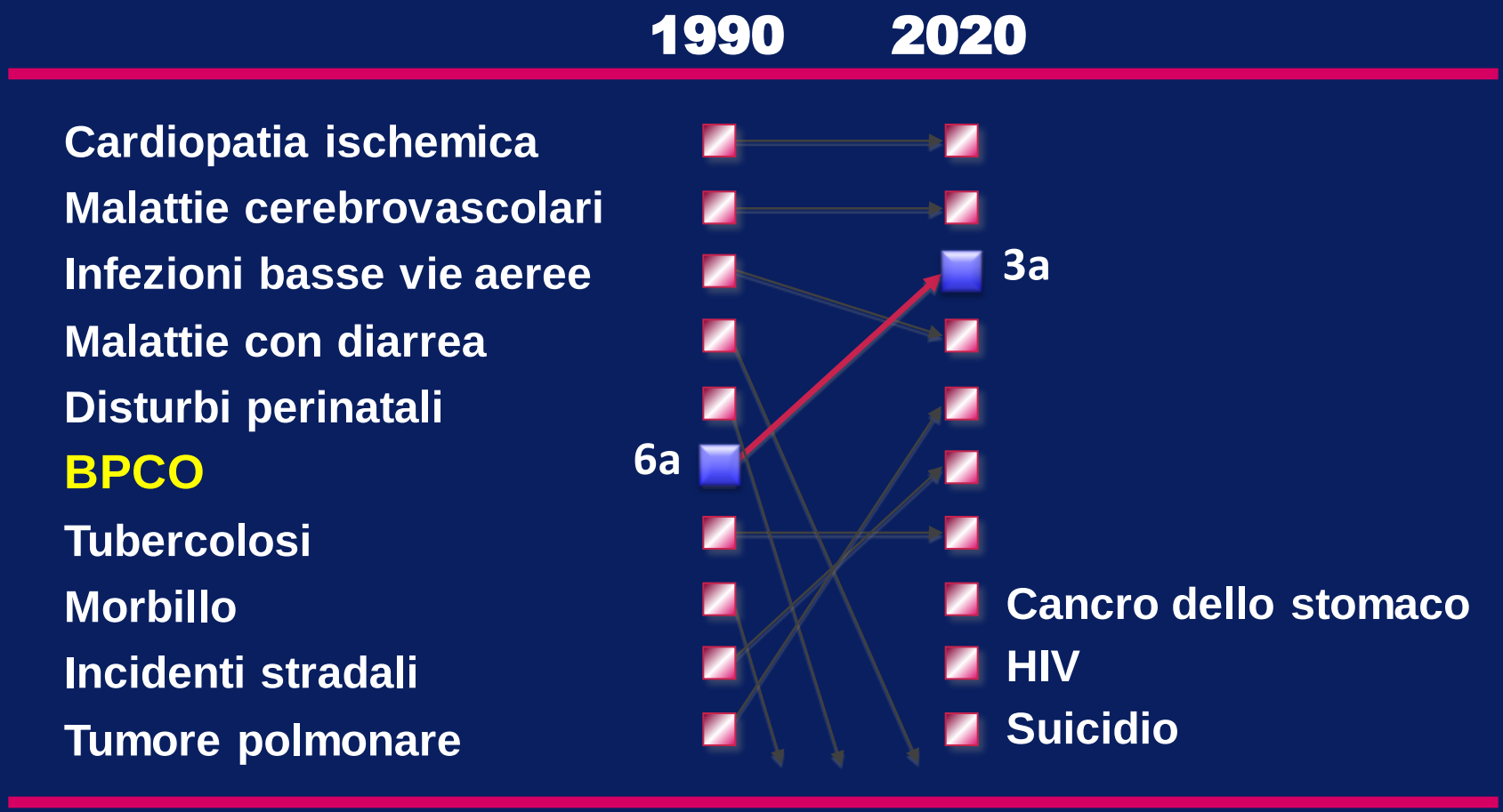
Dipartimento Biomedico di Medicina Interna e Specialistica
Sezione di Pneumologia

Large trial: cosa ci insegna TIOSPIR

Nicola
Scichilone

nicola.scichilone@unipa.it

La BPCO: malattia vecchia, problema attuale.



Murray & Lopez 1997

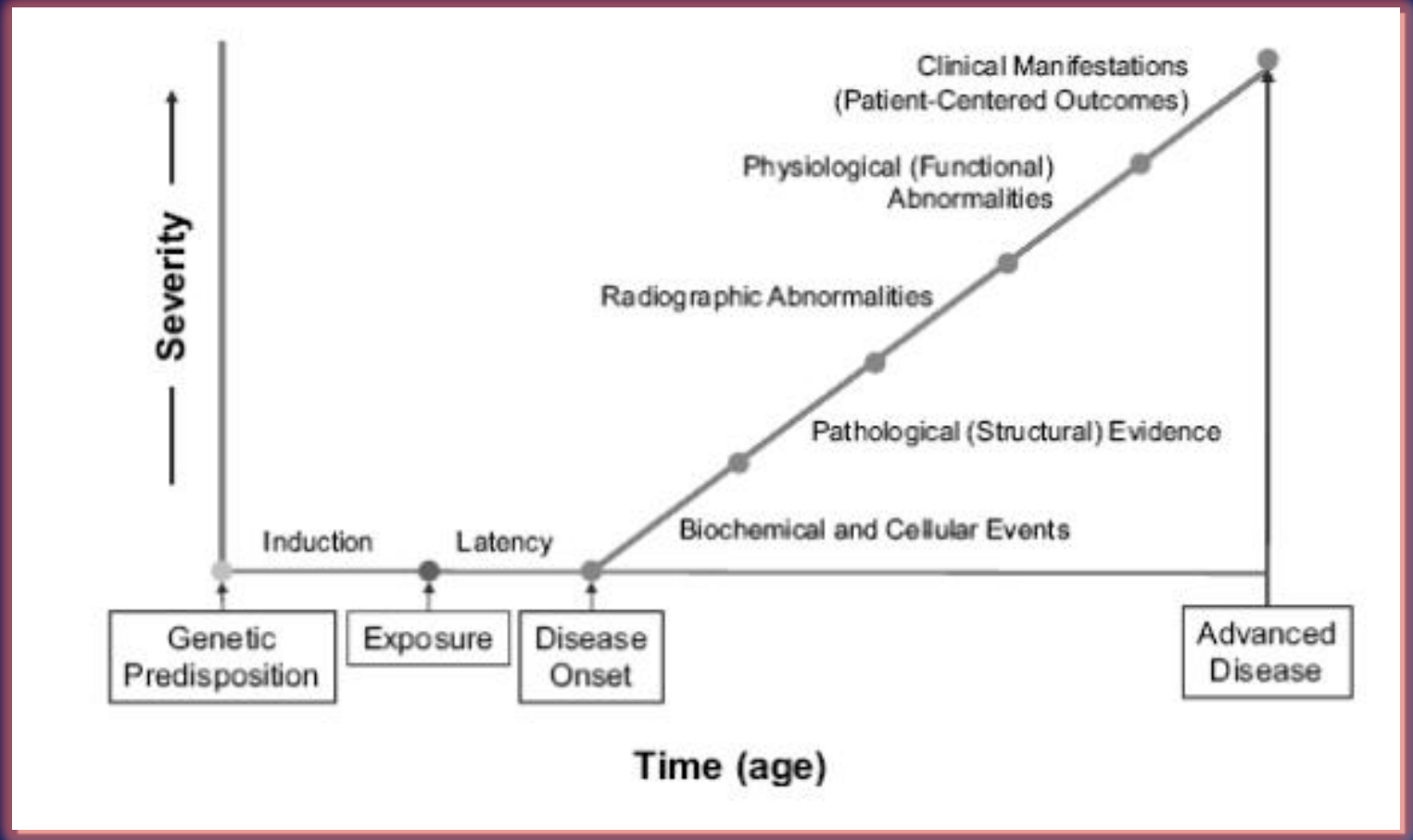
Fenotipo bronchitico

Tipo B o "blue bloater"

Fenotipo enfisematoso

Tipo A o "pink puffer"

Storia naturale della BPCO



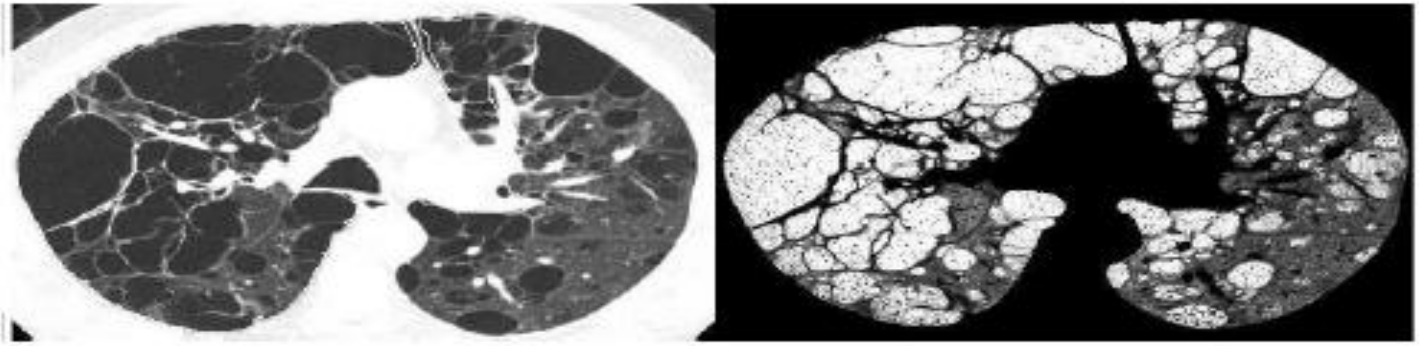
Decramer e Cooper, Thorax 2010

Fattori di rischio per la BPCO

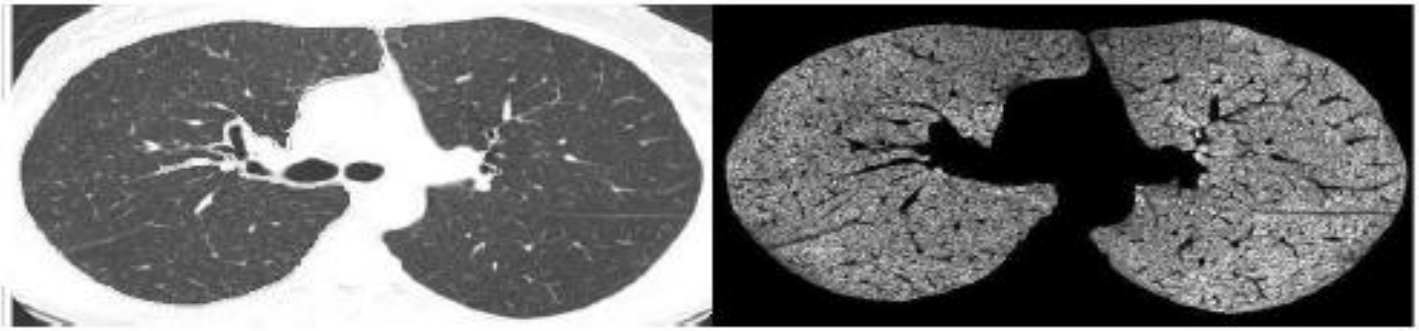
Esposizione al fumo di sigaretta

L’eterogeneità della BPCO

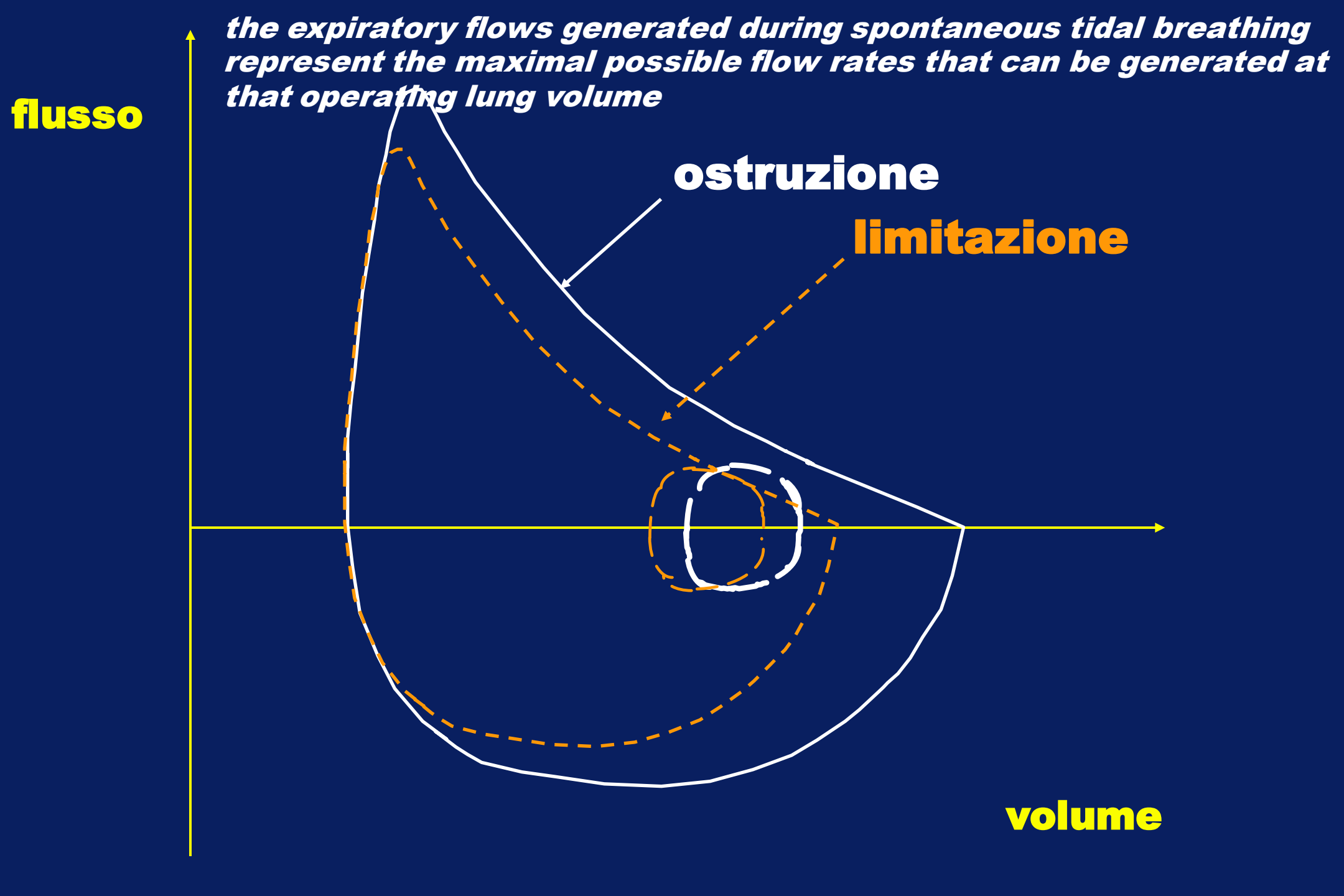
HRCT / Spirometry: (lack of) Correlation



