akyol^b

Abstract

The effect of oral erdosteine on tissue malondialdehyde (MDA) and nitric oxide (NO) levels, and catalase (CAT), glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) activities are investigated in the cisplatin model of acute renal failure in rats. A single dose of cisplatin caused kidney damage manifested by kidney histology as well as increases in plasma creatinine and blood urea nitrogen (BUN) levels. Treatment with free radical scavenger erdosteine attenuated increases in plasma creatinine and BUN, and tissue MDA and NO levels, and provided a histologically-proven protection against cisplatin-induced acute renal failure. Erdosteine also reduced depletion in the tissue CAT, GSH-Px, and SOD activities. These results show that erdosteine may be a promising drug for protection against cisplatin-induced nephrotoxicity. However, further studies with different doses of erdosteine are warranted for clarifying the issue.

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Keywords: Erdosteine; Cisplatin nephrotoxicity; Nitric oxide; Free radicals

Attenuation of bleomycin-induced lung fibrosis by oral sulfhydryl containing antioxidants in rats: erdosteine and *N*-acetylcysteine

Zeki Yildirim^{a,*}, Mahir Kotuk^a, Mustafa Iraz^b, Irfan Kuku^c, Ramazan Ulu^c,
Ferah Armutcu^d, Suleyman Ozen^e

Abstract

Antioxidant therapy may be useful in diseases with impaired oxidant antioxidant balance such as lung fibrosis. The effects of sulfhydryl-containing antioxidant agents *N*-acetylcysteine (NAC) and erdosteine on the bleomycin-induced lung fibrosis were compared in rats. The animals were divided into four groups: Vehicle+vehicle, vehicle+bleomycin (2.5 U/kg), bleomycin+erdosteine (10 mg/kg), and bleomycin+NAC (3 mmol/kg). Bleomycin administration resulted in prominent lung fibrosis as measured by lung hydroxyproline content and lung histology which is almost completely prevented by erdosteine and NAC. Hydroxyproline content was 18.7 ± 3.5 and 11.2 ± 0.6 mg/g dried tissue in bleomycin and saline treated rats, respectively ($P < 0.001$), and this level was 11.3 ± 1.2 and 13.8 ± 1.2 mg/g dried tissue in erdosteine and NAC pretreated, respectively. Erdosteine and NAC significantly reduced depletion of glutathione peroxidase, and prevented increases in myeloperoxidase activities, nitric oxide, and malondialdehyde levels in lung tissue produced by bleomycin. Data presented here indicate that erdosteine and NAC similarly prevented bleomycin-induced lung fibrosis and their antioxidant effects were also similar in this experiment.

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Keywords: Bleomycin; Lung fibrosis; *N*-acetylcysteine; Erdosteine; Rats

Erdostin Etki Mekanizmaları

- *Mukolitik aktivite*
- Balgam viskozitesinde azalma
- Mukosiliyer transport ve klirensde artma
- *Antibakteriyel aktivite*
- Havayolu mukozasına bakterinin invazyonunu engellemesi
- Balgamda antibiyotik konsantrasyonunda artma
- *Antioxidan ve antiinflamatuvar etki*
- BAL GSH de artma
- Lipid peroksidasyon ve ROS üretiminde azalma
- Bronş sekresyonlarında proinflamatuvar sitokinlerde azalma

Antioxidants and Mucolytics in COPD Management: When (if ever) and in Whom?

Georgios Hillas¹, Sofia Nikolakopoulou¹, Sabah Hussain² and Theodoros Vassilakopoulos^{1,*}

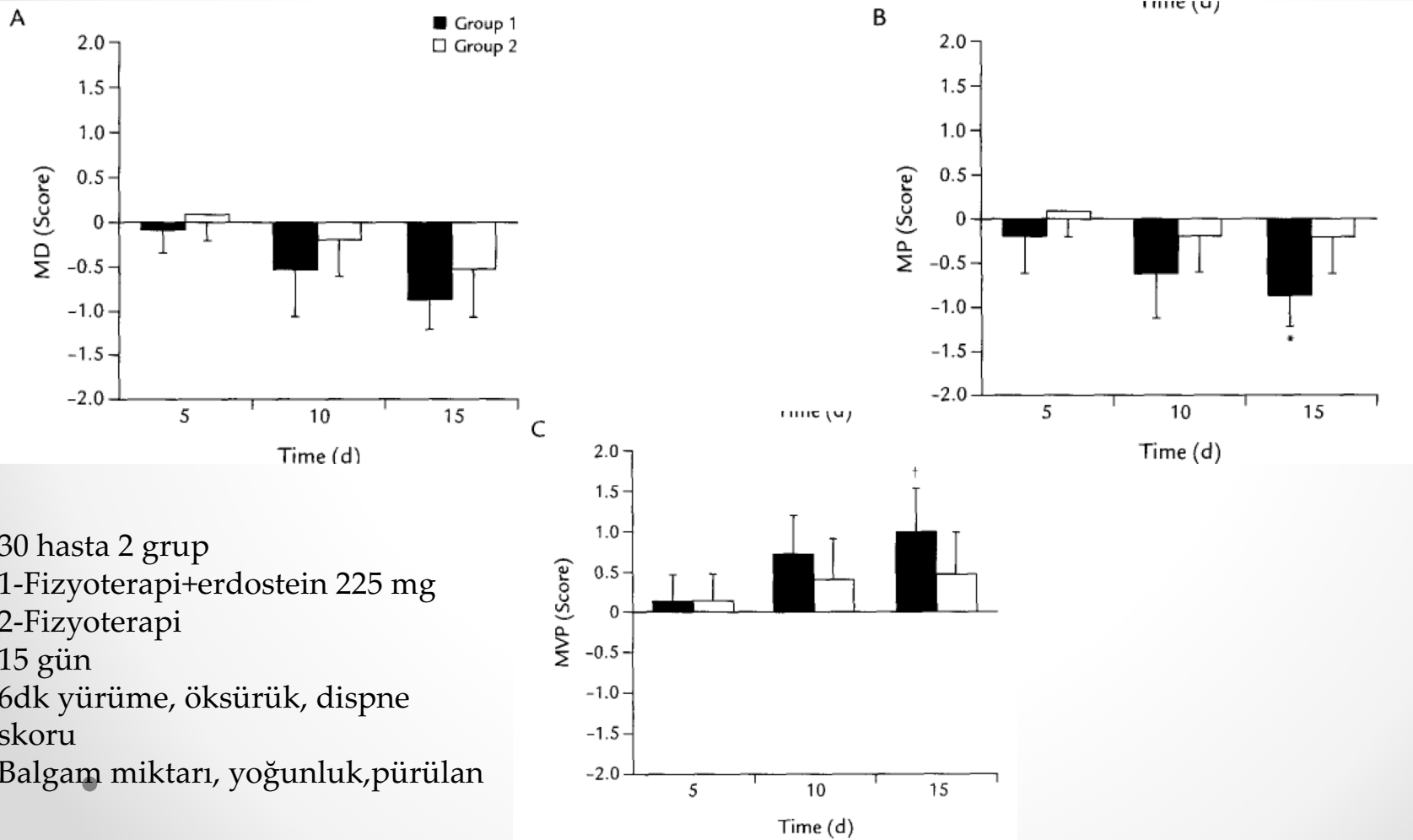
Erdosteine

Erdosteine, a thiol compound and a mucolytic agent which decreases the sputum viscoelastic properties. It also acts as an antioxidant through free radical scavenging, [111, 112]. It has also been shown to have an anti-infective effects through its effects in reducing bacterial adhesiveness [113]. The anti-inflammatory capacity of erdosteine has also been proved by studies documenting significant reduction in the levels of pro-inflammatory eicosanoids in the blood of COPD patients [114]. 'EQUALIFE', a randomized, placebo-controlled clinical trial provided evidence that oral admini-

