Profilo farmacologico e clinico di aclidinio bromuro nel paziente anziano

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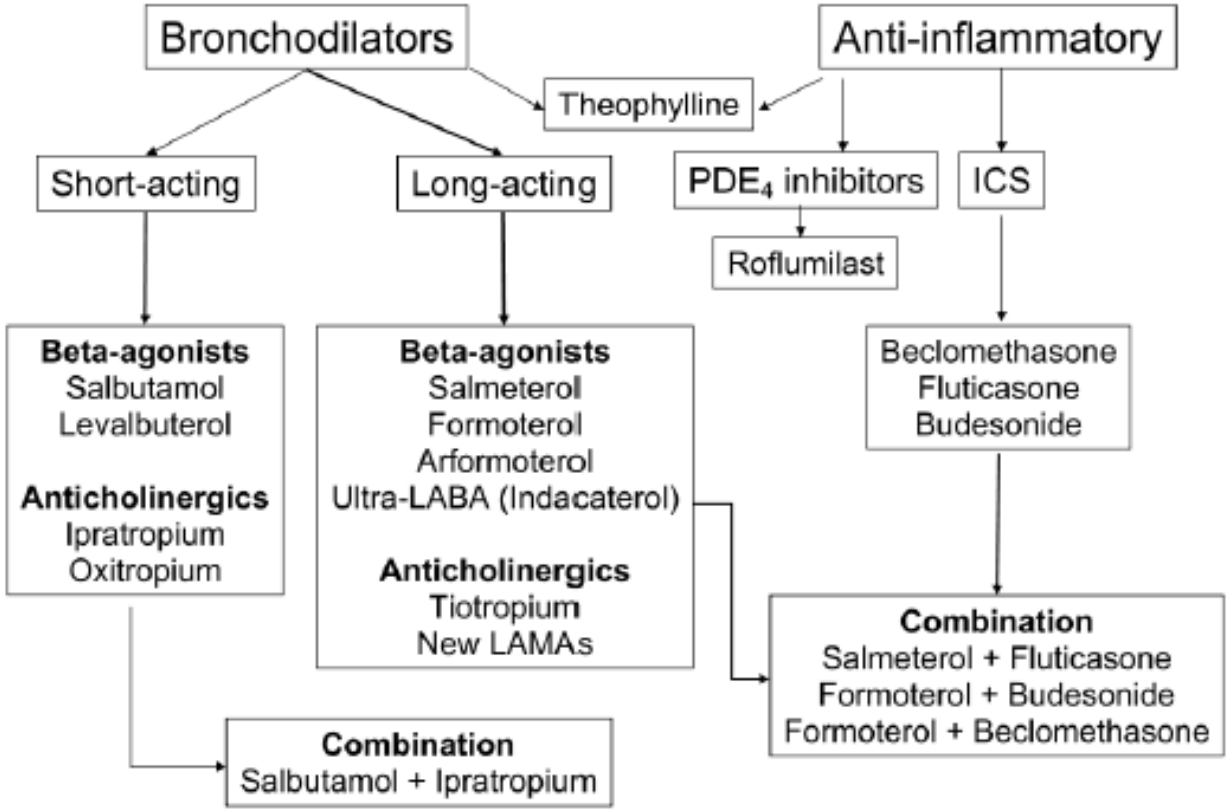
Armamentario terapeutico per la BPCO

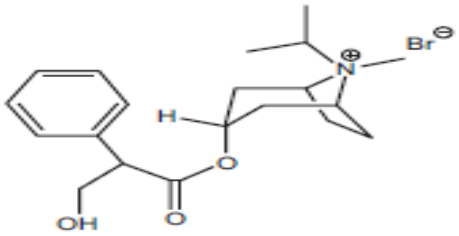
(Montuschi P et al. Curr Med Chem 2013; 20: 1464)



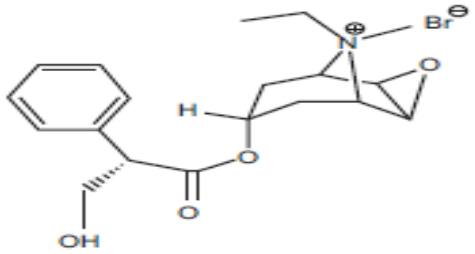
Il recettore muscarinico

- M3: principale responsabile della contrazione muscolare (e secrezione mucosa). Sebbene M2:M3=4:1, M3 regola il tono bronchiale, specie nella BPCO.
- Media effetti intestinali, urinari, oculari e orali.

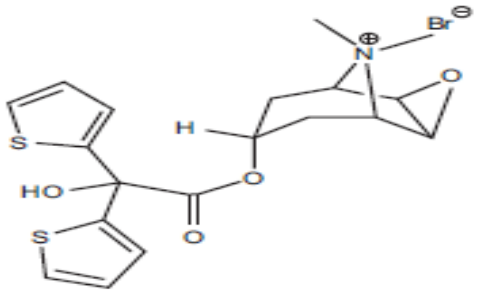
- M1: sito nei gangli parasimpatici delle vie aeree, facilita la neurotrasmissione gangliare
- M2: nelle terminazioni colinergiche, inibisce il rilascio di Ach dal nervo, ma inibisce il beta stimolo (#cAMP). Media l'effetto cronotropo negativo