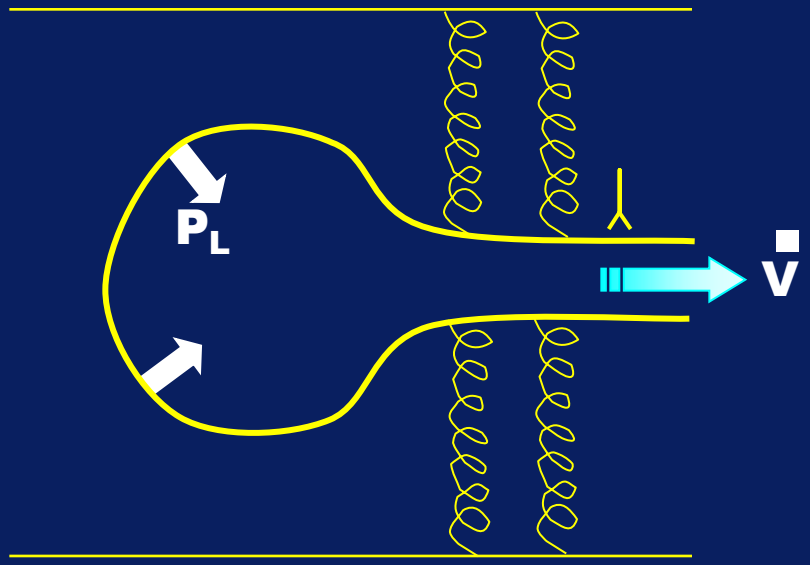
FEV_1 = 35% Predicted
and
Severe Emphysema



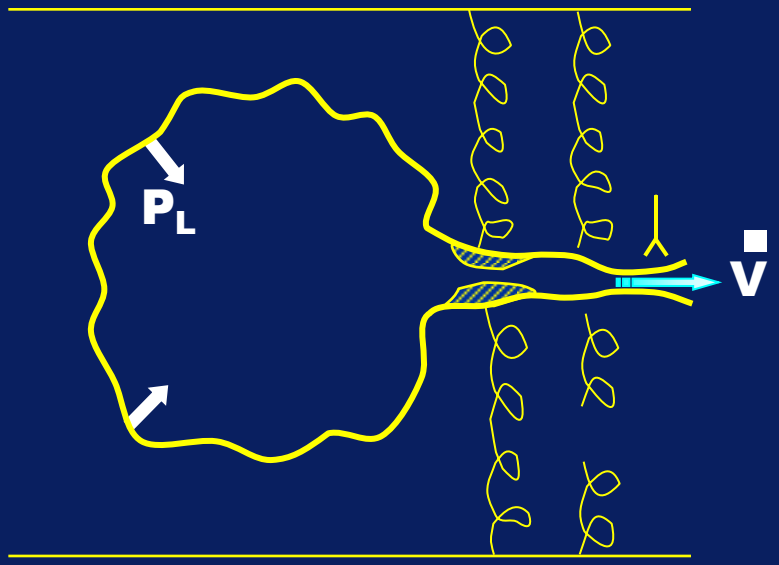
FEV_1 = 35% Predicted
and
Trivial Emphysema


the expiratory flows generated during spontaneous tidal breathing represent the maximal possible flow rates that can be generated at that operating lung volume
flusso
ostruzione
limitazione
volume

Healthy subject



COPD



Reduced lung recoil

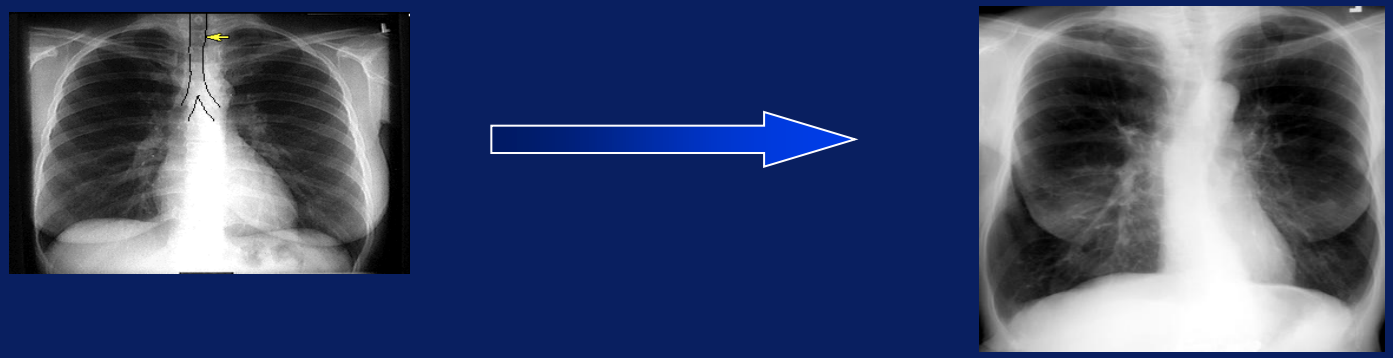
Reduced alveolar attachments

Increased airways resistance

Expiratory flow limitation

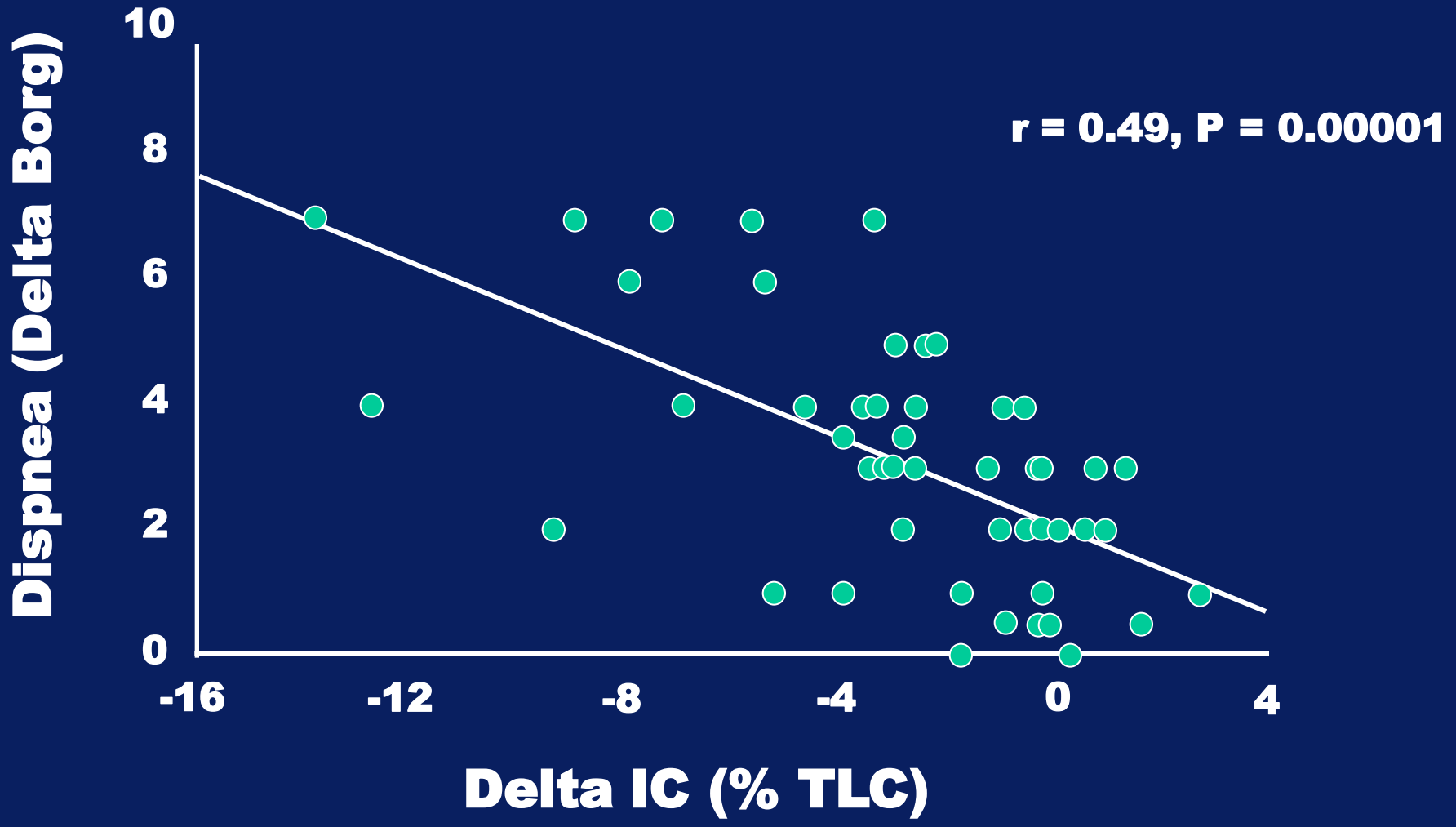
Air trapping

Effetti deleteri dell'iperinflazione



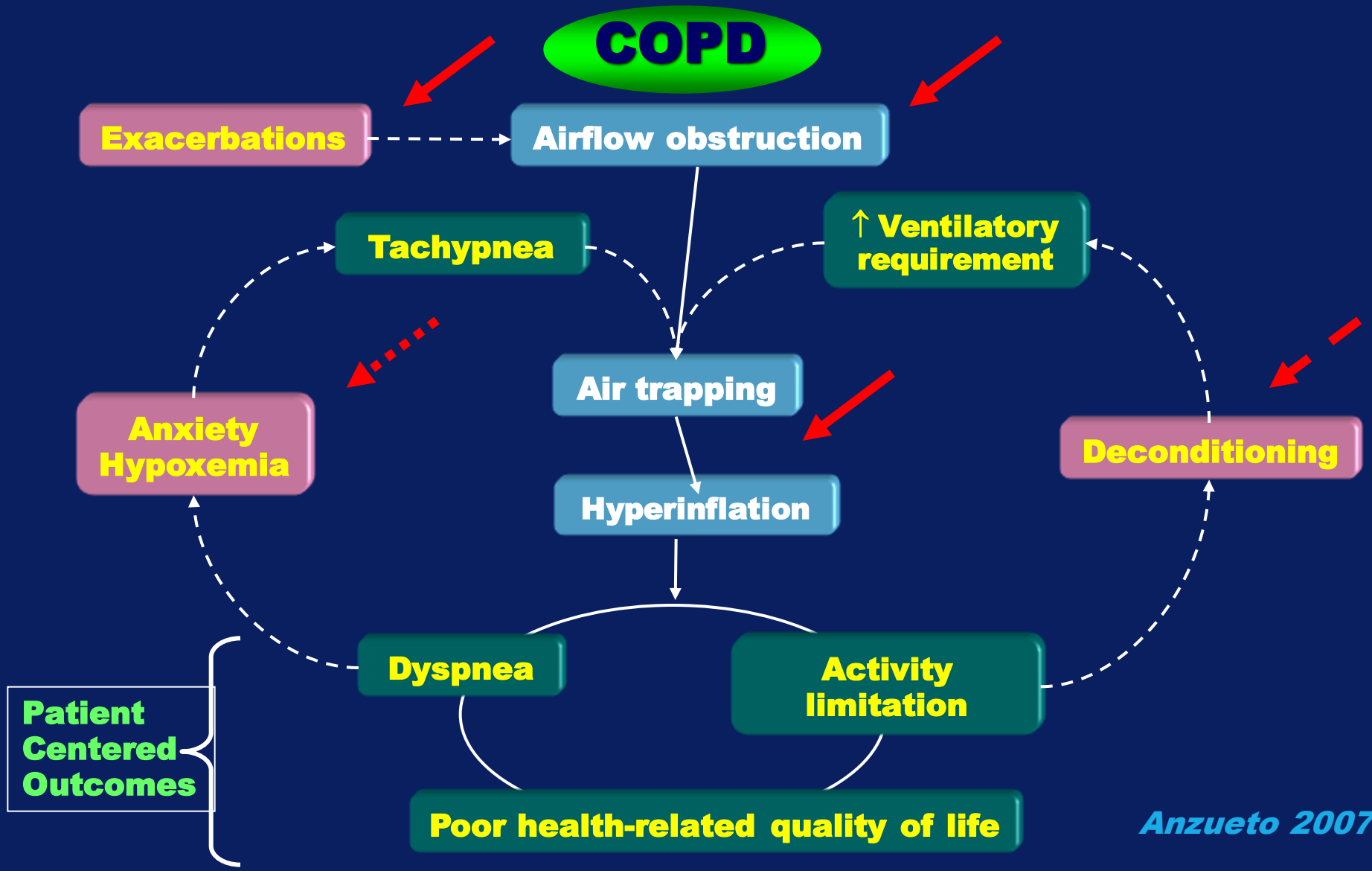
- ↑ Elastic / threshold loads
- Inspiratory muscle weakness
- Reduced V_T expansion
  → tachypnea
- Early ventilatory limitation to exercise
- Negative cardiovascular effects
- Exertional dyspnea