In summary, there is evidence that oral administration of erdosteine improves symptoms and the quality of life of COPD patients and can reduce acute exacerbation and hospitalization rate. A clinical trial on the combination of steroids and erdosteine in patients with COPD is clearly needed

Effectiveness of Erdosteine in Elderly Patients with Bronchiectasis and Hypersecretion: A 15-Day, Prospective, Parallel, Open-Label, Pilot Study

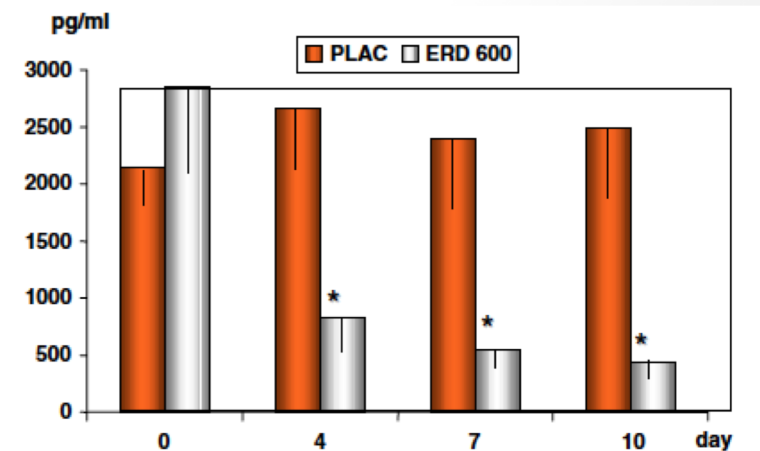
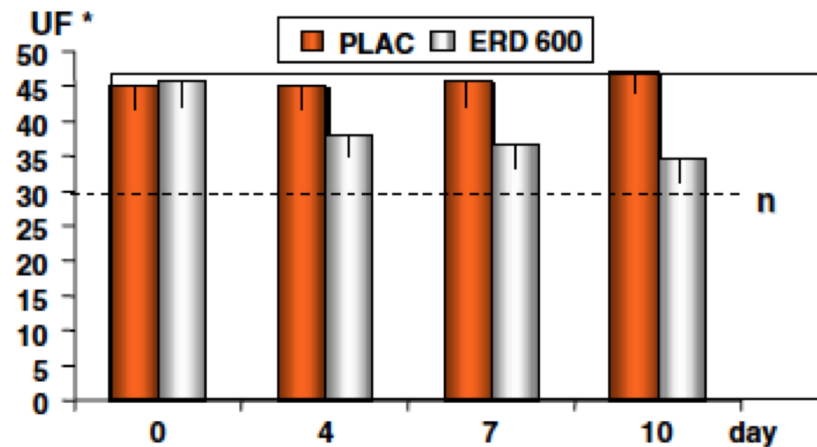
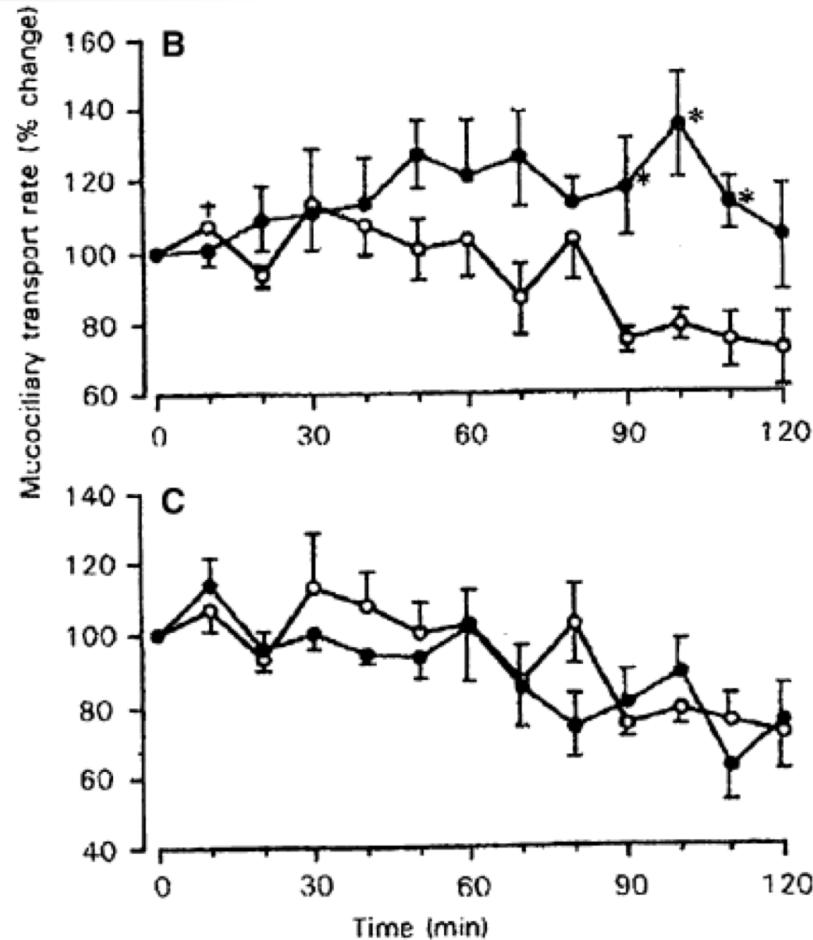
Ernesto Crisafulli, MD¹; Orietta Coletti, MD¹; Stefania Costi, RT²; Emanuela Zanasi, MD¹; Cristina Lorenzi, RT¹; Sasa Lucic, MD¹; Leonardo M. Fabbri, MD²; Marco Bertini, MD³; and Enrico M. Clini, MD^{1,2}



30 hasta 2 grup
1-Fizyoterapi+erdosteine 225 mg
2-Fizyoterapi
15 gün
6dk yürüme, öksürük, dispne
skoru
Balgam miktarı, yoğunluk,pürülan