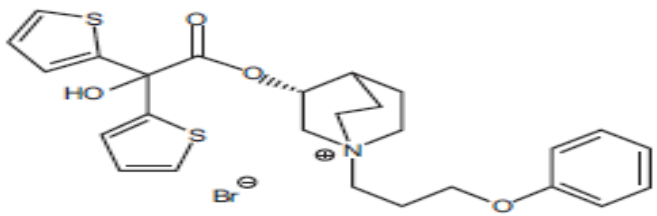
Ipratropium bromide



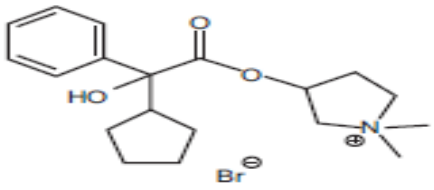
Oxitropium bromide



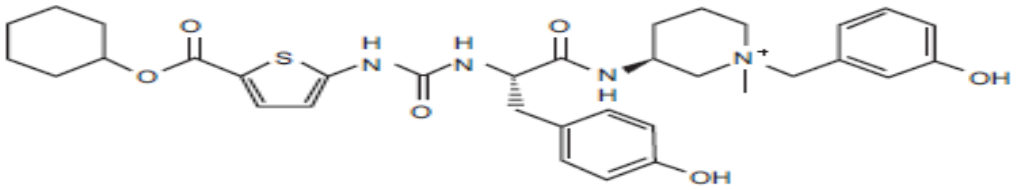
Tiotropium bromide



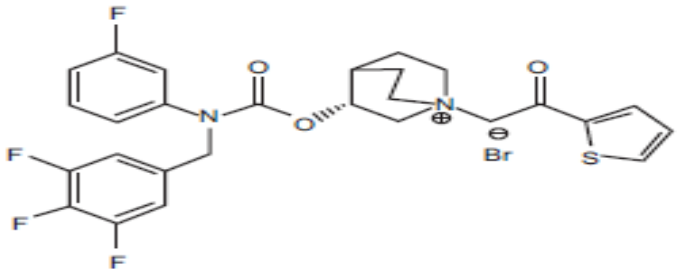
Aclidinium bromide



Glycopyrronium bromide



Umeclidinium bromide



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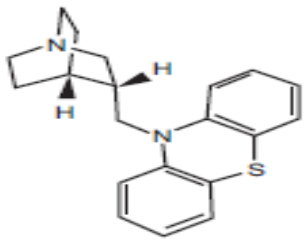

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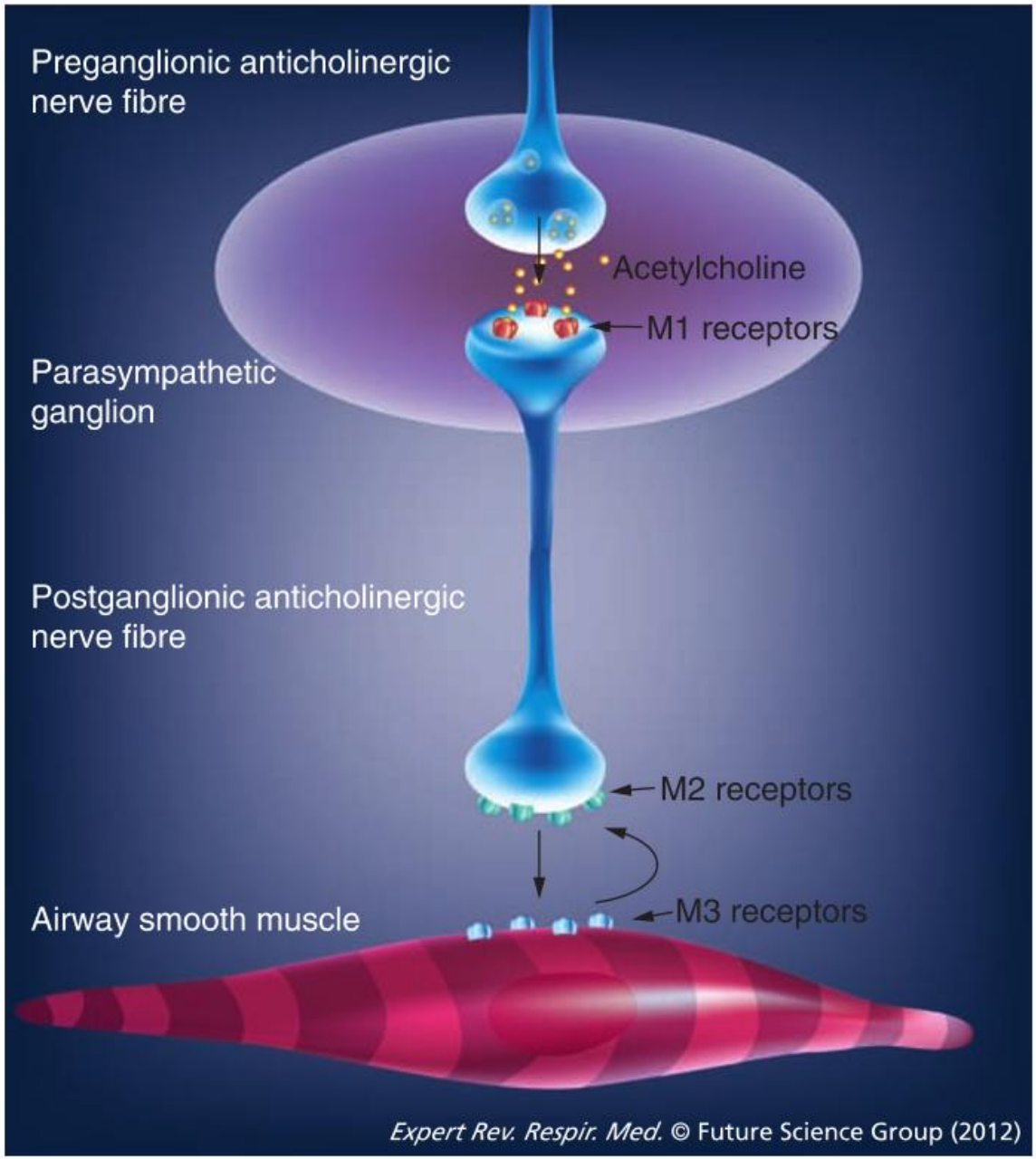