La dispnea si associa ad iperinsufflazione



Marin JM et al. Am J Respir Crit Care Med 2001

Bersagli del trattamento



Anzueto 2007 mod

Definizione

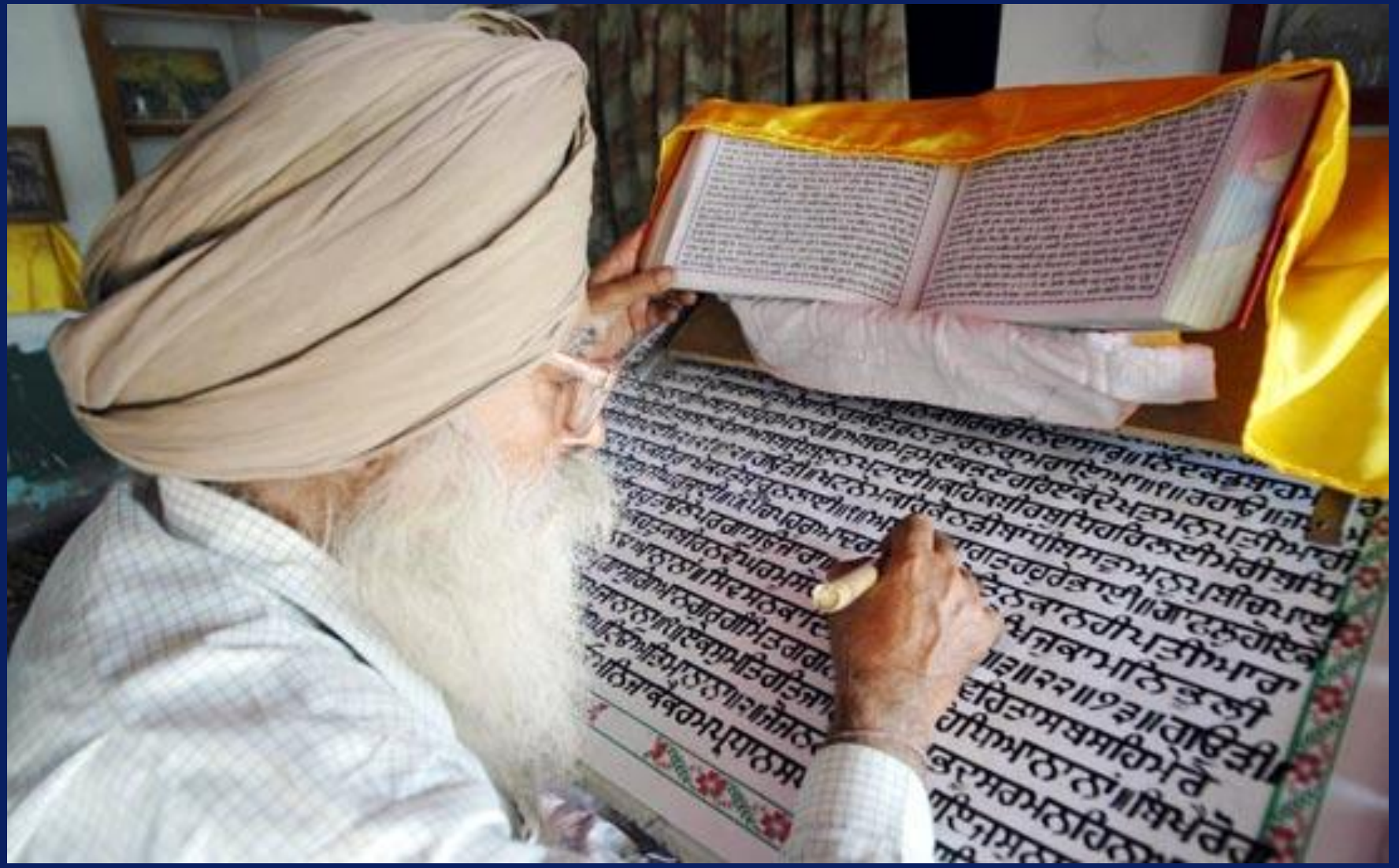
- La BroncoPneumopatia Cronica Ostruttiva (BPCO) è una malattia respiratoria cronica **prevenibile** e **trattabile** associata a significativi effetti e comorbidità extrapolmonari che possono contribuire alla sua gravità

- Le alterazioni broncopolmonari sono costituite da una ostruzione al flusso persistente ed evolutiva legata a rimodellamento delle vie aeree periferiche ed enfisema

- L'ostruzione, il rimodellamento delle vie aeree periferiche e l'enfisema sono dovuti ad una abnorme risposta infiammatoria delle vie aeree, del parenchima polmonare e sistemica all'inalazione di fumo di sigaretta o di altri inquinanti

Aggiornamento GOLD italiano 2009

Writing Guidelines...



Il trattamento della BPCO in fase stabile

Capisaldi

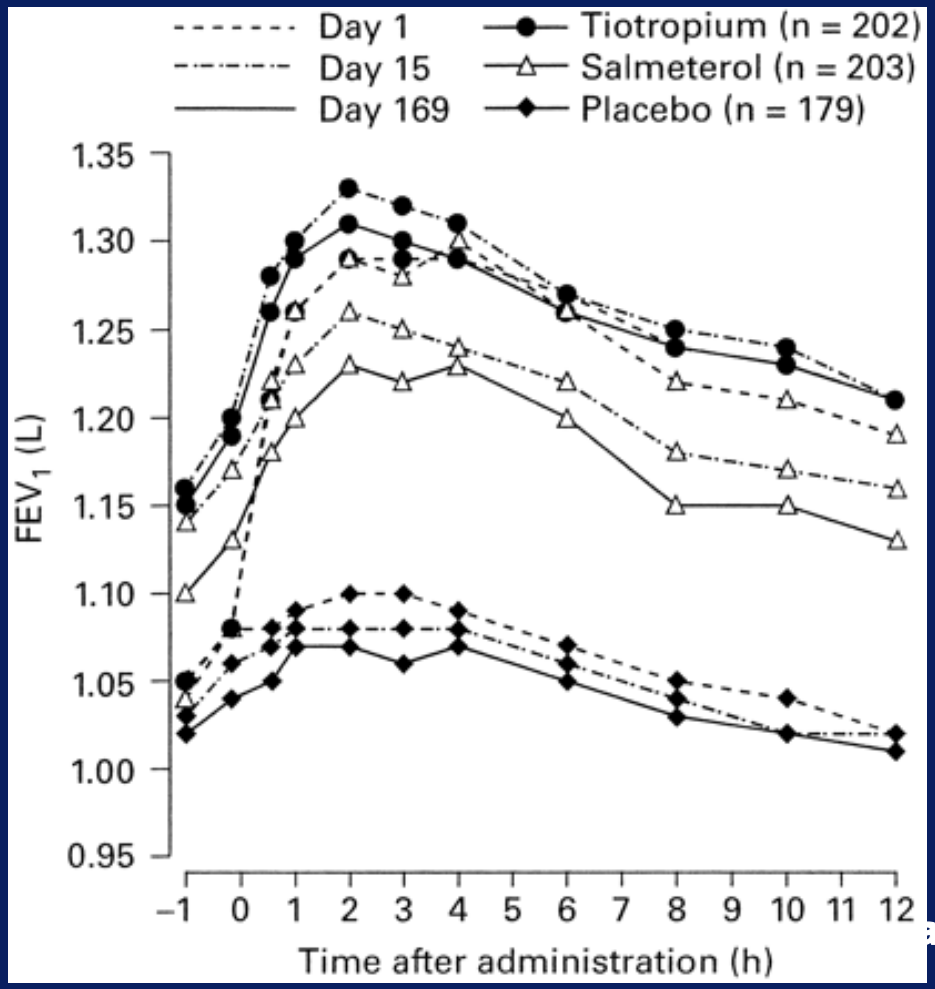
- I broncodilatatori hanno un ruolo centrale nel trattamento della BPCO.
- La via di somministrazione raccomandata è quella inalatoria.
- I broncodilatatori a lunga durata d'azione sono i farmaci più efficaci nel trattamento regolare (A) per controllare o migliorare i sintomi e lo stato di salute.
- I beta$_2$-agonisti e gli anticolinergici a lunga durata d'azione sono i broncodilatatori di prima scelta (A).

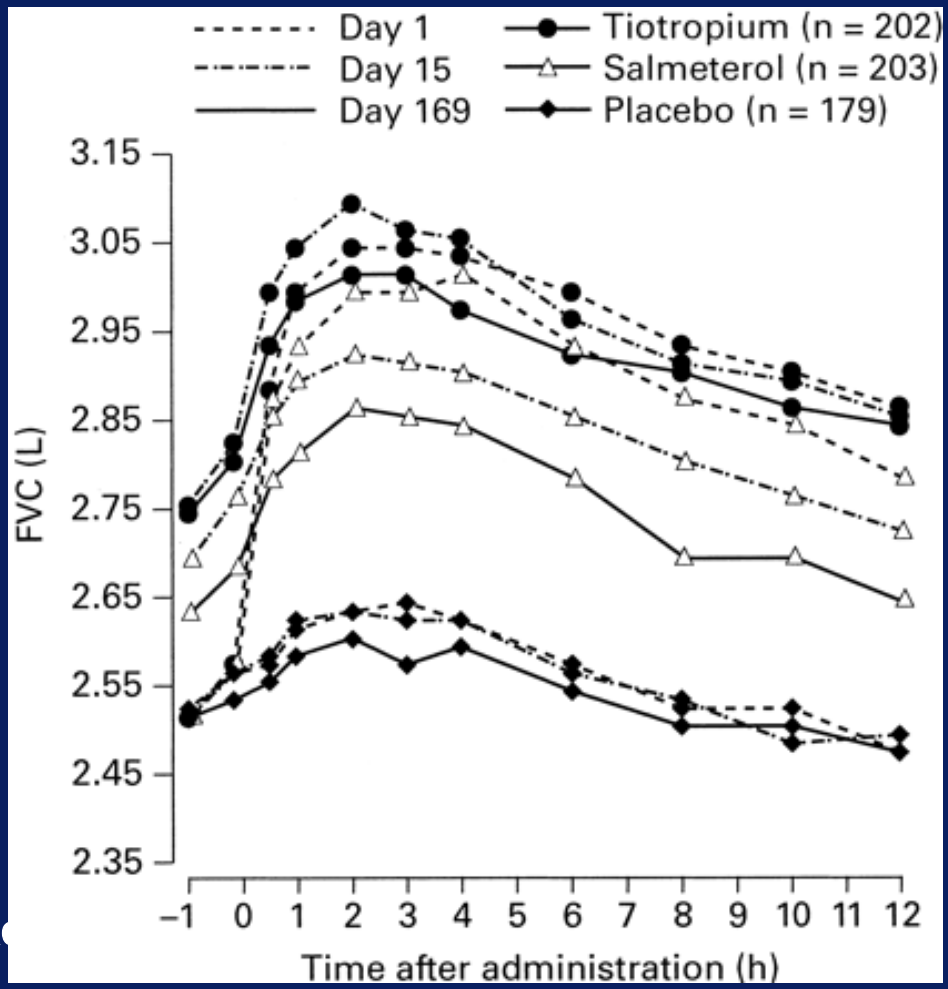
Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

Patient	First choice	Second choice	Alternative Choices
A	SAMA prn *or* SABA prn	LAMA *or* LABA *or* SABA and SAMA	Theophylline
B	LAMA *or* LABA	LAMA and LABA	SABA *and/or* SAMA Theophylline
C	ICS + LABA *or* LAMA	LAMA and LABA	PDE4-inh. SABA and/*or* SAMA Theophylline
D	ICS + LABA *or* LAMA	ICS and LAMA *or* ICS + LABA and LAMA *or* ICS+LABA and PDE4-inh. *or* LAMA and LABA *or* LAMA and PDE4-inh.	*C*arbocysteine SABA and/*or* SAMA Theophylline

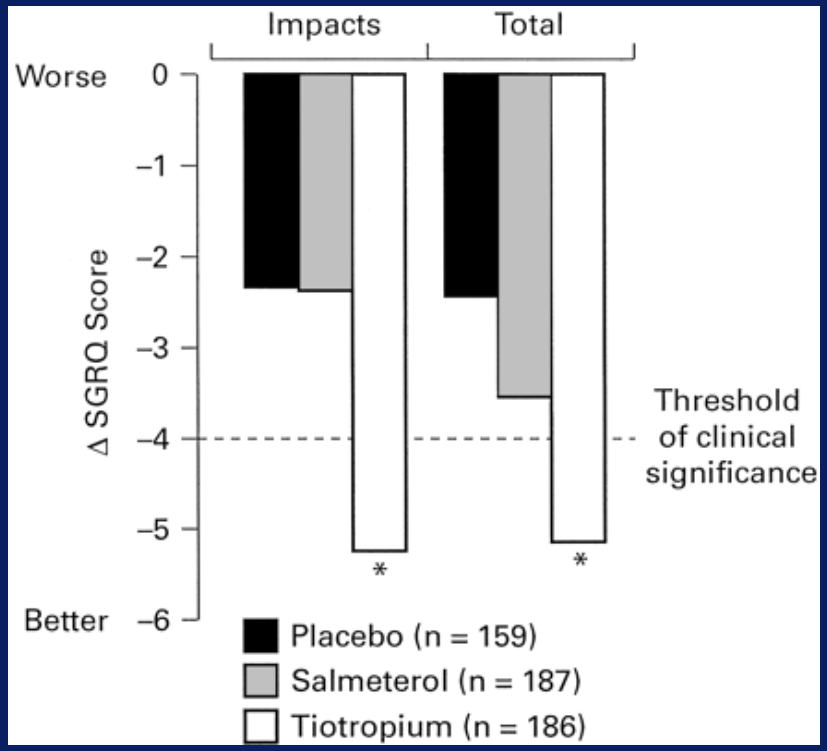
Effetti dei broncodilatatori a lunga durata d'azione sulla funzione respiratoria nella BPCO