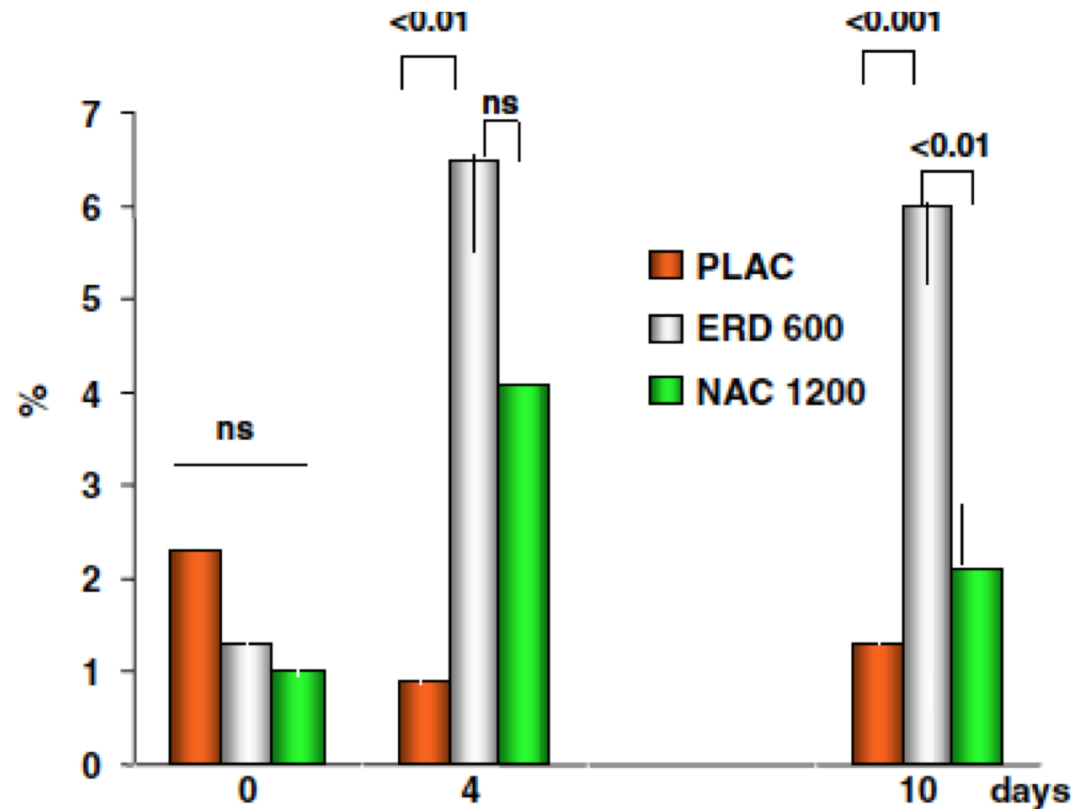
Erdosteine: Antitussive and Anti-inflammatory Effects

Roberto W. Dal Negro



Erdosteine: Antitussive and Anti-inflammatory Effects

Roberto W. Dal Negro

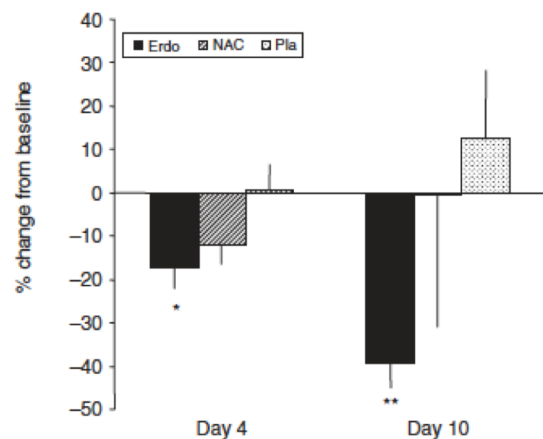


Erdosteine enhances airway response to salbutamol in patients with mild-to-moderate COPD

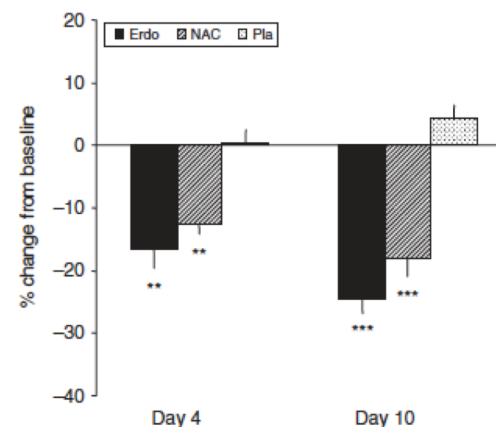
Therapeutic Advances in Respiratory Disease

(2008) 2(5) 271-277

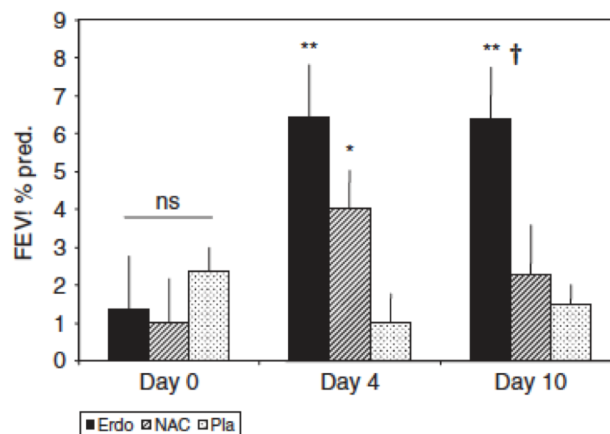
Roberto Dal Negro, Maria Visconti, Fiorenza Trevisan, Stefano Bertacco, Claudio Micheletto and Silvia Tognella