Preganglionic anticholinergic nerve fibre
Acetylcholine
M1 receptors
Parasympathetic ganglion
Postganglionic anticholinergic nerve fibre
M2 receptors
M3 receptors
Airway smooth muscle
Expert Rev. Respir. Med. © Future Science Group (2012)

Il tiotropio: un LAMA efficace e sicuro

- Tiotropium Respimat at a dose of 5 µg or 2.5 µg had a safety profile and exacerbation efficacy similar to those of tiotropium HandiHaler at a dose of 18 µg in patients with COPD. (Wise RA et al ; N Engl J Med 2013; 369:1491) …)

- In patients with COPD, therapy with tiotropium was associated with improvements in lung function, quality of life, and exacerbations during a 4-year period but did not significantly reduce the rate of decline in FEV1. (Tashkin DP et al N Engl J Med 2008;359:1543)

Aclidinio: razionale e specificità

- Perché un altro LAMA dopo il Tiotropio?
- - Problemi di clearance nell'insufficienza renale
- - Aumento tono bronchiale a fine dose in una minoranza, non trascurabile, di pazienti
- - Opportunità di sincronizzare uso di LABA e LAMA in alcuni pazienti che usano LABA b i d

L'effetto nel sano (Shelfout VJ et al. Br J Clin Pharmacol 2010; 69: 458)

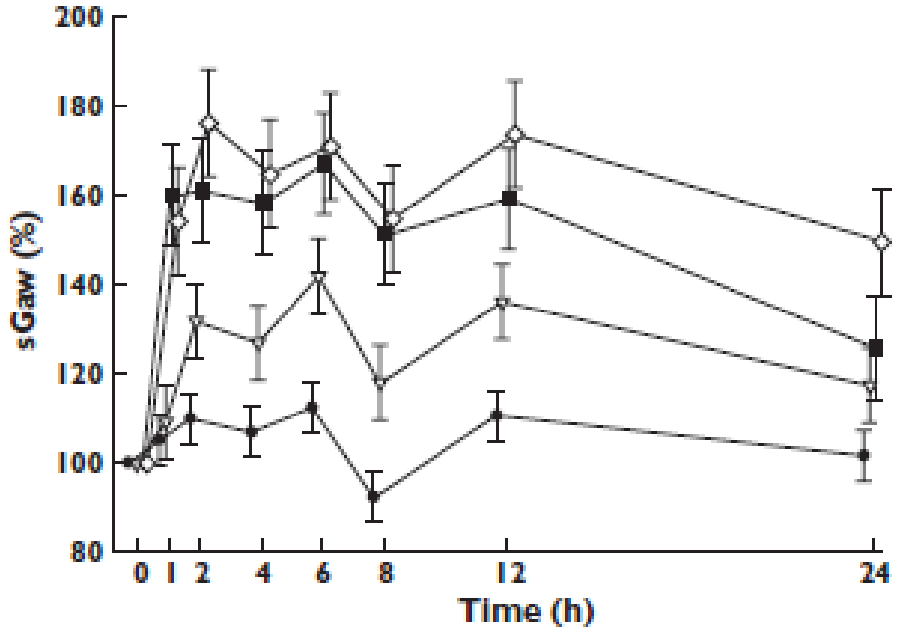


Figure 1

Mean (± SE) changes in specific airway conductance (sGaw, %) over 24 h as a percentage of baseline value. Placebo (—●—); 50 µg aclidinium bromide (—▽—); 300 µg aclidinium bromide (—■—); 600 µg aclidinium bromide (—◇—)

L'effetto nel sano (Shelfout VJ et al. Br J Clin Pharmacol 2010; **69:** 458)