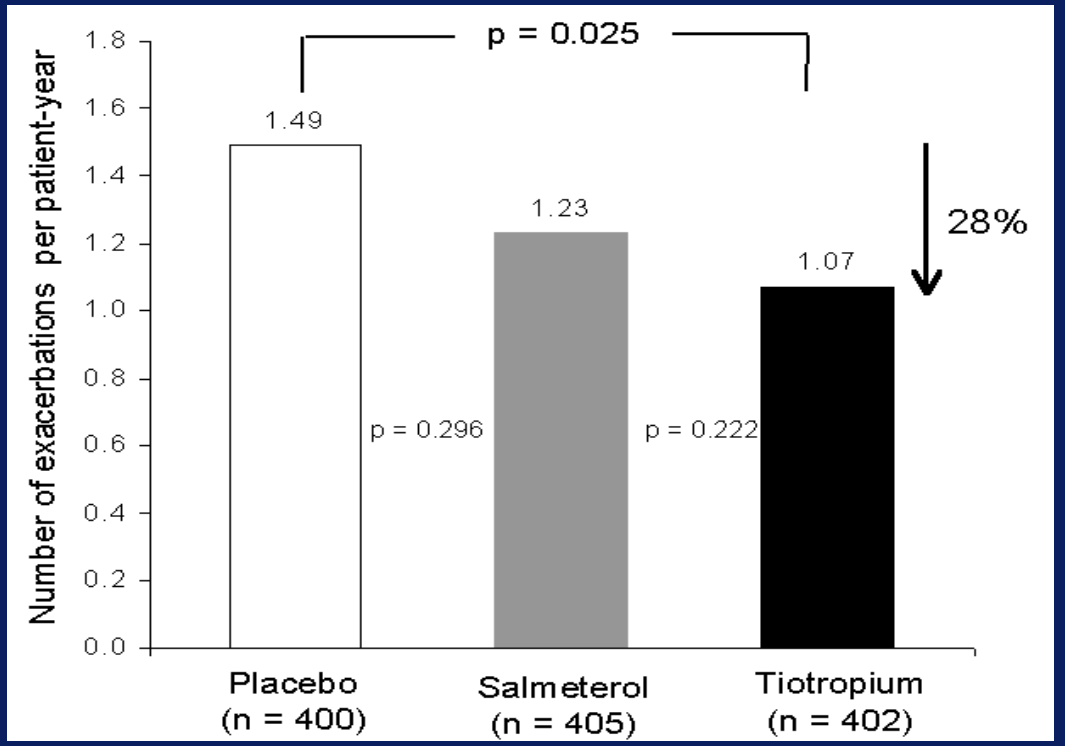


Donohue et al., Chest 2002

Effetti dei broncodilatatori a lunga durata d'azione sulla qualità di vita nella BPCO

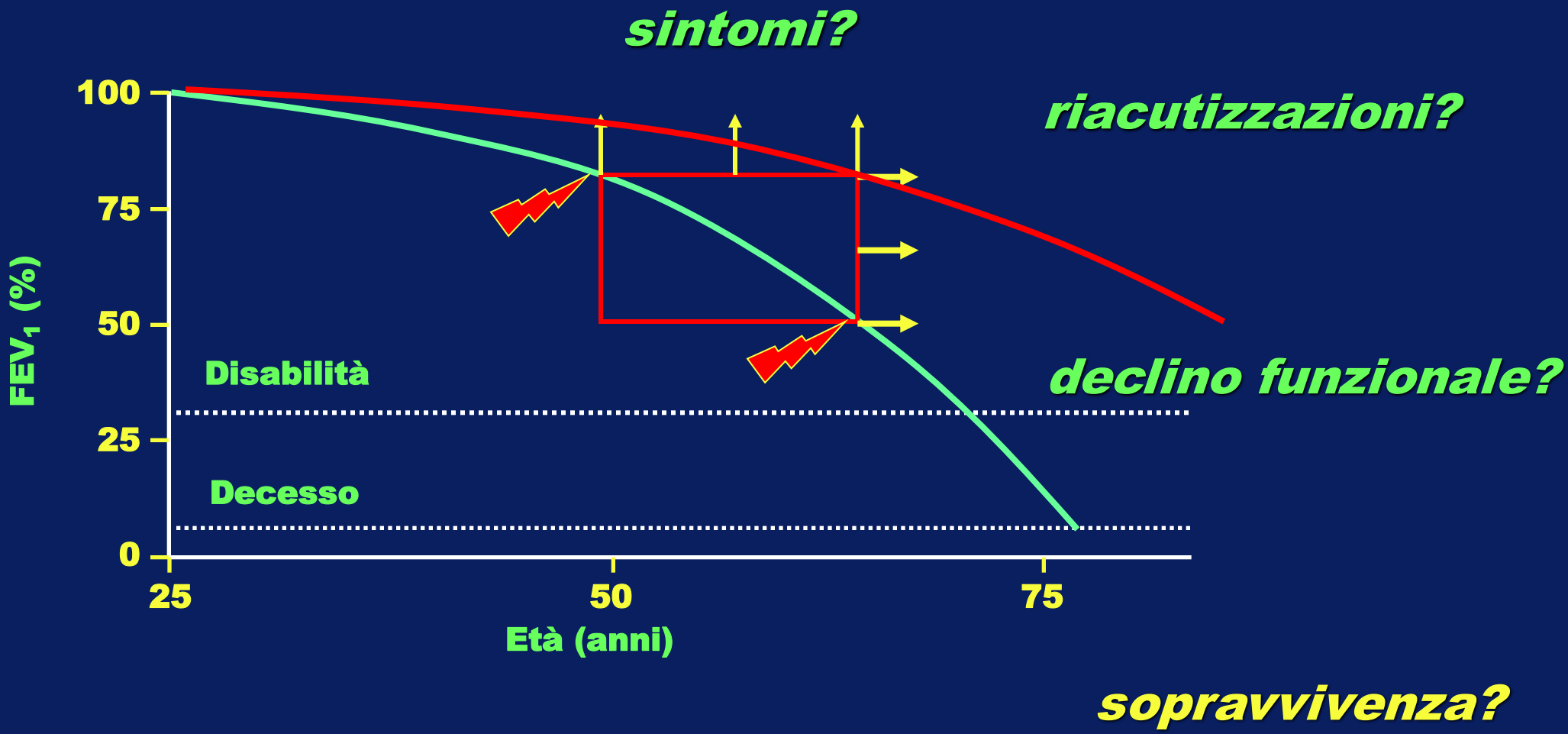


Donohue et al., Chest 2002



Brusasco et al., Thorax 2003

Abbiamo tutte le risposte?



Il razionale dei diversi trattamenti: I megatrial

TORCH STUDY

The NEW ENGLAND JOURNAL of MEDICINE

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

Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

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

ABSTRACT

6112 pazienti arruolati

UPLIFT STUDY

The NEW ENGLAND JOURNAL of MEDICINE

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

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

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

ABSTRACT

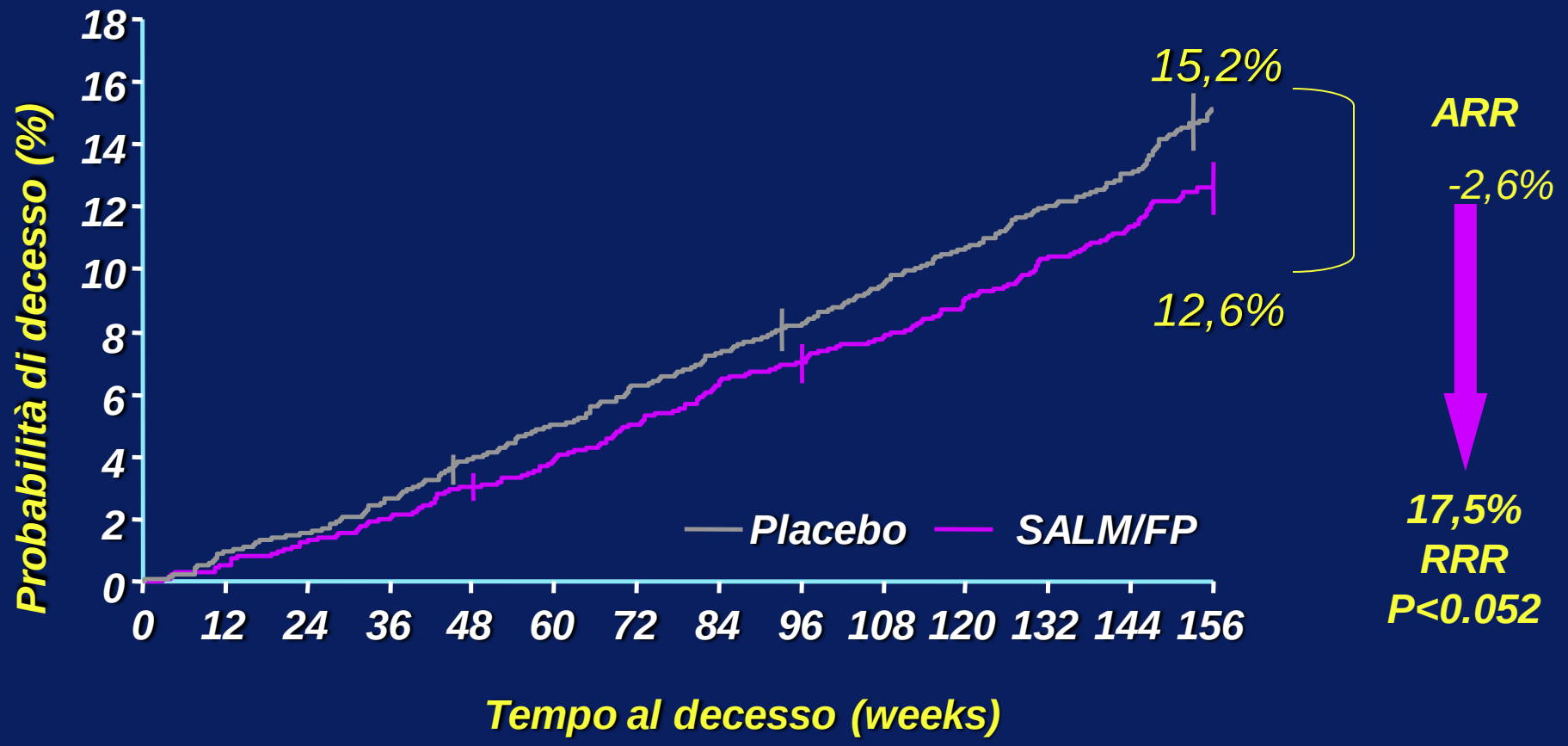
BACKGROUND

Previous studies showing that tiotropium improves multiple end points in patients with chronic obstructive pulmonary disease (COPD) led us to examine the long-

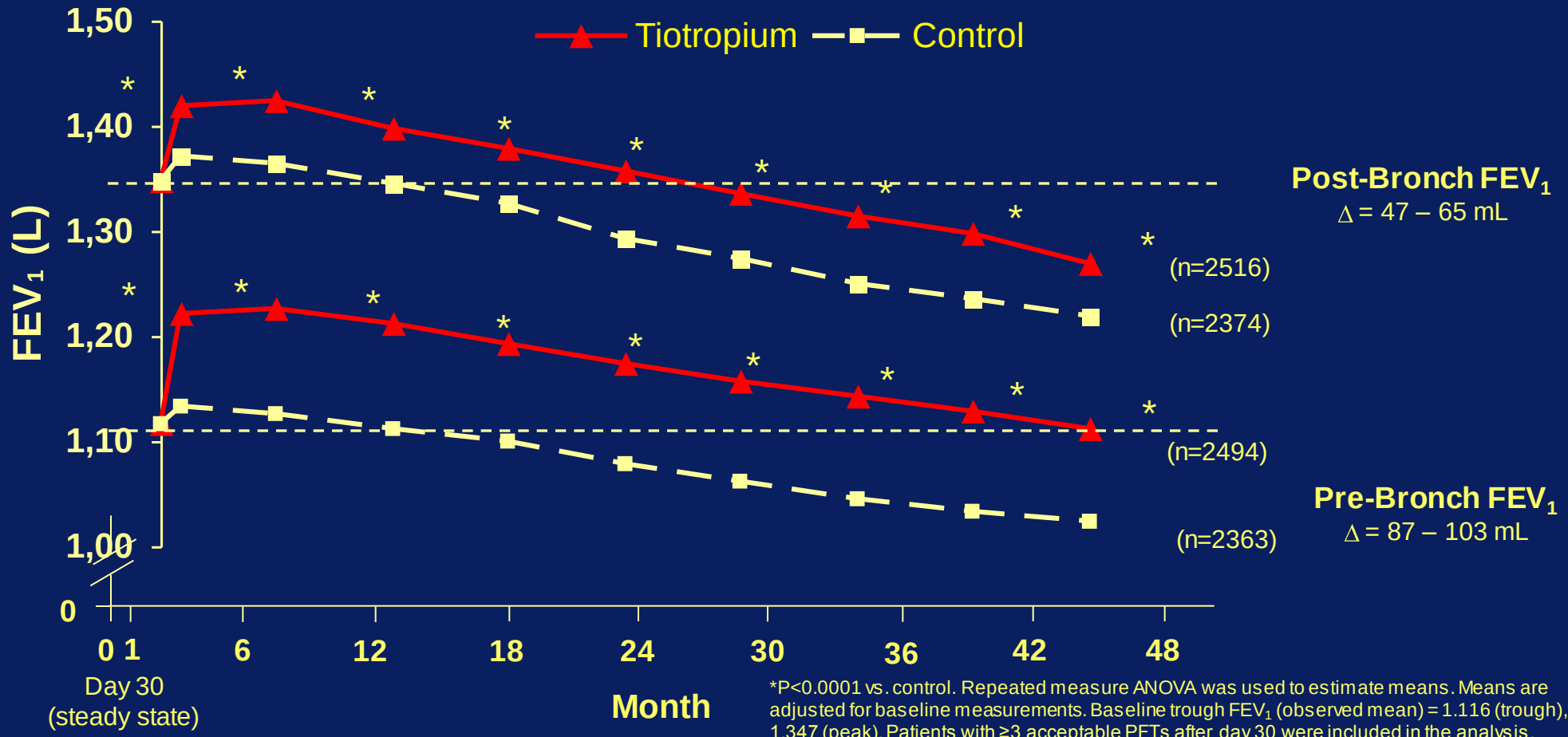
From the David Geffen School of Medicine at the University of California, Los Angeles (D.P.T.); Caritas St. Elizabeth's