FEV₁ response (% pred.) after salbutamol



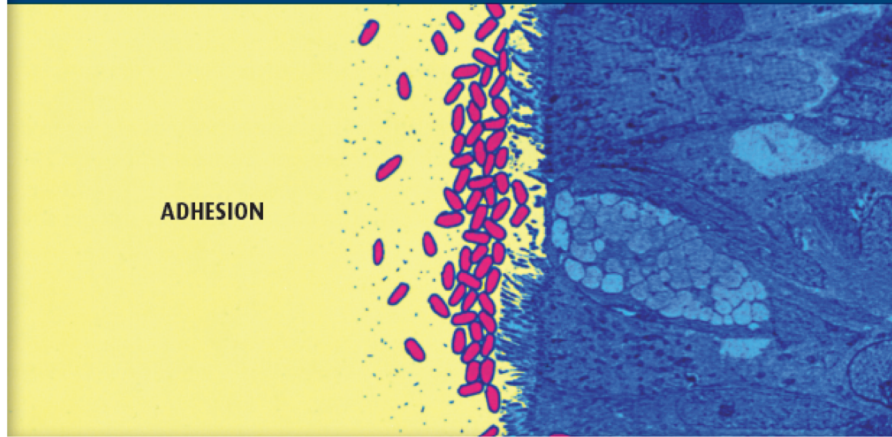
Reduction of ROS concentrations



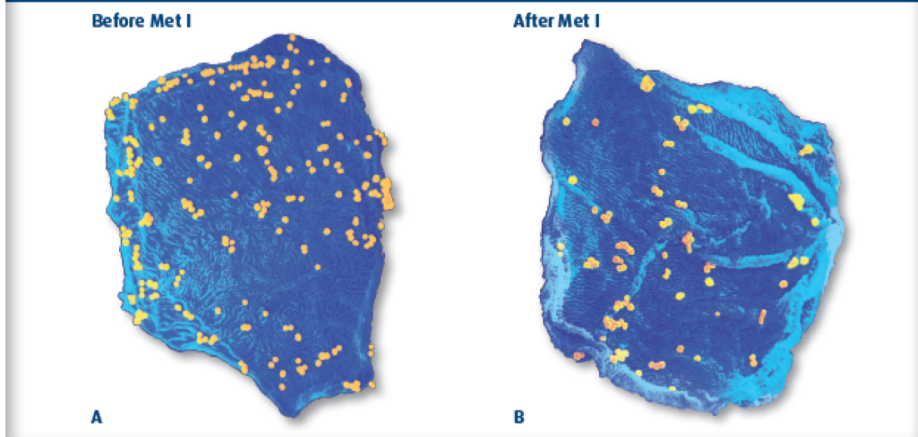
Reduction of 8-isoprostane

Antibakteriyel etki

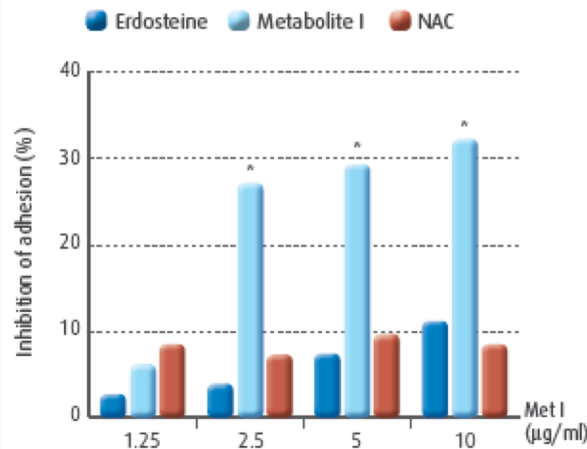
Bacterial adhesion to mucosal cells¹⁵



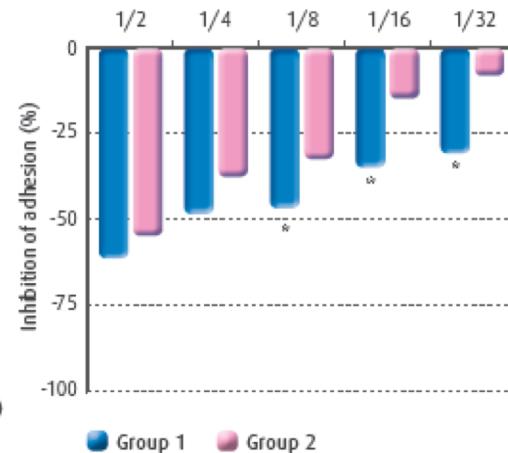
Inhibition of *Staphylococcus aureus* adhesion to buccal epithelial cells¹³



Inhibition of *Staphylococcus aureus* adhesion to human mucosal cells^{13,16}



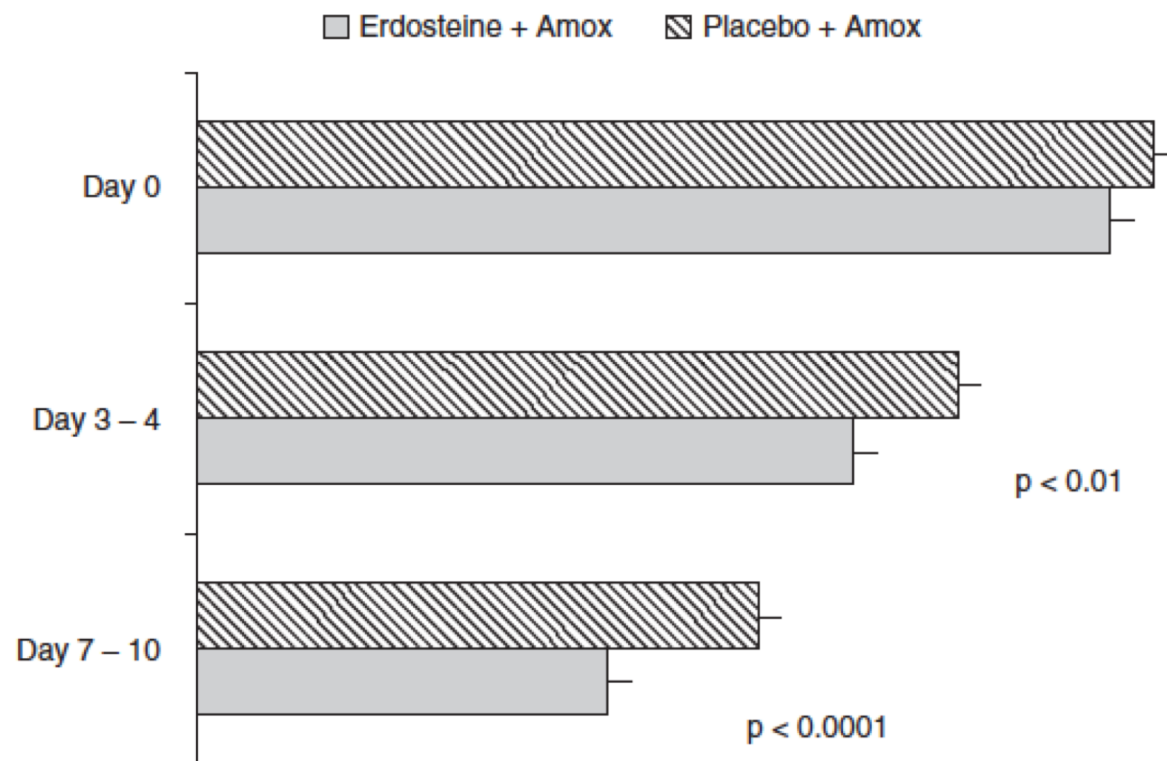
A



B

Evaluation of efficacy and safety of erdosteine in patients affected by chronic bronchitis during an infective exacerbation phase and receiving amoxycillin as basic treatment (ECOBES, European Chronic Obstructive Bronchitis Erdosteine Study)

C.F. MARCHIONI¹, J.M. POLU², A. TAYTARD³, T. HANARD⁴, G. NOSEDA⁵ and C. MANCINI⁶



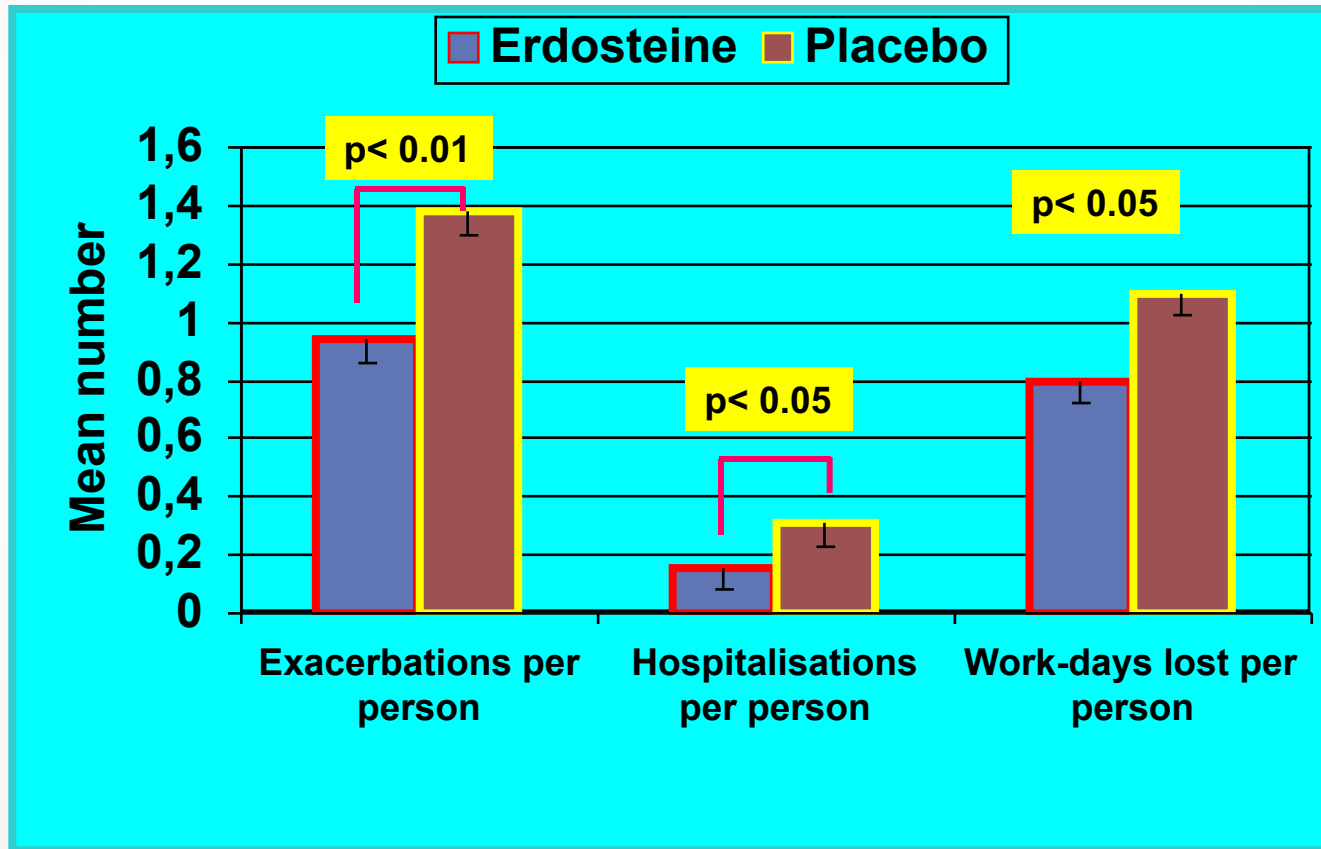
The effect of long-term treatment with erdosteine on chronic obstructive pulmonary disease: The EQUALIFE study