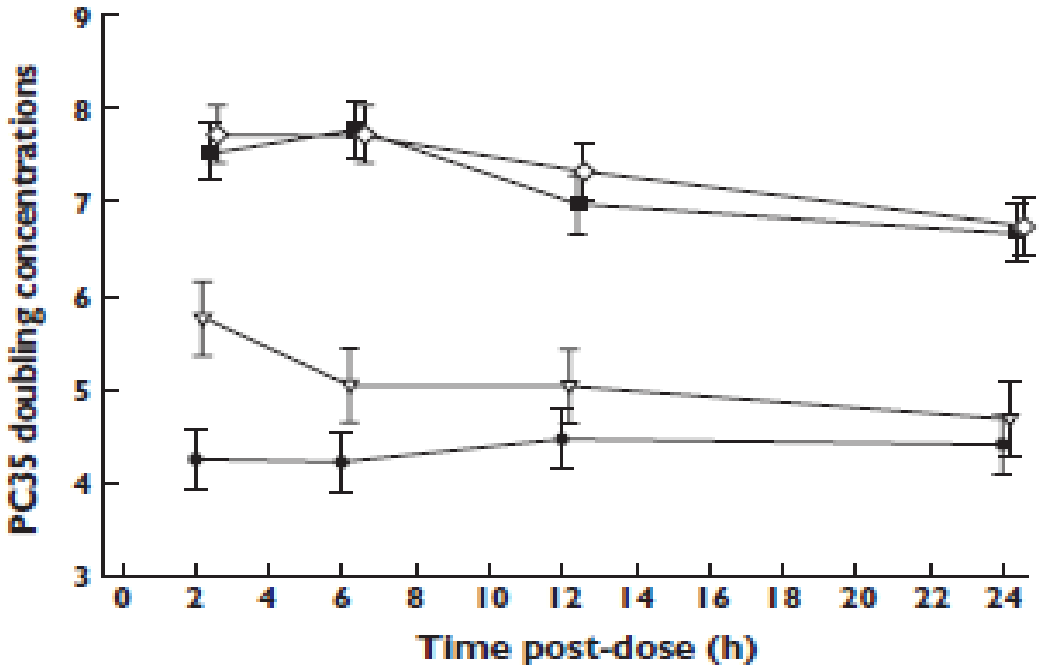
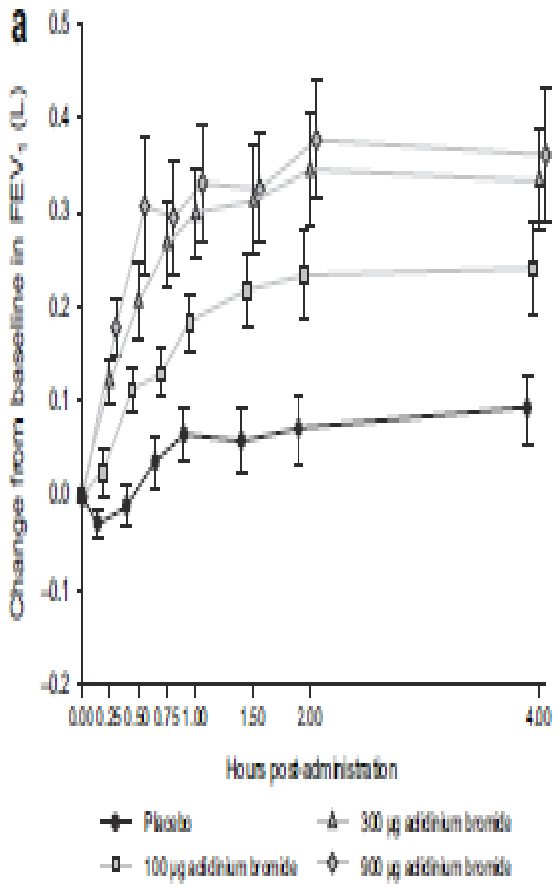
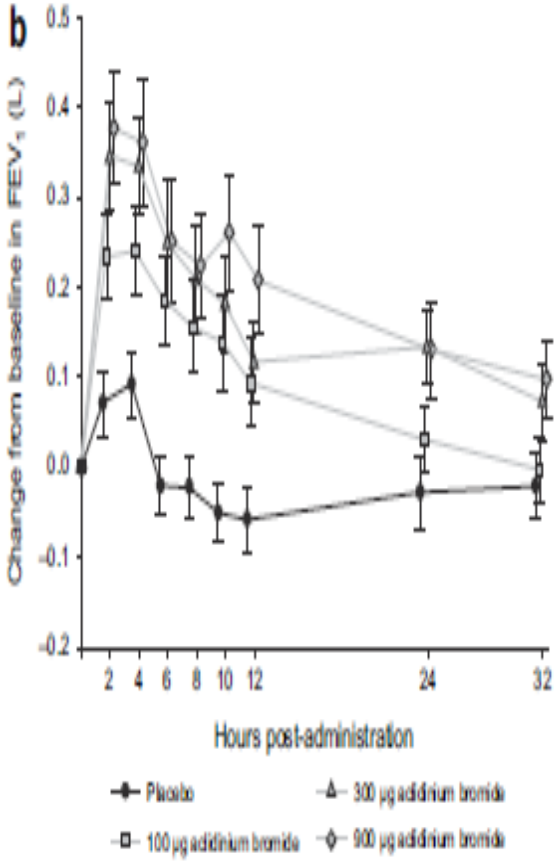


Figure 3

Effect of aclidinium on methacholine-induced bronchoconstriction, as measured by PC35 sGaw doubling concentrations (data shown as least squares means ± SE). Placebo (—●—); 50 µg aclidinium bromide (—▽—); 300 µg aclidinium bromide (—■—); 600 µg aclidinium bromide (—◇—)

..e nel malato BPCO (Joos GF et al. Respir Med 2010; 104:, 865)





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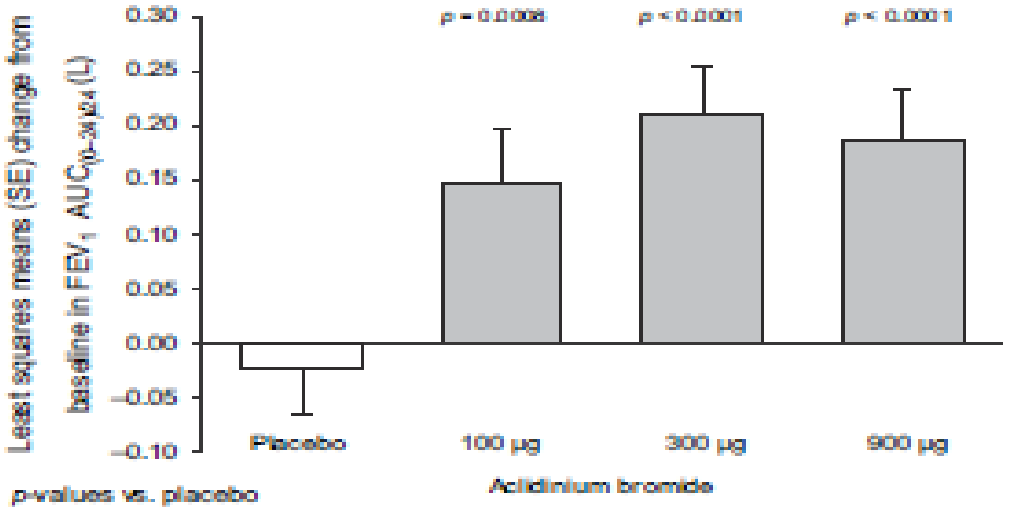