5993 pazienti arruolati

Mortalità per tutte le cause a 3 anni
Studio TORCH



Il tiotropio determina persistente miglioramento del FEV_1 lungo i quattro anni



*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.

Tashkin et al. NEJM 2008

Inhaled Anticholinergics and Risk of Major Adverse Cardiovascular Events in Patients With Chronic Obstructive Pulmonary Disease
A Systematic Review and Meta-analysis

Meta-analisi di 17 studi clinici controllati su pazienti con BPCO, condotta con l'obiettivo di valutare il rischio di eventi cardiovascolari maggiori associati all'uso di anticolinergici per inalazione (tiotropio o ipratropio).

I risultati mostrano che gli anticolinergici aumentano significativamente di circa il 58% il rischio di eventi cardiovascolari gravi (infarto miocardico, stroke o morte) rispetto ad altre terapie di confronto (placebo, salmeterolo da solo o con ICS, salbutamolo). Tale rischio è ancora più elevato nel trattamento a lungo termine (RR 1.73, CI 95%, 1.27-2.36, $p<0.001$).

Singh S et al., JAMA 2008

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

the *UPLIFT* Trial

Table 4. Incidence Rate of Serious Adverse Events per 100 Patient-Years.*

Adverse Event	Tiotropium (N=2986)	Placebo (N=3006)	Relative Risk for Tiotropium vs. Placebo (95% CI)
Cardiac	3.56	4.21	0.84 (0.73–0.98)†
Angina	0.51	0.36	1.44 (0.91–2.26)
Atrial fibrillation	0.74	0.77	0.95 (0.68–1.33)
Cardiac failure	0.61	0.48	1.25 (0.84–1.87)
Congestive heart failure	0.29	0.48	0.59 (0.37–0.96)†
Coronary artery disease	0.21	0.37	0.58 (0.33–1.01)
Myocardial infarction	0.69	0.97	0.71 (0.52–0.99)†
Lower respiratory	11.32	13.47	0.84 (0.77–0.92)†
Bronchitis	0.37	0.31	1.20 (0.73–1.98)
COPD exacerbation	8.19	9.70	0.84 (0.76–0.94)†
Dyspnea	0.38	0.62	0.61 (0.40–0.94)†
Pneumonia	3.28	3.46	0.95 (0.81–1.11)
Respiratory failure	0.90	1.31	0.69 (0.52–0.92)†

* Listed are the incidence rates of serious adverse events (excluding lung cancer) that were reported by more than 1% of patients in either study group, according to organ class during the study period (from the first day of administration of a study drug until the last day plus 30 days).

† $P<0.05$.

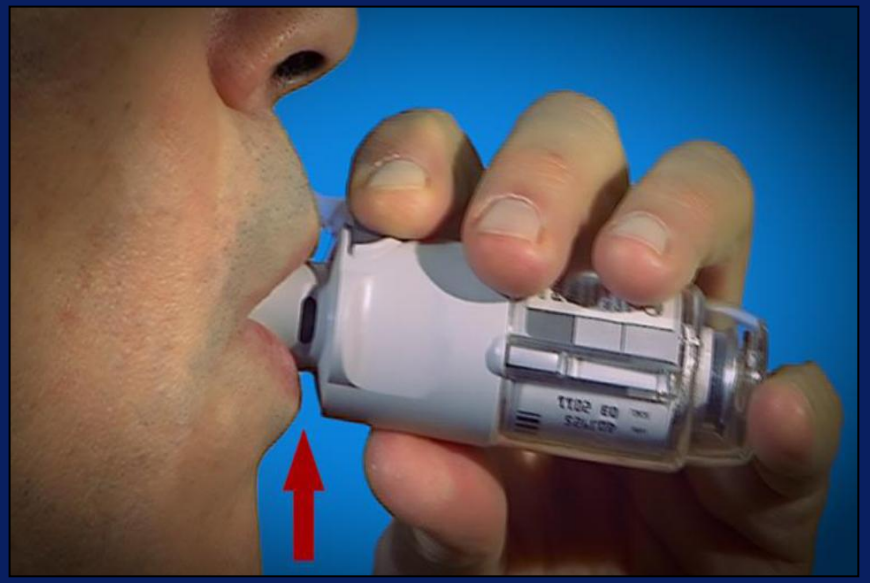
Taskin DP, et al. N Engl J Med 2008

Punti critici della metanalisi

1. Gli studi inclusi non erano stati disegnati per valutare in modo predefinito e specifico il rischio cardiovascolare
2. Molti trials erano a brev
3. Confronto tra principi a
4. Confronto tra dosaggi d
5. I dati di esito cardiovascolare possono essere stati riportati in modo incompleto e le fonti originali dei dati non erano disponibili

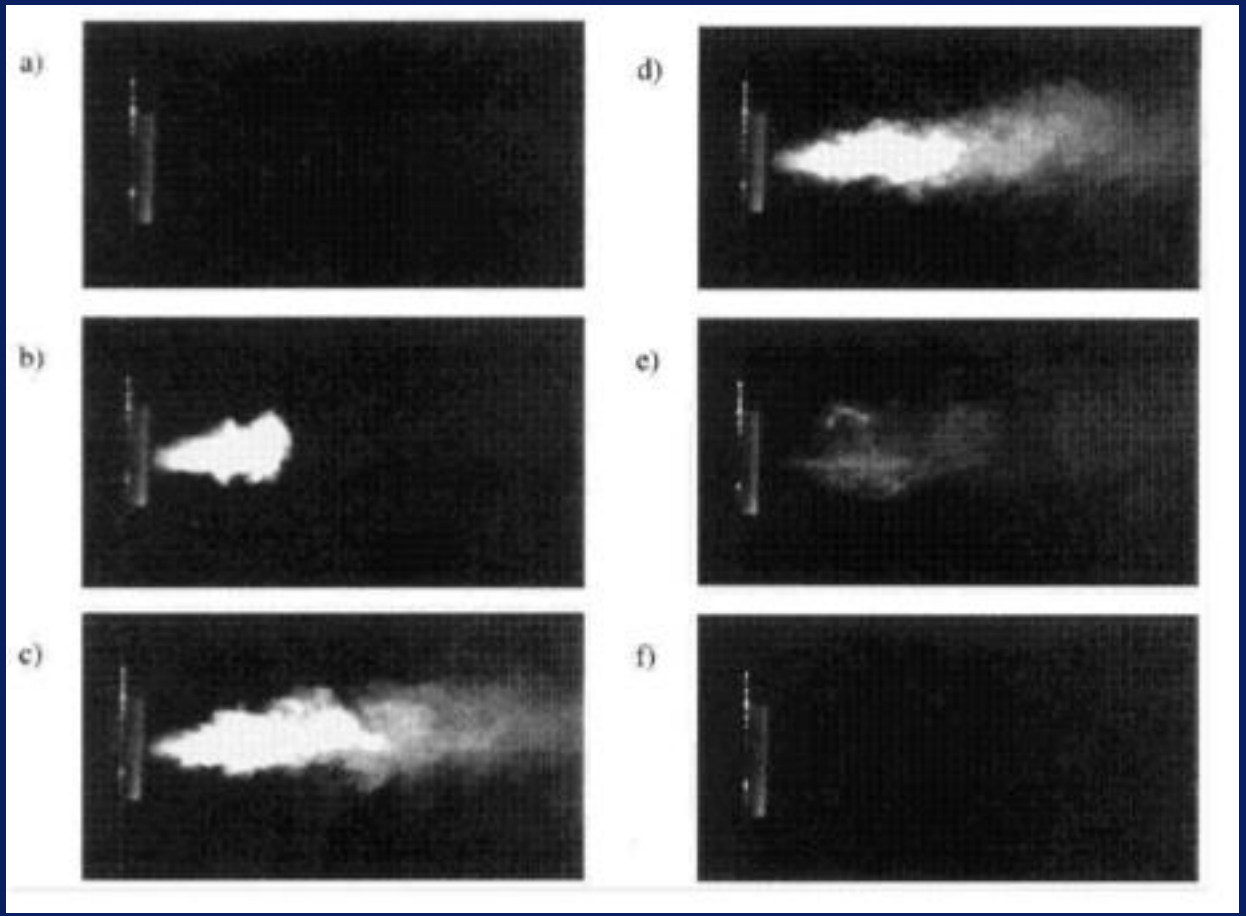
Respimat *device*: una nuova opportunità in più

Next-generation portable inhalers, such as the Respimat SMI device combine some of the advantages of DPIs (propellant-free), pMDIs (inspiratory flow independence) and nebulizers (liquid formulations), while minimizing limitations such as low lung dose and high oropharyngeal dose