*Moretti M., Bottrighi P., Dallari R., Da Porto R., Dolcetti A., Grandi P., Garuti G., Guffanti E., Roversi P., De Gugliemo M., Potena A.
For the EQUALIFE Study Group*

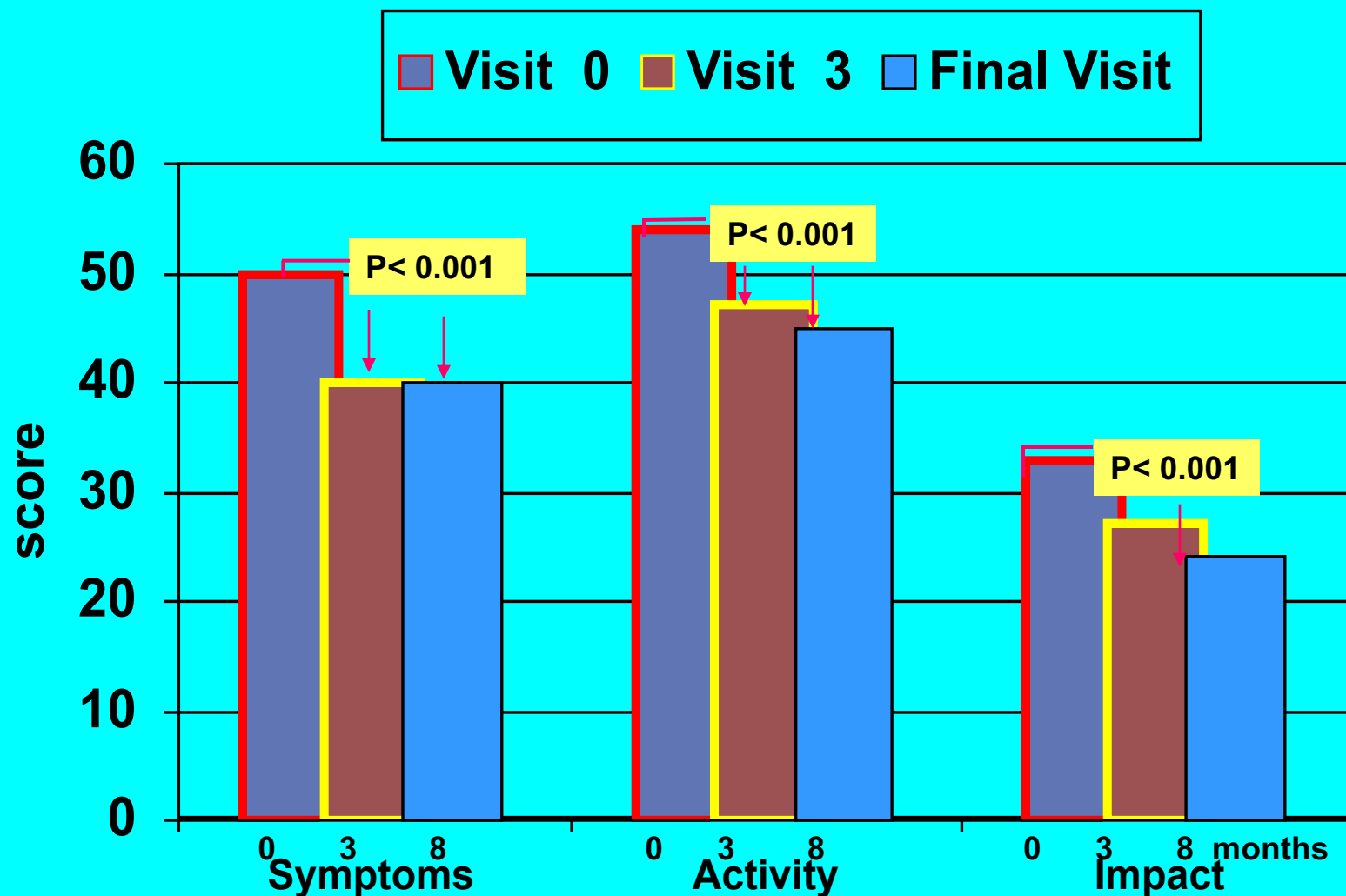
Characteristics	Erdosteine	Placebo
Patients (n)	79	76
Age (yrs)	67.4 (8.3)	67.5 (8.3)
Male (%)	84.8	75.0
FEV1 % pred	59.4 (7.2)	59.0 (5.1)

Data are presented as mean (SD) or numbers where indicated

Ataklar, Hastaneye yatış ve and İş kaybı



Erdosteine grubunda SGRQ Anket



The therapeutic efficacy of erdosteine in the treatment of chronic obstructive bronchitis: a meta-analysis of individual patient data

M. Cazzola ^{a,*}, I. Floriani ^b, C.P. Page ^c

Table 1
Main characteristics of RCTs included in the meta-analysis.