Figure 1 Change from baseline in area under the normalised concentration time curve of forced expiratory volume in 1 s over the 24-h time period (FEV_1 $AUC_{[0–24]/24}$).

Aclidinio: un metabolismo specialmente plasmatico (Albertì J et al. DMD 2010; 38:1202)

TABLE 1

Aclidinium hydrolysis and BChE activities in different human subcellular fractions

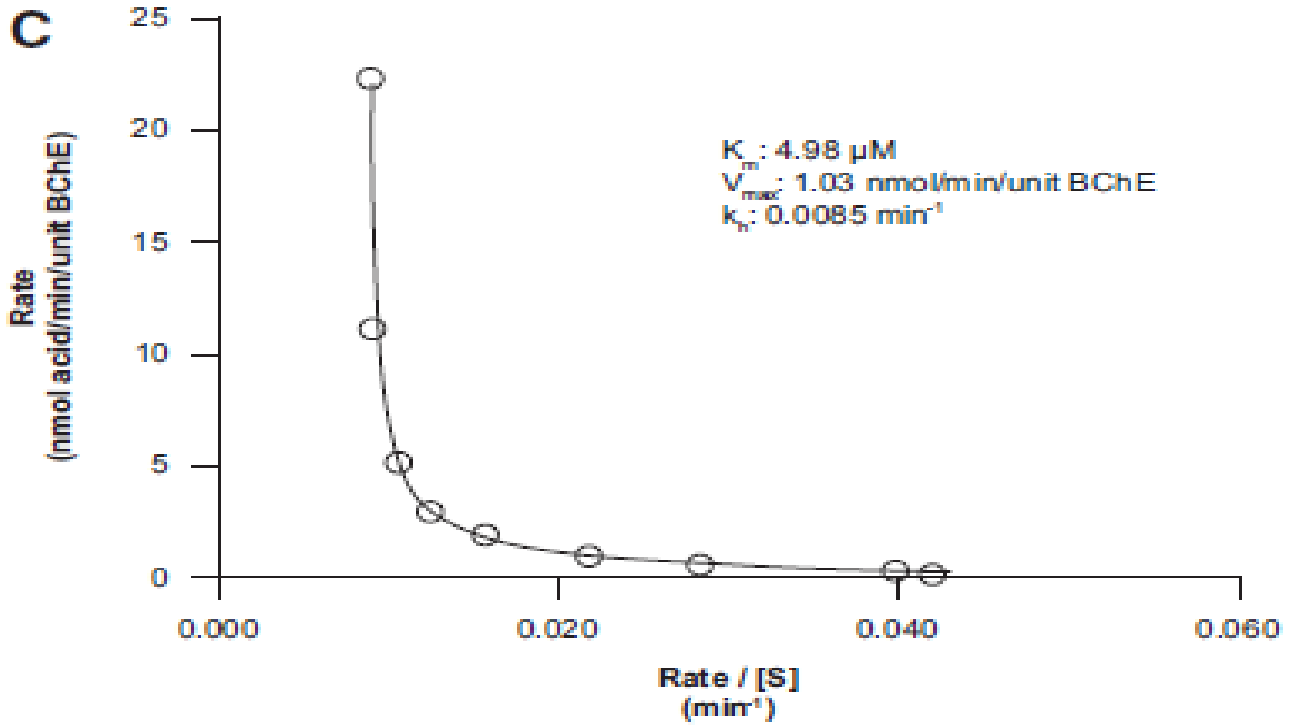
The net enzymatic hydrolysis results are expressed as the mean of duplicate measurements. BChE activities were determined as reported in the experimental section and expressed as the mean of three measurements ± S.D. unless indicated otherwise.

Tissue	Fraction	Source/Batch	Net Enzymatic Aclidinium Hydrolysis	BChE Activity
			pmol alcohol/min/mg protein	*nmol thiocholine/min/mg protein*
Blood	Plasma	Almirall, S.A./NA	93.2	50.9 ± 16.0[a]
	Red blood cells	Almirall, S.A./NA	1.1	1.9 ± 0.1
Liver	Microsomal	XenoTech,/0210002	19.0	7.0 ± 0.1
	S9	Human Biologics International/1.0	42.0	4.2 ± 0.1
Lung	Microsomal	XenoTech,/0210354	38.0	15.5 ± 0.2
	S9	XenoTech,/0210352	54.0	13.3 ± 0.2

NA, not applicable.