Rau, Respiratory Care 2005

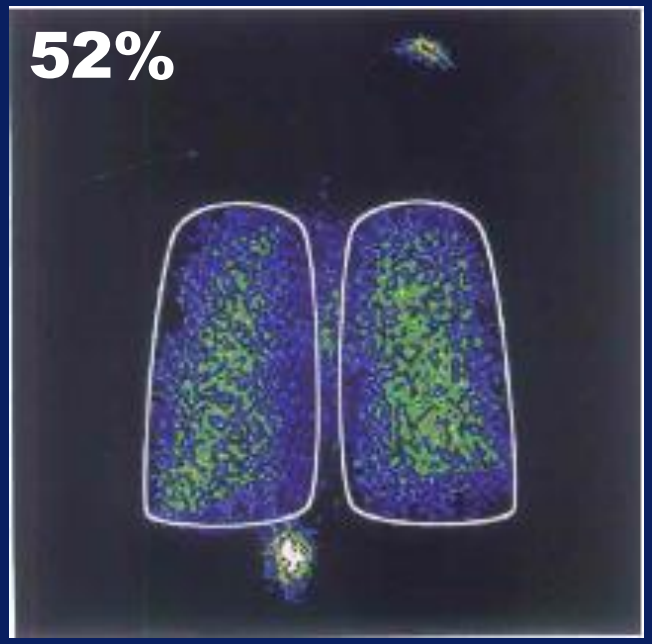
Velocità e durata dello spruzzo



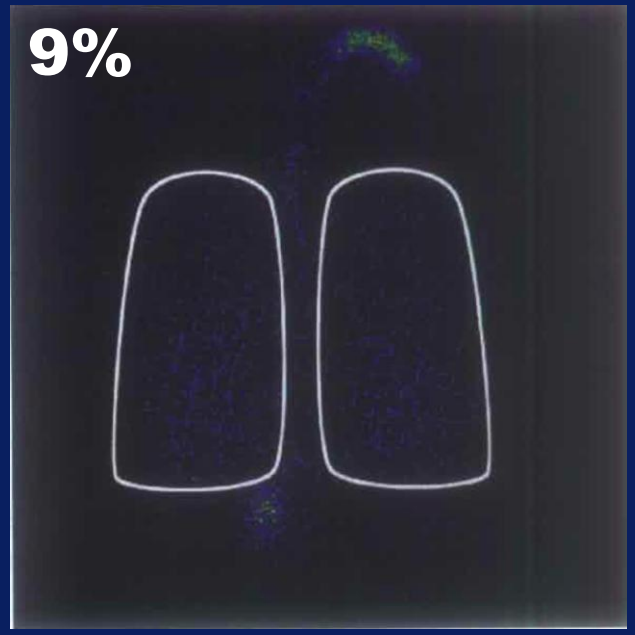
Tecnologia Respimat

Hochrainer et al. Aerosol Medicine 2005

Deposizione polmonare del farmaco in funzione del tipo di erogatore



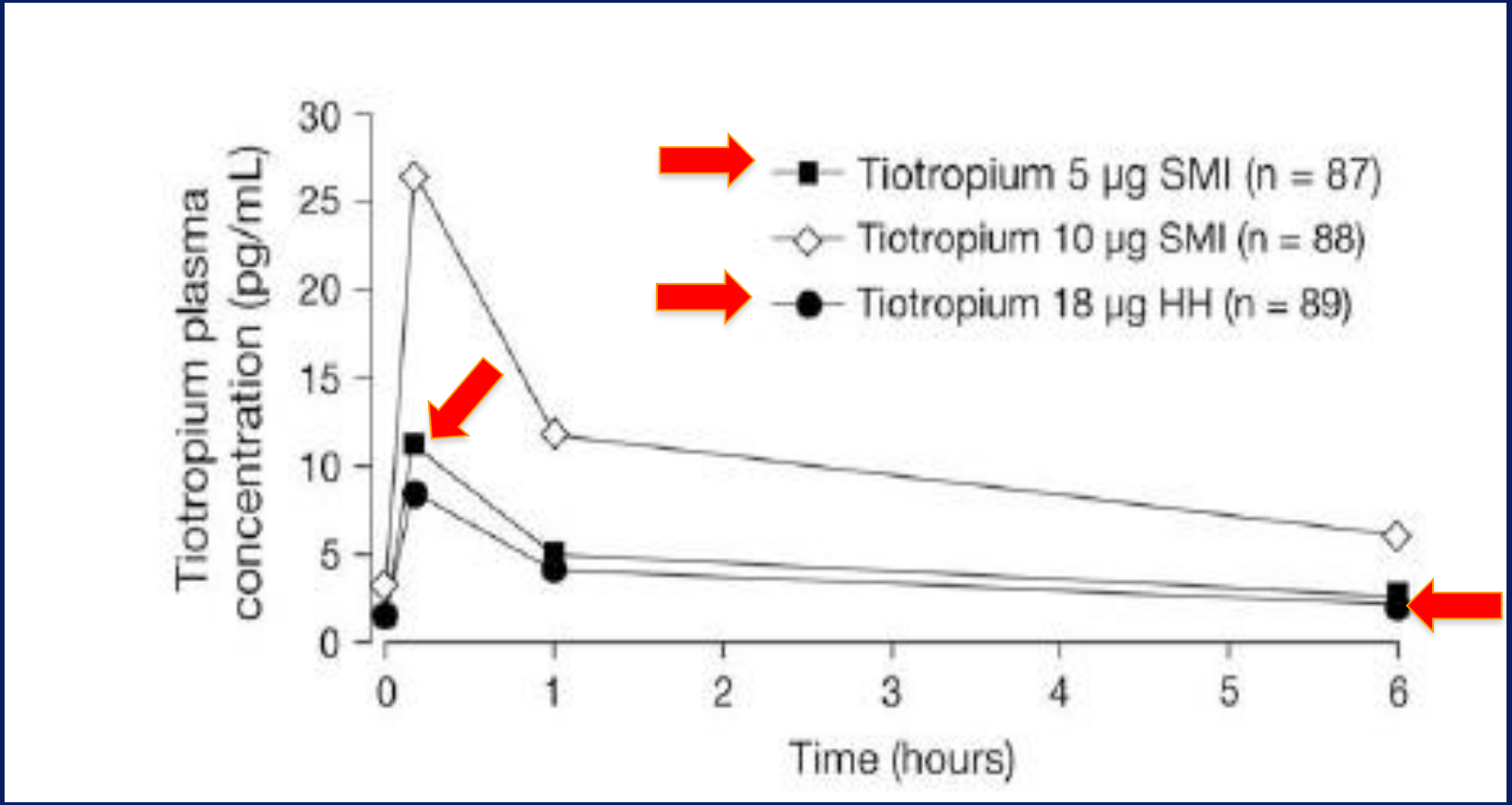
Respimat



pMDI

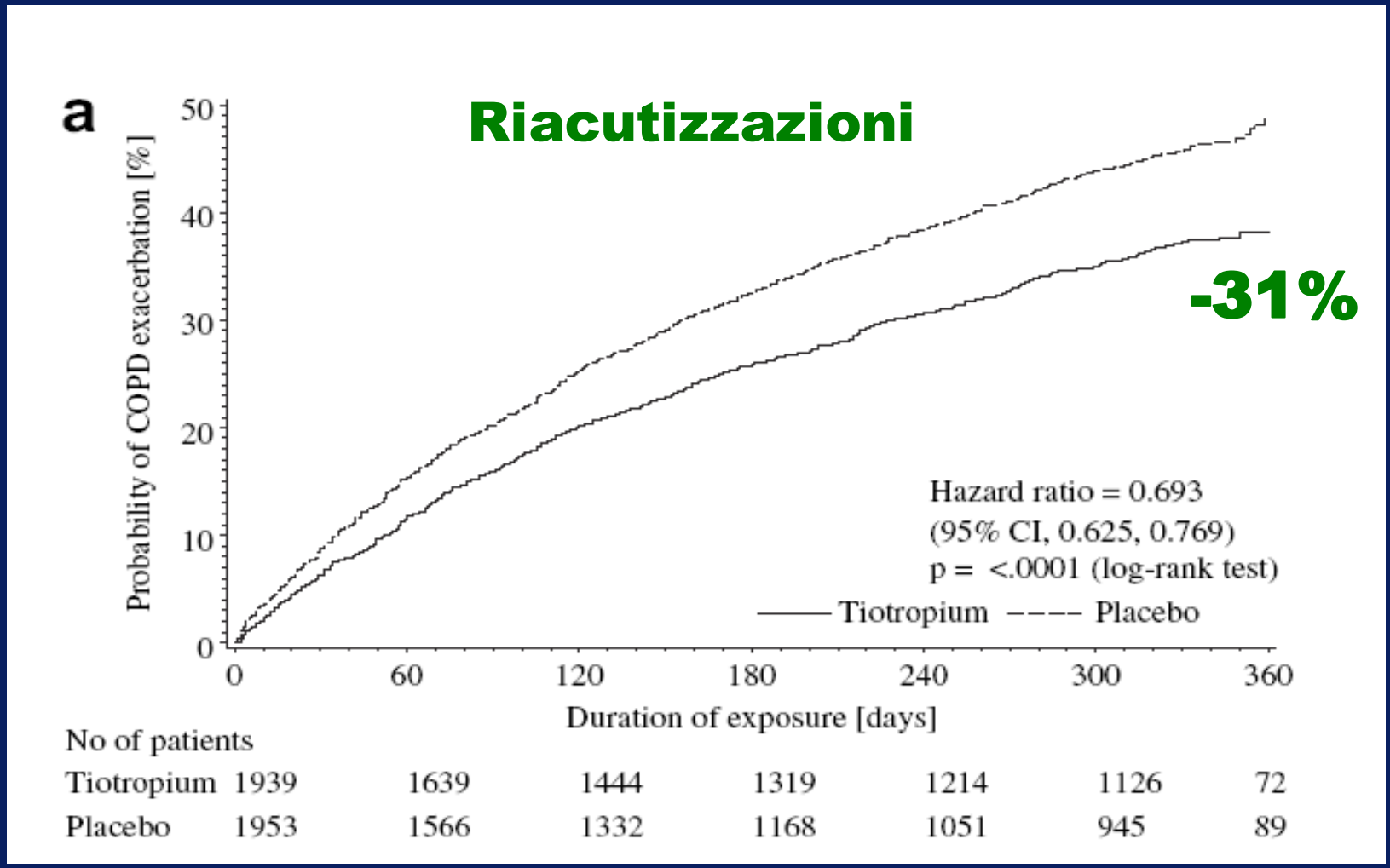
Pitcairn et al. J Aerosol Med 2005

Bioequivalenza
Concentrazioni plasmatiche a confronto



Van Noord DE, et al. Respir Med 2009

Trattamento della BPCO con Tiotropio Respimat® integrato nella terapia

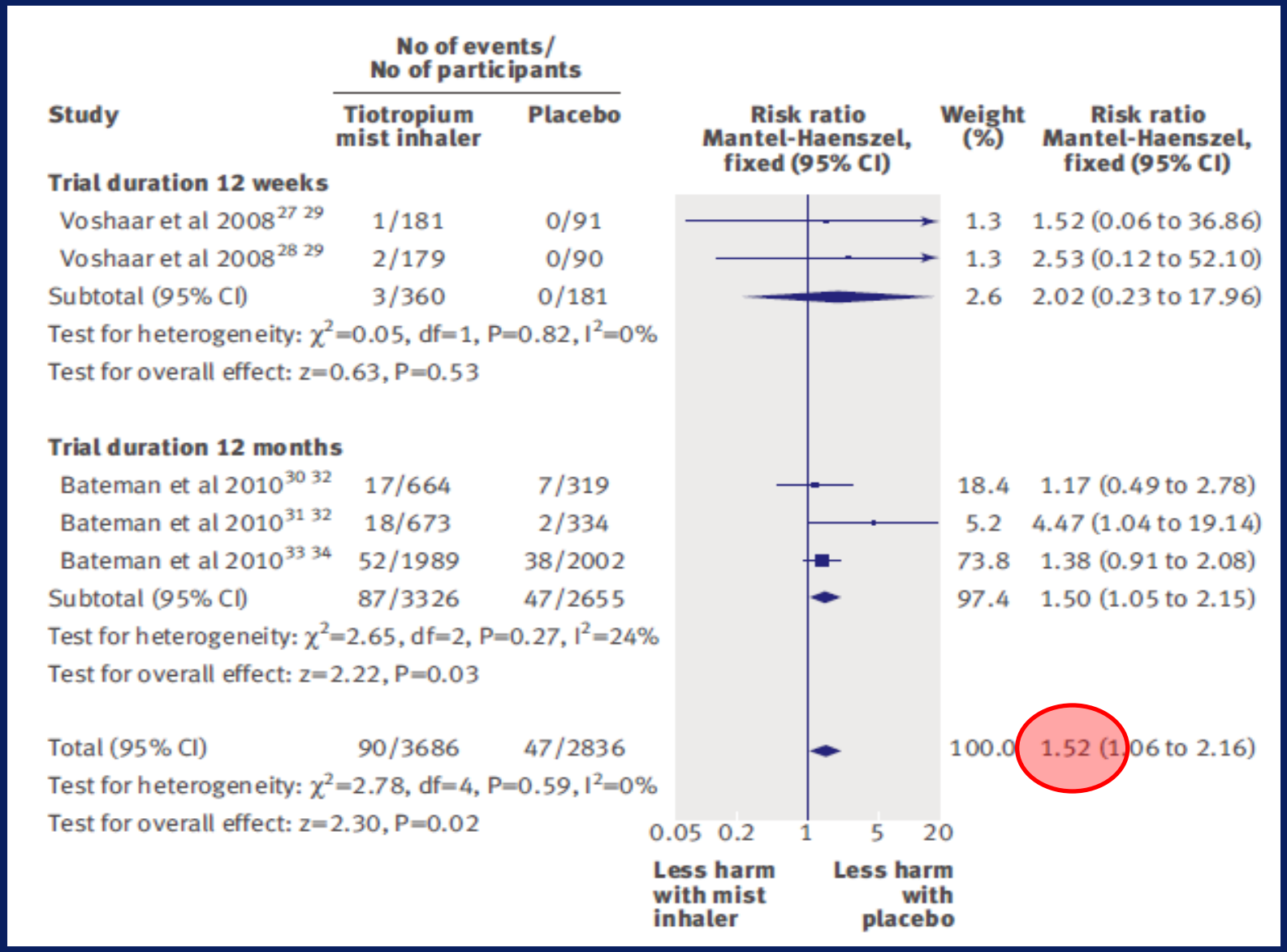


Bateman et al, Respir Med 2010

Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials

Sonal Singh, assistant professor,[1] Yoon K Loke, senior lecturer,[2] Paul L Enright, professor,[3] Curt D Furberg, professor[4]

BMJ 2011;342:d3215



Tiotropium Respimat increases the risk of mortality

Christine R Jenkins,[1] Richard Beasley[2]

Thorax January 2013 Vol 68 No 1

The sixth critique is that the findings from the tiotropium Respimat studies may be flawed in some way as the risk was not observed in the larger UPLIFT study in which there was no increased risk of mortality. Certainly, there is a significant difference in risk of mortality between the Handihaler and Respimat inhaler as reported in the two independent meta-analyses.[1 12] There are

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tiotropium Respimat Inhaler and the Risk of Death in COPD

Robert A. Wise, M.D., Antonio Anzueto, M.D., Daniel Cotton, M.S., Ronald Dahl, M.D., Theresa Devins, Dr.Ph., Bernd Disse, M.D., Daniel Dusser, M.D., Elizabeth Joseph, M.P.H., Sabine Kattenbeck, Ph.D., Michael Koenen-Bergmann, M.D., Gordon Pledger, Ph.D., and Peter Calverley, D.Sc., for the TIOSPIR Investigators*

Wise RA, et al. N Engl J Med. 2013

Obiettivi dello studio

- **Co-primari**
  - **Tempo alla morte (per tutte le cause)**
  - **Tempo alla prima riacutizzazione di BPCO**

- **Secondari**
  - **Numero di riacutizzazioni da BPCO**
  - **Tempo alla prima riacutizzazione moderata o grave (con ospedalizzazione)**
  - **Numero e tempo alle riacutizzazioni gravi (con ospedalizzazione)**

- **Safety**
  - **Eventi avversi seri**
  - **Eventi avversi correlati al trattamento o che hanno portato all'interruzione della terapia**
  - **MACE (Major Adverse Cardiovascular Event) che includono:**
    - **Stroke, attacco ischemico transitorio, IM, morte improvvisa, morte cardiaca improvvisa o morte per cause cardiache**

Wise RA, et al. N Engl J Med. 2013

TIOSPIR™ - Overview

- Nazioni: 50
- Centri: 1202
- Pazienti con BPCO (II-IV)
  - 17,183 randomizzati
  - 17,135 trattati
  - 77% completati
  - 99.7% vital status follow up
- Timelines:
  - Arruolamenti Maggio 2010 – Aprile 2011
  - Fine dello studio: Maggio 2013