Ref.	Study design	Patient N			Study Population		Schedule Erdosteine	Schedule Comparator
		Randomised/ Analysed	Dropouts (E / C)	Median Age, yr./ Proportion Male, %	Diagnosis at inclusion	Concomitant medication		
Erdosteine vs placebo								
Ricevuti [14]	DB, CT	24/24	0/0	57.0/42	Acute infective exacerbation of chronic bronchitis (amoxicillin-sensitive bacteria isolated from sputum)	Amoxicillin 500 mg tid	300 mg TID	Placebo ^a
Voisin [40]	MC, DB, RCT	88/82	4 / 2	57.5 / 74	Stable chronic obstructive bronchitis (FEV ₁ /FVC at least 10% below normal theoretical value)	Not available	300 mg BID	Placebo ^a
Hotzinger [15]	DB, RCT	40/40	0 / 0	49.0 / 75	Hypersecretory infective bronchitis (acute bronchitis or relapses of chronic bronchitis)	Co-trimoxazole 160 + 800 mg bid	300 mg TID	Placebo ^a
Bisetti [39]	DB, RCT	28/27	0 / 1	62.0 / 68	Acute exacerbation of chronic bronchitis	Antibiotics Xanthines, β ₂ -agonists	300 mg BID	Placebo ^a
Marchioni [11]	MC, DB, RCT	237/226	6 / 5	66.0 / 76	Acute exacerbation of chronic obstructive bronchitis (amoxicillin-sensitive bacteria isolated from sputum; FEV ₁ /FVC at least 10% below normal theoretical value)	Amoxicillin 500 mg tid Xanthines, β ₂ -agonists	300 mg BID	Placebo ^a
Aubier [12]	MC, DB, RCT	170/166	1 / 3	59.0 / 58	Stable chronic obstructive bronchitis (FEV ₁ /FVC at least 10% below normal theoretical value)	Xanthines, β ₂ -agonists	300 mg BID	Placebo ^a

The therapeutic efficacy of erdosteine in the treatment of chronic obstructive bronchitis: a meta-analysis of individual patient data

M. Cazzola ^{a,*}, I. Floriani ^b, C.P. Page ^c

Erdosteine vs mucolytics

Marchioni [43]	DB, RCT	30/30	0/0	64.5/93	Acute exacerbation of chronic bronchitis	Antibiotics Xanthines, β_2 -agonists, steroids	300 mg BID	Sobrerol 200 mg BID
Scarpazza [44]	DB, RCT	30/27	1/2	64.0/43	Acute exacerbation of chronic bronchitis	Antibiotics Xanthines, β_2 -agonists	150 mg TID	Sobrerol 100 mg TID
Fumagalli [45]	DB, RCT	30/30	0/0	65.0/53	Acute or chronic exacerbated bronchitis	Antibiotics Xanthines, β_2 -agonists, steroids	300 mg BID	Ambroxol 30 mg BID
Ginesu [16]	SB, CT	30 / 30	0/0	62.5/100	Bronchopulmonary diseases characterized by expectoration and cough	Antibiotics Xanthines, β_2 -agonists	150 mg TID	Ambroxol 30 mg TID
Tellings [38]	SB, RCT	30/30	0/0	67.0/100	Acute exacerbation of chronic bronchitis	Bacampicillin 800 mg bid	300 mg BID	Ambroxol 30 mg TID
Materazzi [46]	DB, RCT	40/40	0/0	66.0/50	Acute exacerbation of chronic bronchitis	Amoxicillin 1000 mg bid Xanthines	300 mg BID	N-Acetylcysteine 300 mg BID
Zanasi [17]	DB, RCT	50/50	0/0	58.0/62	Acute exacerbation of chronic bronchitis	Parenteral antibiotics	225 mg TID	N-Acetylcysteine 200 mg TID
Franco [18]	SB, RCT	24/24	0/0	66.5/83	Chronic bronchitis requiring mucus-fluidifying treatment	Antibiotics Xanthines, β_2 -agonists, steroids	300 mg TID	Carbocysteine 750 mg TID
Arnaud [13]	MC, DB, RCT	195/187	5/3	61.0/73	Acute exacerbation of chronic obstructive bronchitis requiring antibiotic treatment (FEV ₁ /FVC at least 10% below normal theoretical value)	Antibiotics Xanthines, β_2 -agonists, steroids	300 mg TID	N-Acetylcysteine 200 mg TID

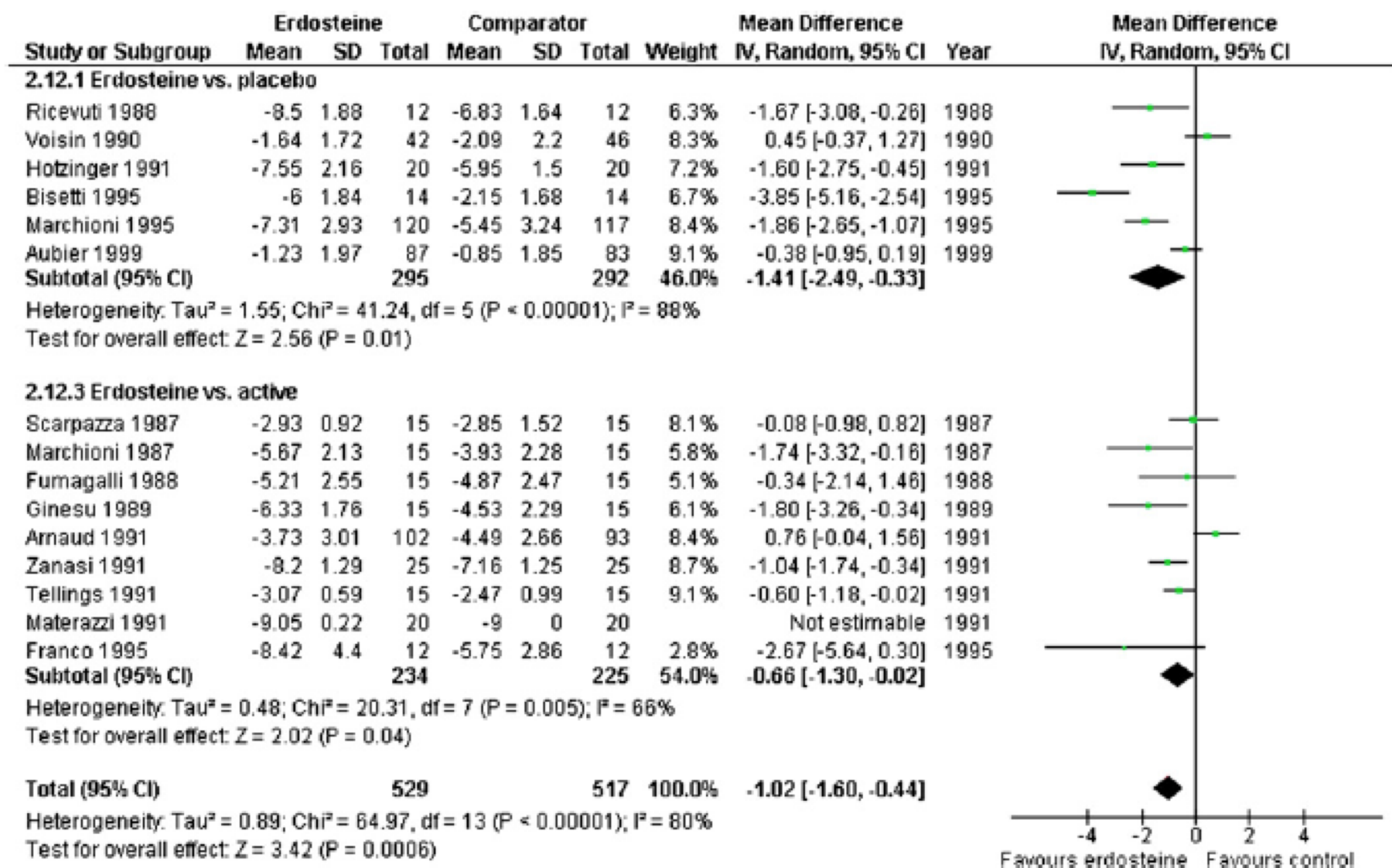


Fig. 2. Comparison of erdosteine vs placebo and other mucolytics. Outcome: cumulative global efficacy index (cGEI).