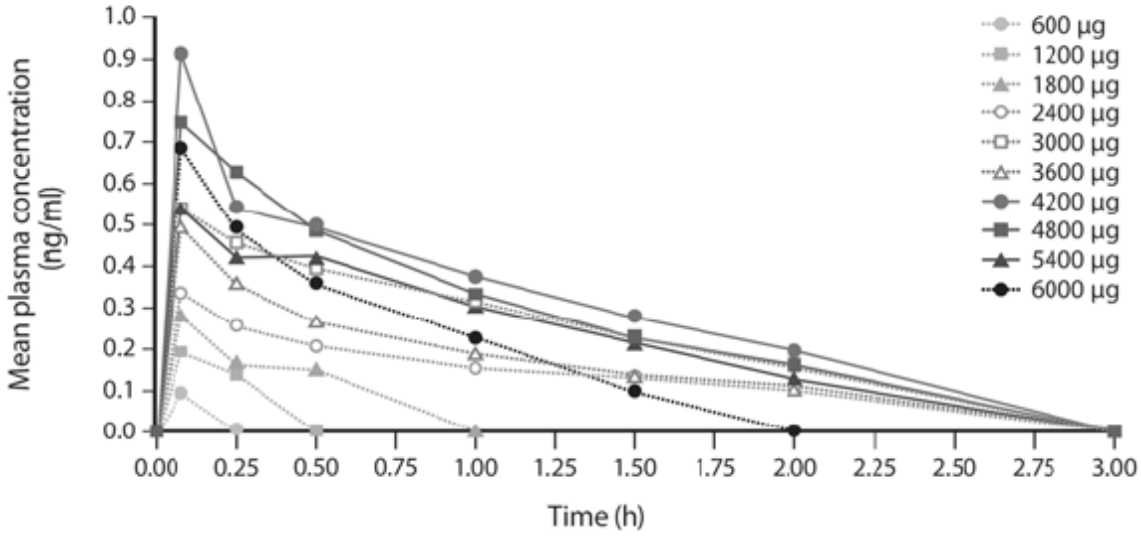
[a] Mean value ± S.D. (n = 6).

…e molto rapido (Albertì J et al. DMD 2010; 38:1202)



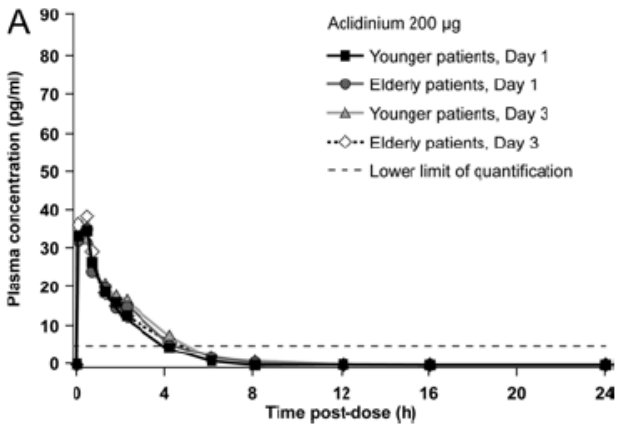
Rapida clearance anche ad alte dosi

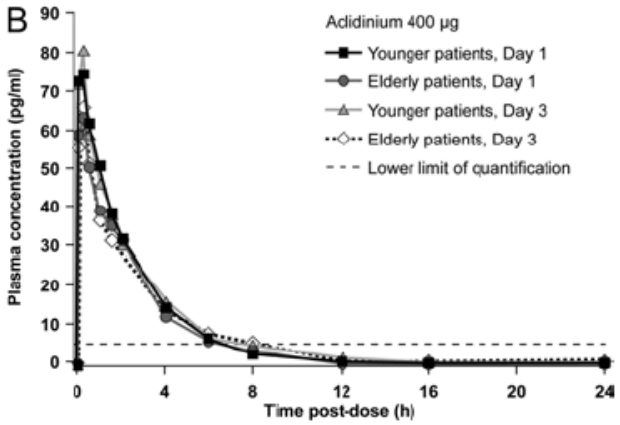
(Jansat JM et al. *Intern J Clin Pharmacol Ther 2009; 47: 460)*

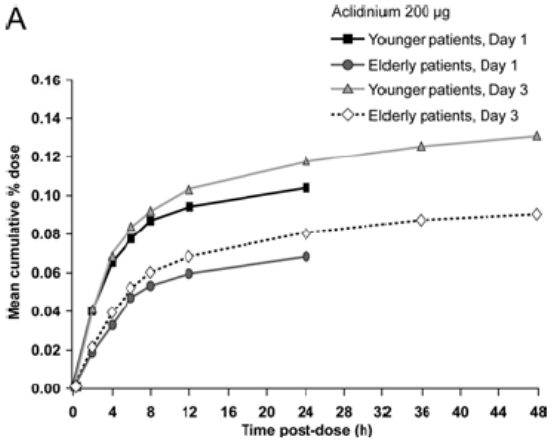


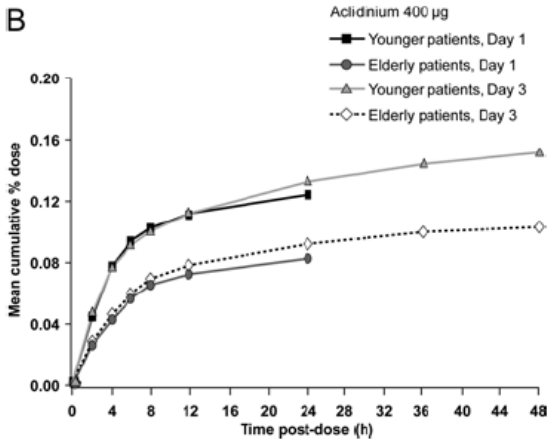
Non servono aggiustamenti posologici nell'anziano

(de la Motte S et al. Int J Clin Pharmacol Ther 2012; 50:403)