- Popolazione dello studio “real life”:
  - Consentite tutte le terapie respiratorie concomitanti
  - Presenza di co-morbidità incluse le CV
  - Assenza del braccio placebo

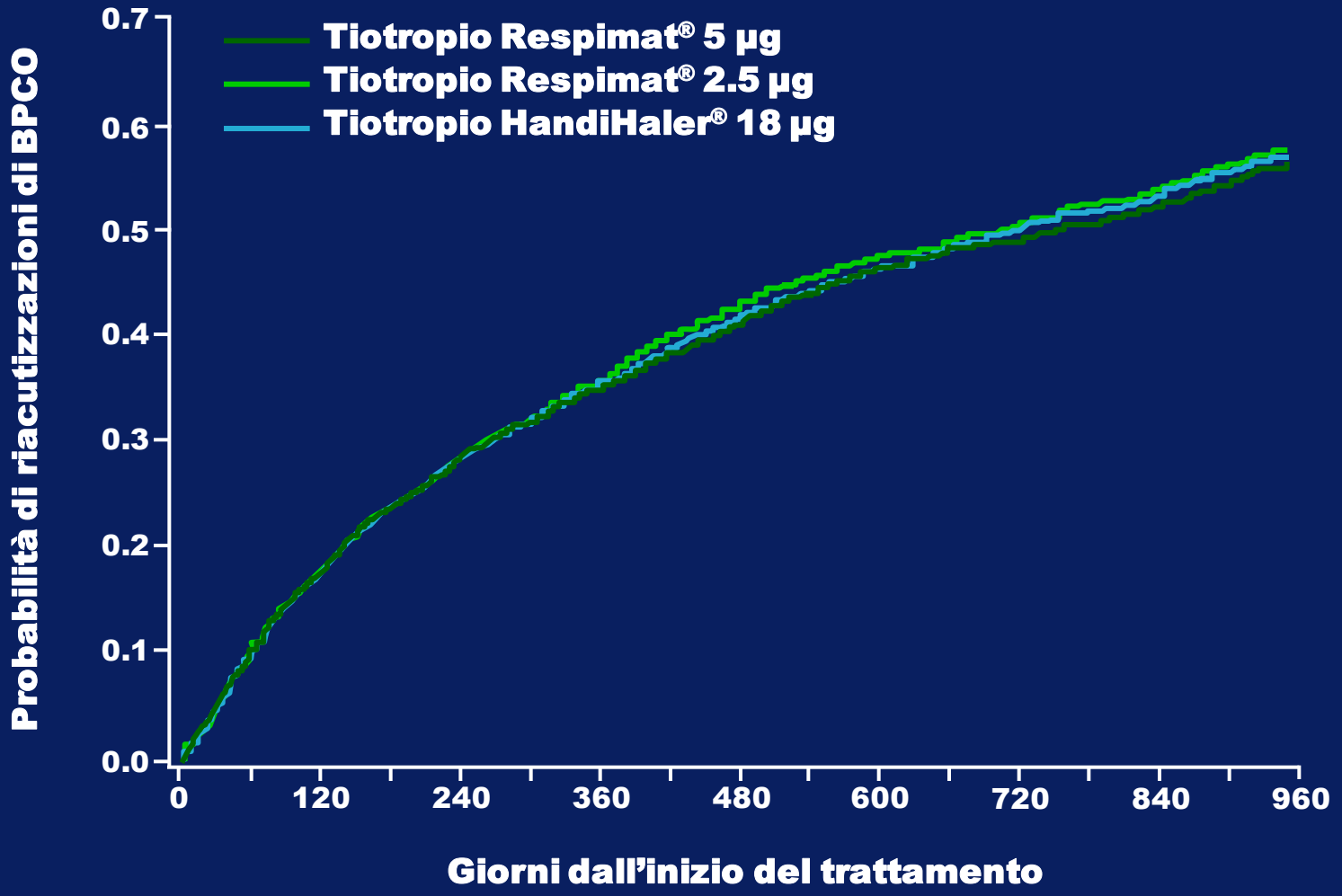
Wise RA, et al. N Engl J Med. 2013

Criteri di inclusione

- **Diagnosi di BPCO**
  - **$FEV_1 \leq$ 70% del predetto**
  - **FEV_1/FVC post-bronchodilatore $\leq$ 0,7**
- **Età $\geq$40 anni**
- **Fumatori $\geq$ 10 pacchetti/anno**
- **Pazienti con concomitanti malattie cardiache potevano essere inclusi, a meno che non avessero avuto:**
  - **Infarto miocardico negli ultimi 6 mesi**
  - **Ospedalizzazione per scompenso cardiaco (classe NYHA III /IV) negli ultimi 12 mesi**
  - **Aritmia instabile o pericolosa per la vita che richiedeva un intervento o il cambio di terapia farmacologica negli ultimi 12 mesi**

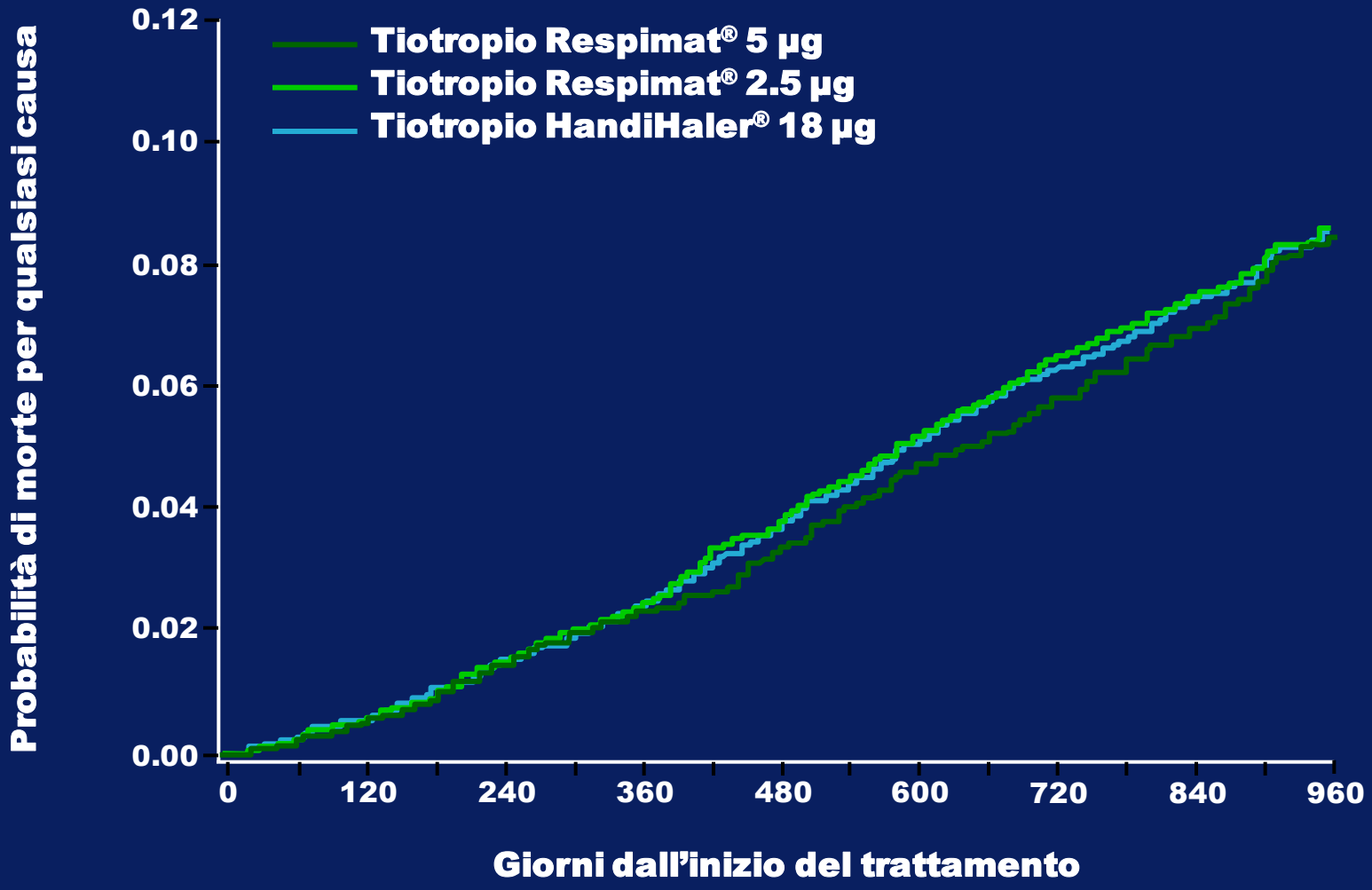
Wise RA, et al. N Engl J Med. 2013

Tempo alla comparsa di riacutizzazione
Nessuna differenza tra i trattamenti



Wise RA, et al. N Engl J Med. 2013

Tempo alla morte per tutte le cause
Nessuna differenza tra i trattamenti



Wise RA, et al. N Engl J Med. 2013

Eventi avversi gravi e MACE
Nessuna differenza tra i trattamenti

Table 4. Serious Adverse Events and Major Adverse Cardiovascular Events.*

Event	Tiotropium Respimat 2.5 μg (N = 5724)	Tiotropium Respimat 5 μg (N = 5705)	Tiotropium HandiHaler 18 μg (N = 5687)	Tiotropium Respimat 2.5 μg vs. HandiHaler		Tiotropium Respimat 5 μg vs. HandiHaler	
				Hazard Ratio (95% CI)†	P Value	Hazard Ratio (95% CI)†	P Value
	number of patients (percent)						
Any serious adverse event	1937 (33.8)	1846 (32.4)	1842 (32.4)				
Respiratory, thoracic, or mediastinal disorder	1017 (17.8)	957 (16.8)	964 (17.0)				
Infection or infestation	497 (8.7)	502 (8.8)	495 (8.7)				
Cardiac disorder	293 (5.1)	273 (4.8)	270 (4.7)				
Major adverse cardiovascular events ‡	224 (3.9)	222 (3.9)	202 (3.6)	1.11 (0.91–1.34)	0.30	1.10 (0.91–1.33)	0.33
Stroke	56 (1.0)	52 (0.9)	57 (1.0)	0.98 (0.68–1.41)	0.90	0.91 (0.63–1.33)	0.63
Transient ischemic attack	25 (0.4)	30 (0.5)	20 (0.4)	1.24 (0.69–2.24)	0.47	1.50 (0.85–2.65)	0.16
Myocardial infarction	70 (1.2)	73 (1.3)	52 (0.9)	1.34 (0.94–1.92)	0.11	1.41 (0.98–2.00)	0.06

Wise RA, et al. N Engl J Med. 2013

Mortalità in pazienti con alterazioni del ritmo cardiaco

- **Il tasso di mortalità era simile tra i gruppi, nei pazienti con aritmie cardiache al basale:**
  - **Con aritmie (n=1221):**
    - **10.6% vs 12.9% (Respimat® 5 µg vs HandiHaler®)**
    - **HR 0.81 (95% CI, 0.58-1.12)**

Respimat 2.5µg	Respimat 5µg	Handihaler 18µg	Confronto	HR (95%CI)
79 (13.1%)	65 (10.6%)	78 (12.9%)	Respimat 5 vs HandiHaler 18	**0.81** (0.58, 1.12)
			Respimat 2.5 vs HandiHaler 18	**1.02** (0.74,1.39)

Wise RA, et al. N Engl J Med. 2013

TIOSPIR - Conclusioni

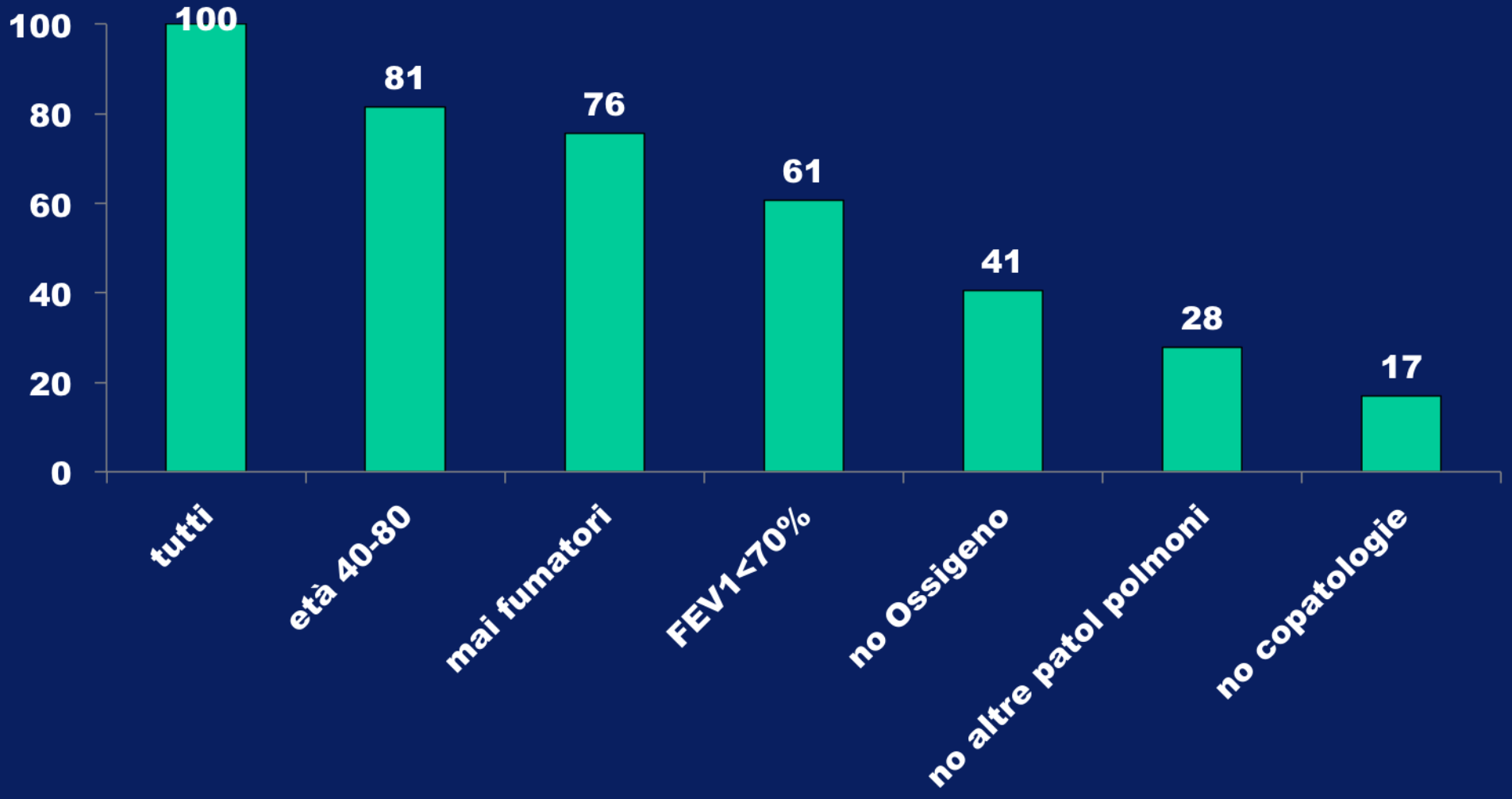
- **Tiotropio Respimat (5 e 2.5µg) ha dimostrato di avere un profilo di sicurezza e di efficacia sulle riacutizzazioni simile a quello di tiotropio HandiHaler**