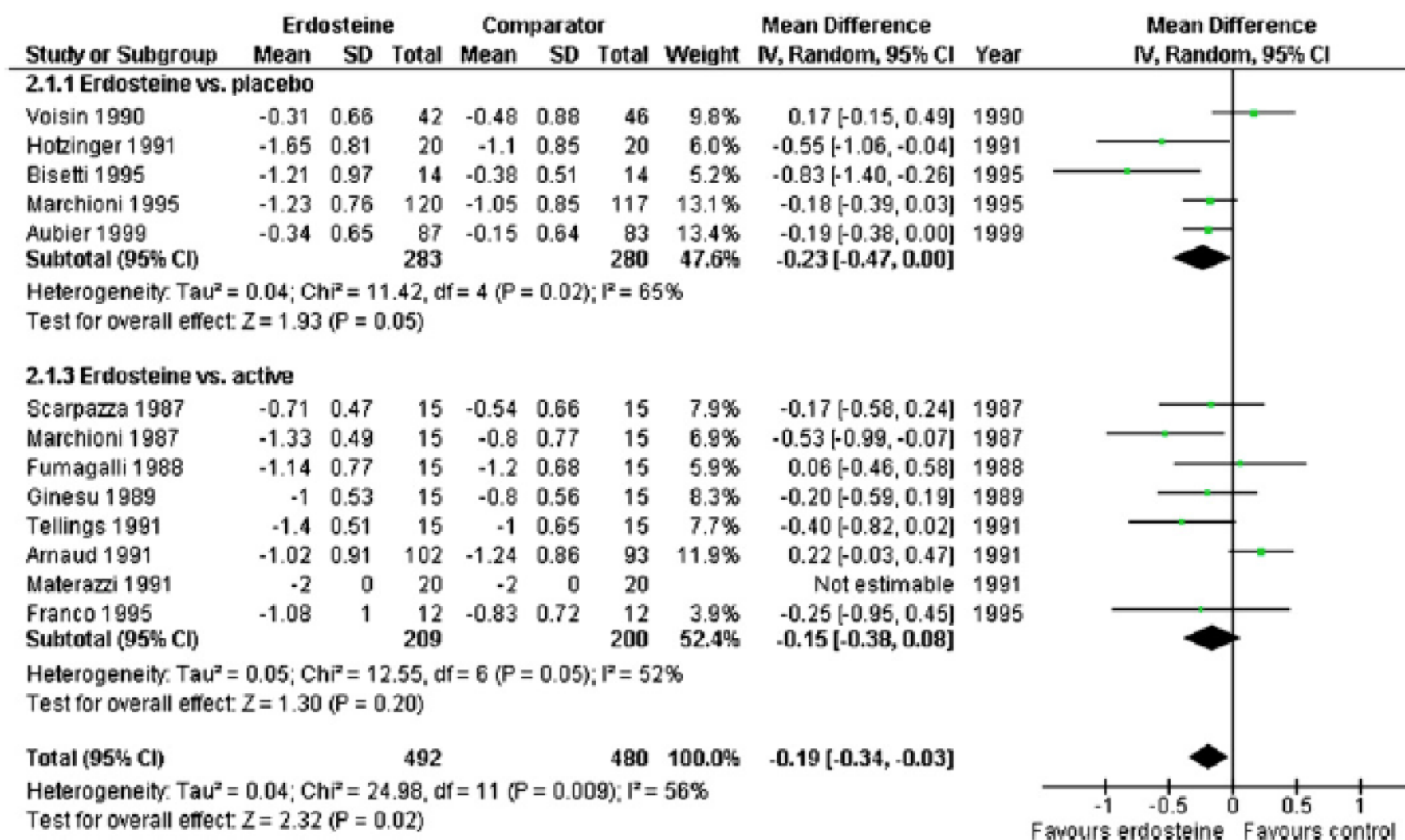


Fig. 3. Comparison of erdosteine vs placebo and other mucolytics. Outcome: cough frequency.