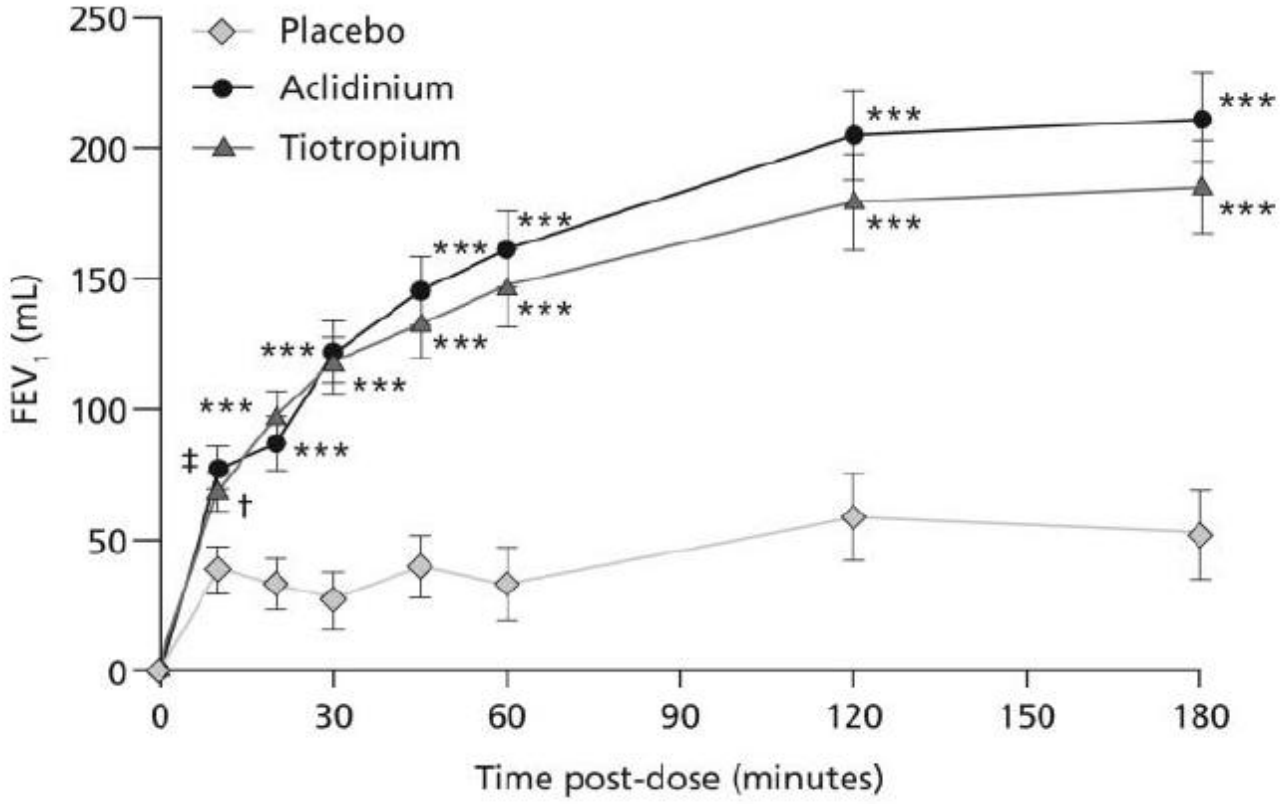






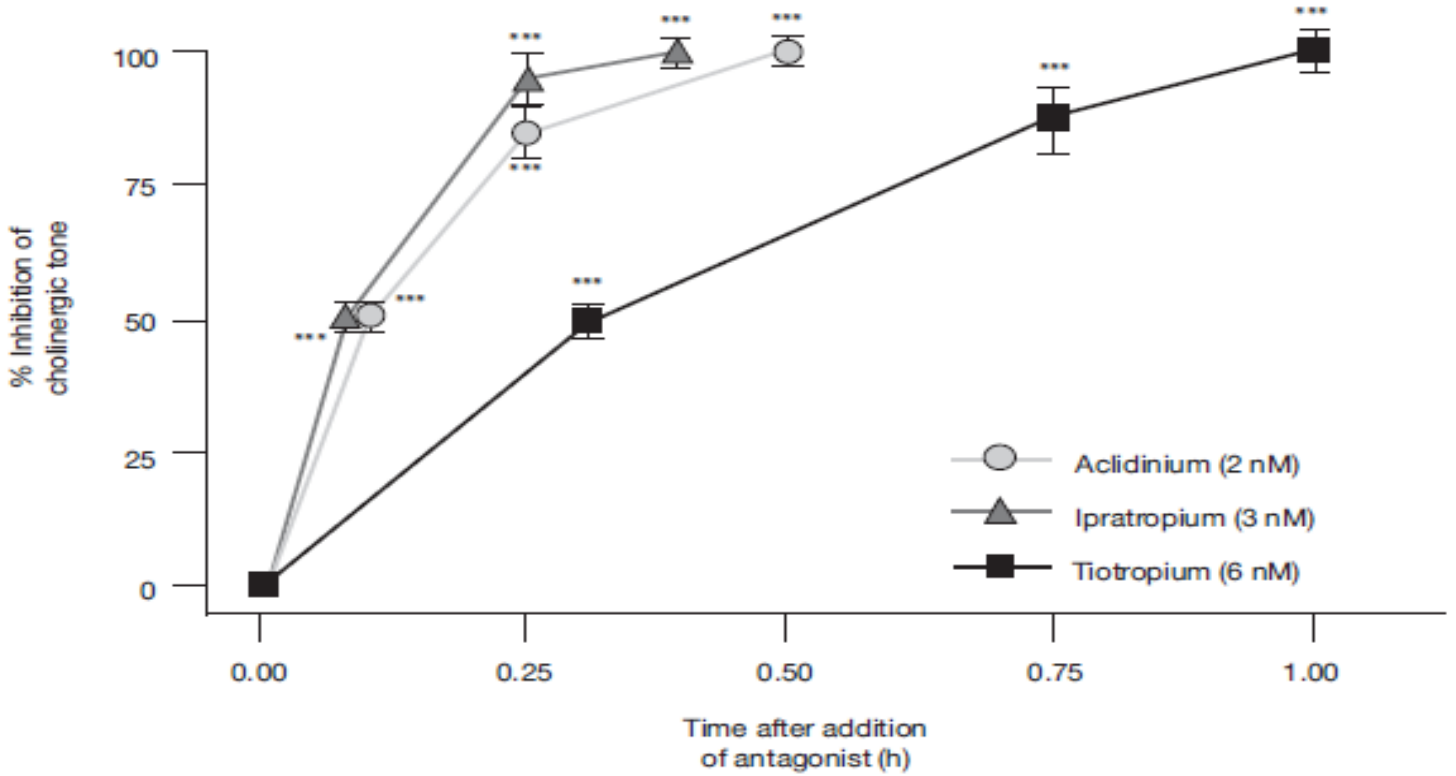


Efficace come il tiotropio sul FEV1 (Vestbo J et