- **Lo studio TIOSPIR™ fornisce dati robusti sulla sicurezza ed efficacia di tiotropio Respimat® verso HandiHaler® in pazienti con BPCO**

- **I risultati di questo large-trial indicano che i dati provenienti da metanalisi condotte su set di dati limitati e da studi osservazionali devono essere interpretati con cautela**

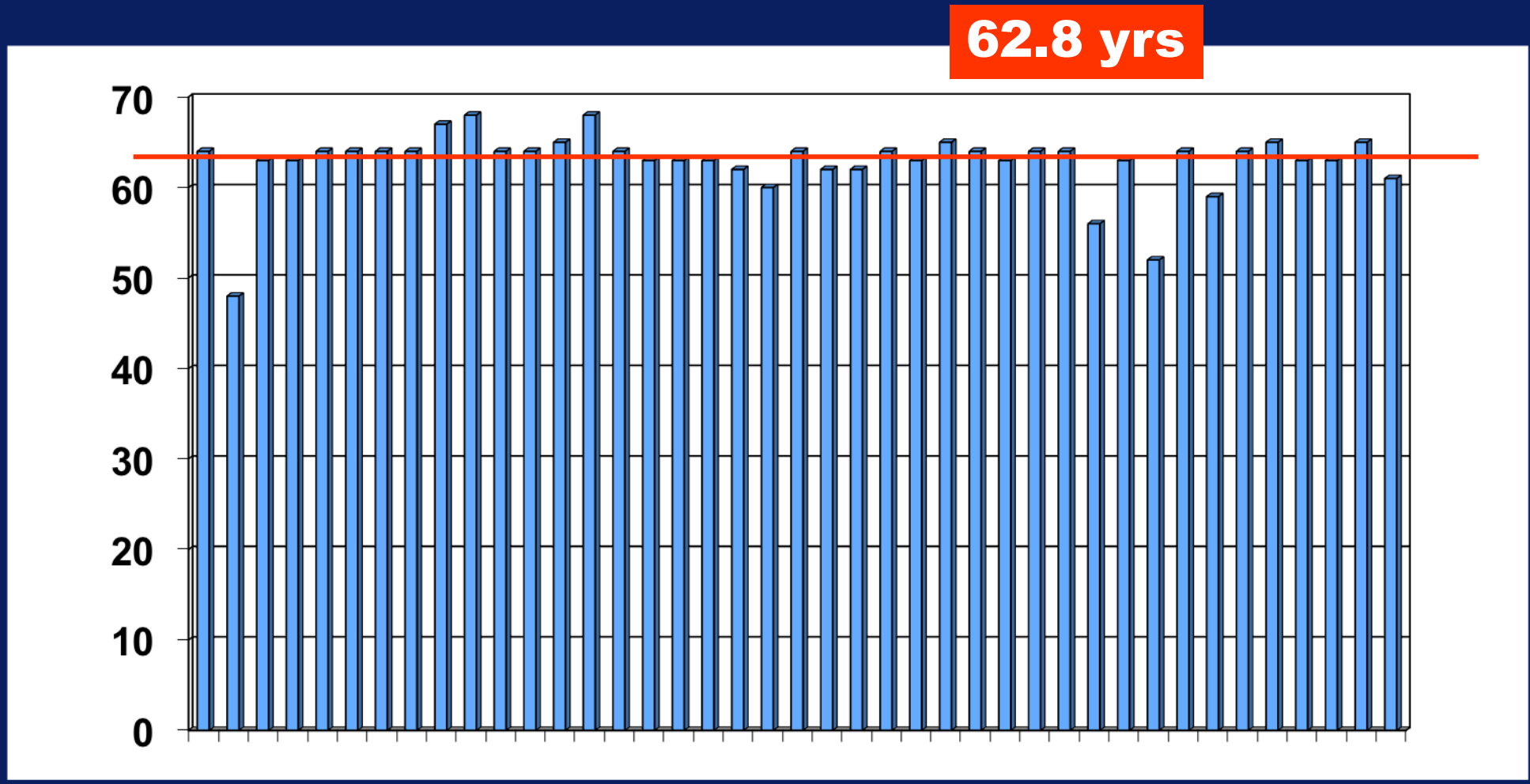
Wise RA, et al. N Engl J Med. 2013

Quanto la popolazione dei megatrial è rappresentativa dei pazienti *real-life*?



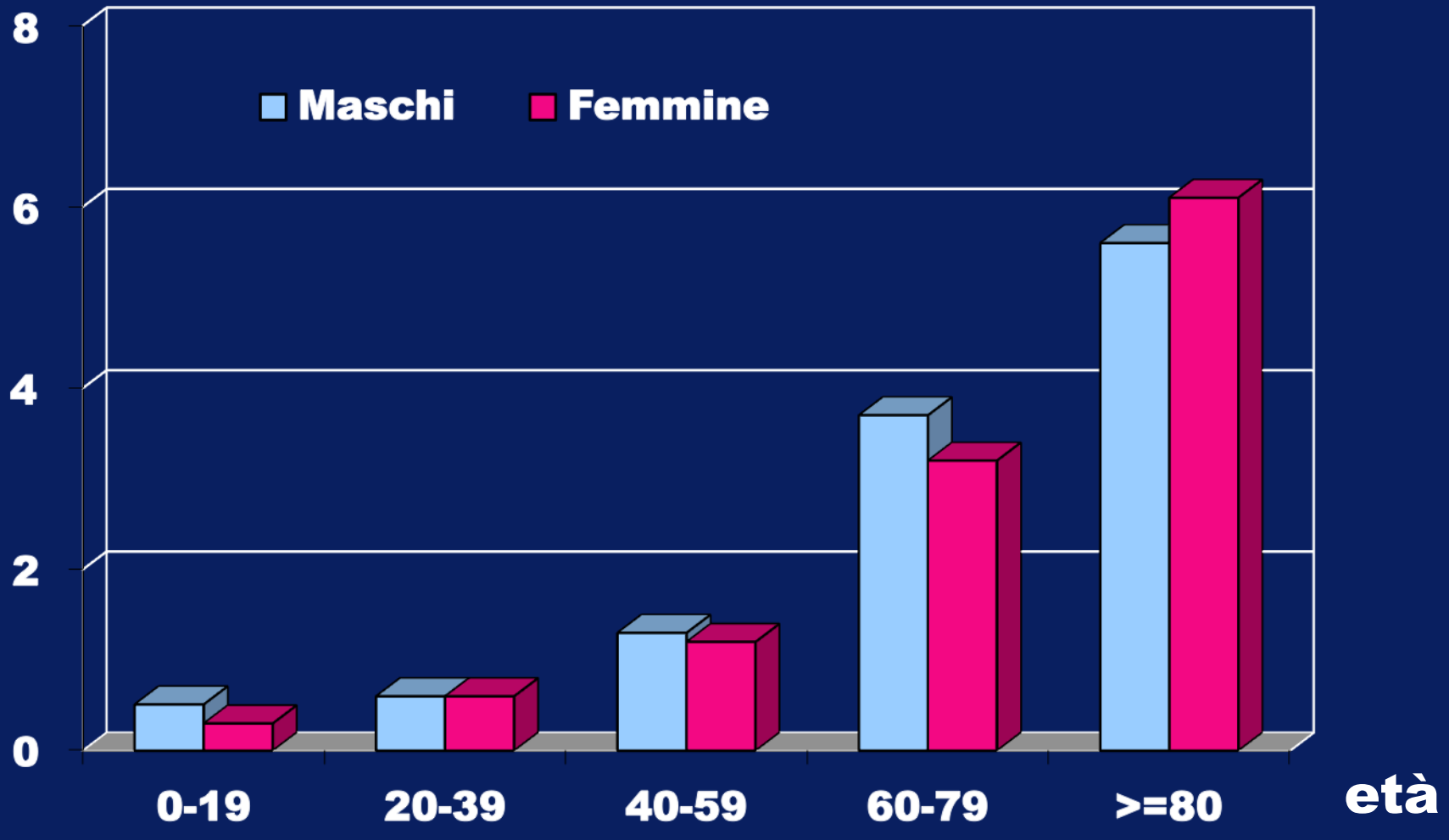
Scichilone et al. Respiration 2013

Età media nei trial clinici dell'anziano (n=42)



Courtesy of Prof. Gambassi

Invecchiamento e patologie prevalenti



van den Akker et al: J Clin Epidemiol 1998

How applicable are clinical practice guidelines to elderly patients with comorbidities?

Donatus R. Mutasingwa MD MPhil PhD CCFP Hong Ge MD MHSc CCFP Ross E.G. Upshur MD MSc CCFP FRCPC

Table 3. Clinical practice guidelines that include indicators of applicability to elderly patients with multiple comorbidities

INDICATORS	NO. OF CPGs ACTUALLY	ACTUALLY CPGs, BY DISEASE
Treatment of elderly	7	Osteoporosis,[24] dyslipidemia,[25] diabetes,[26] HTN,[27] CHF,[28] depression,[31] dementia[32-38]
People with comorbidities	8	Osteoarthritis,[ ] diabetes,[ ] HTN,[ ] CHF,[ ] depression,[ ] dementia,[ ] COPD,[ ] dyslipidemia[35]
Time needed to treat to benefit in the context of life expectancy	4	CHF,[28] COPD,[30] depression,[31] diabetes[26]
Barriers to implementation	5	Diabetes,[26] HTN,[27] CHF,[28] depression,[31] dementia[32-38]
Quality of evidence	7	Dyslipidemia,[25] HTN,[27] CHF,[28] depression,[31] diabetes,[26] dementia,[32-38] COPD[30]

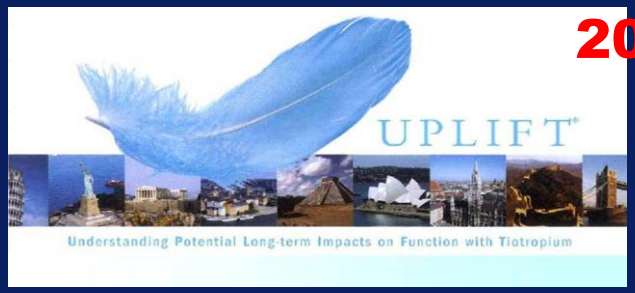
CHF—congestive heart failure, COPD—chronic obstructive pulmonary disease, CPGs—clinical practice guidelines, HTN—hypertension.

Conclusion This study shows that although most CPGs discuss the elderly population, only a handful of them adequately address issues related to elderly patients with comorbidities. In order to make CPGs more patient centred rather than disease driven, guideline developers should include information on elderly patients with comorbidities.

Mutasingwa et al. Can Fam Physician 2011

Cosa ci insegna TIOSPIR: Tiotropio e i megatrial

2008



Tiotropio HandiHaler vs Usual care
Durata:4 anni - **5.993 pz**
Outcomes:
- Funzione polmonare - Riacutizzazioni
- Mortalità

2010

A one-year trial of tiotropium Respimat® plus usual therapy in COPD patients

Tiotropio RMT vs Usual Care
Durata: 1 anno - **3.991 pz**
Outcomes:
- Riacutizzazioni – Funzione Polmonare

2011

Tiotropio HH vs salmeterolo
Durata: 1 anno - **7.376 pz**
Outcomes:
- Riacutizzazioni

2013

Tiotropio Respimat vs Tiotropio HH
Durata 2.3 anni – **17.135 pz**
- Riacutizzazioni
- Mortalità per tutte le cause

1.Tashkin D P et al N Engl J Med 2008 Vol 359; N°15 pp 1543-1554; 2. Beteman AD et All, Respiratory Medicine 2010 ; 3. Vogelmeier C et al. N Engl J Med 2011; 364: 1093-1103; 4. Wise RA, et al. N Engl J Med. 2013 Aug 30. [Epub ahead of print