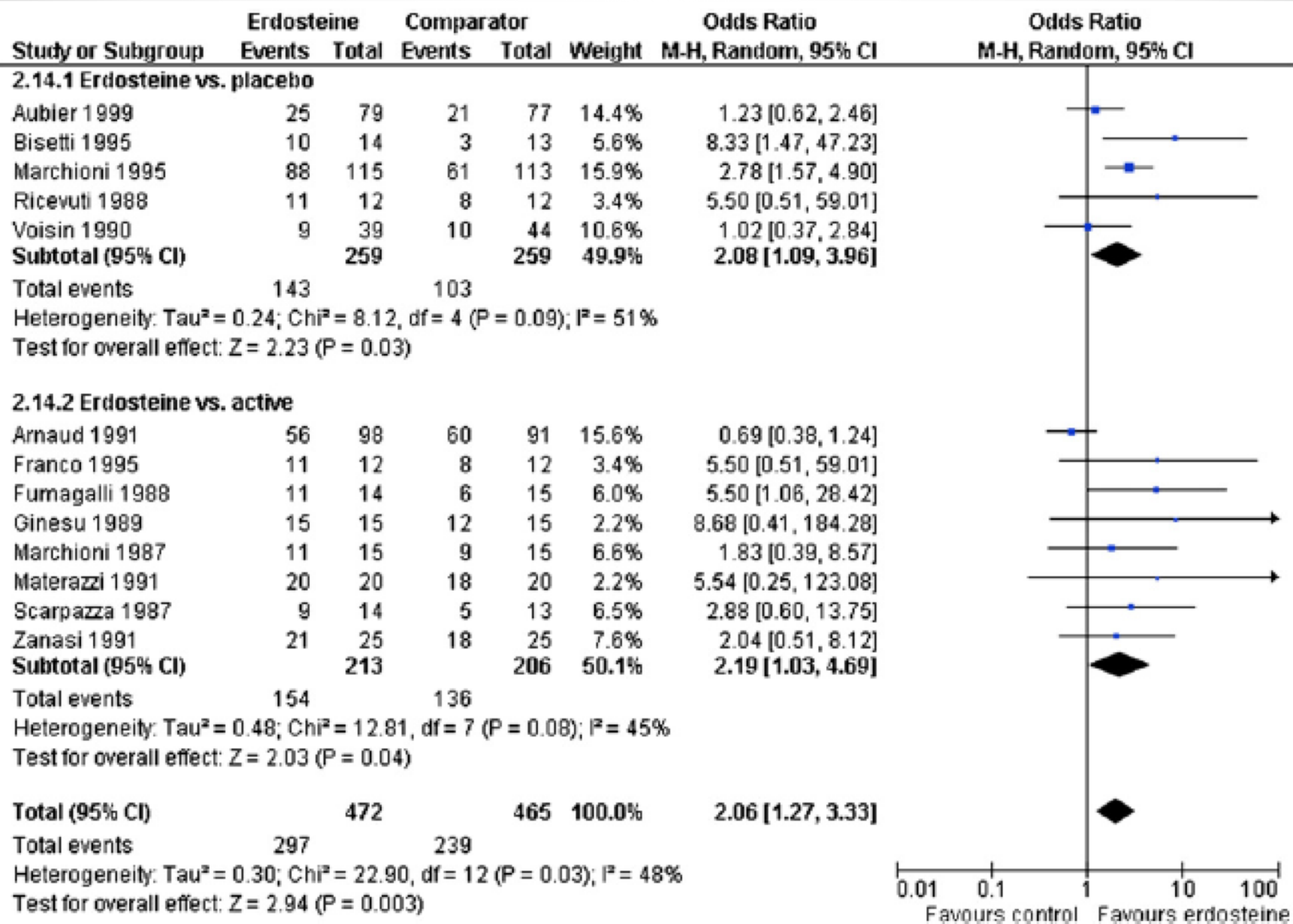
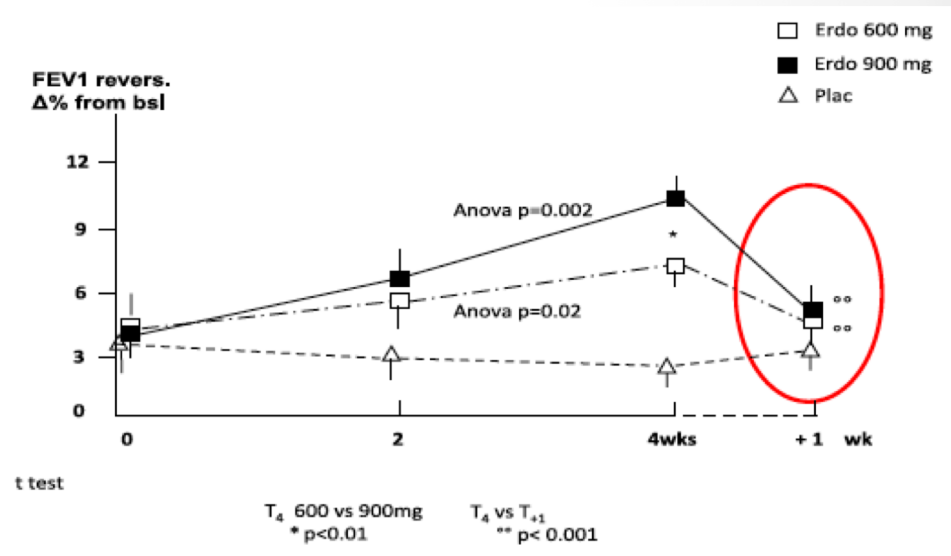
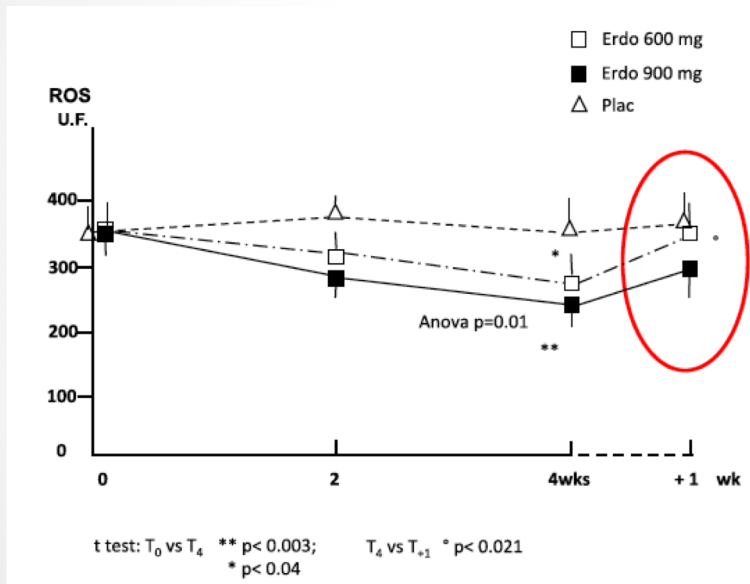


Fig. 5. Treatment success in patients treated with erdosteine vs placebo and other mucolytics.

Efficacy of erdosteine 900 versus 600 mg/day in reducing oxidative stress in patients with COPD exacerbations: Results of a double blind, placebo-controlled trial

R.W. Dal Negro ^{a,*}, M. Visconti ^b, P. Turco ^c



Efficacy and safety of erdosteine in COPD: Results of a 12-month prospective, multinational study (RESTORE study)

ERS-2015

Roberto W. Dal Negro, Martin Iversen, Peter M.A. Calverly

Amaç: antioksidan, antiinflamatuvar, antibakteriyel etki

Atak süresi, sistemik steroid ve antibiyotik kullanımı

12 ay süreli bir çalışma, multisenter (47 merkez, 10 ülke) ülke

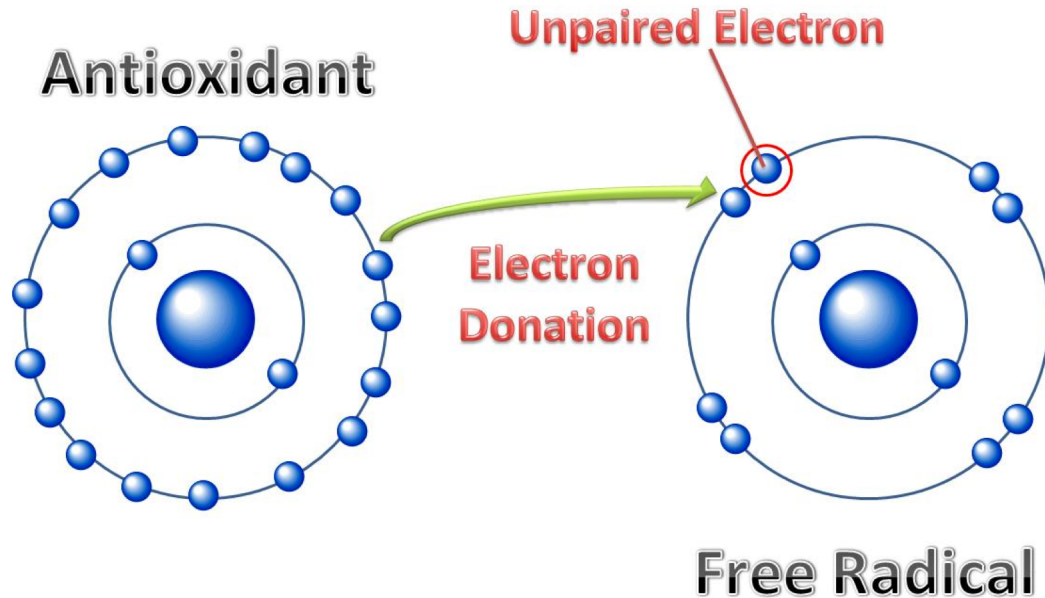
Methods: Randomize, çift kör plasebo kontrollü, paralel grup, 40-80 yaş GOLD II, III KOAH hastaları 300 mg 2x1 cap erdosteine

	Erdosteine	Placebo		p value
AECOPD rate (n)	615	744	-17.33%	
AECOPD duration (m. days x exacerbation)	4.37	7.82	-44.1%	p<0.002
Use of steroids (days)	1.604	2.184	-26.5%	p<0.002
Use of antibiotics (days)	2.654	3.362	-21.1%	p<0.05

Conclusions: E reduced rate and duration of AECOPDs and decreased steroid/antibiotic use, confirming its anti-inflammatory and bacterial anti-adhesive properties with an excellent safety profile.

Sonuç

- Oksidatif stres var
 - O zaman
- Antioksidan tedavi
 - Ne zaman, Nasıl, Ne kadar
- Kanıta dayalı tıp ölçüsünde olmalı



Teşekkürler