al. *J COPD 2010;* 7:331)



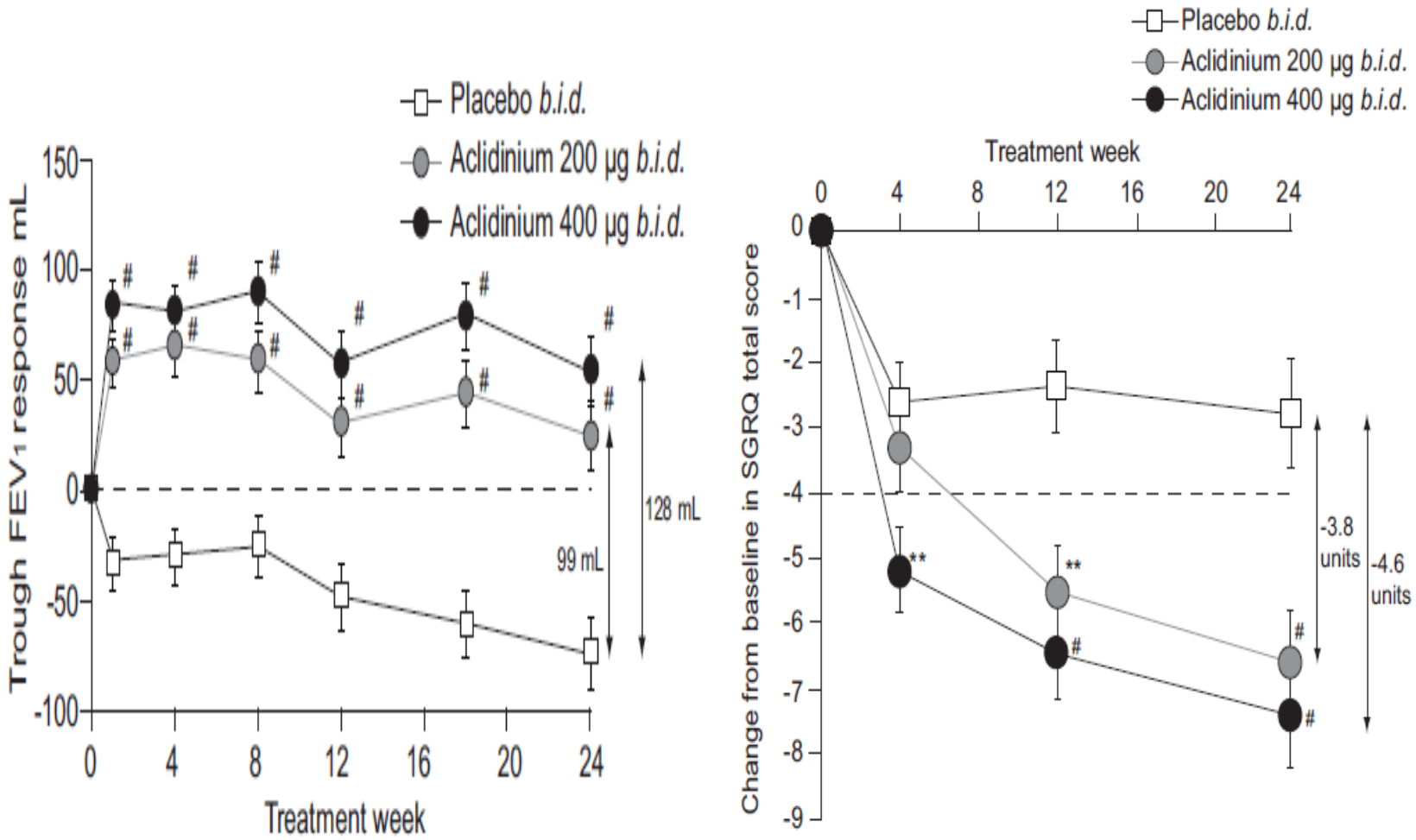
. . . comparabile con l'ipratropio (Gavaldà A et al

JPET 2009; 331:740)



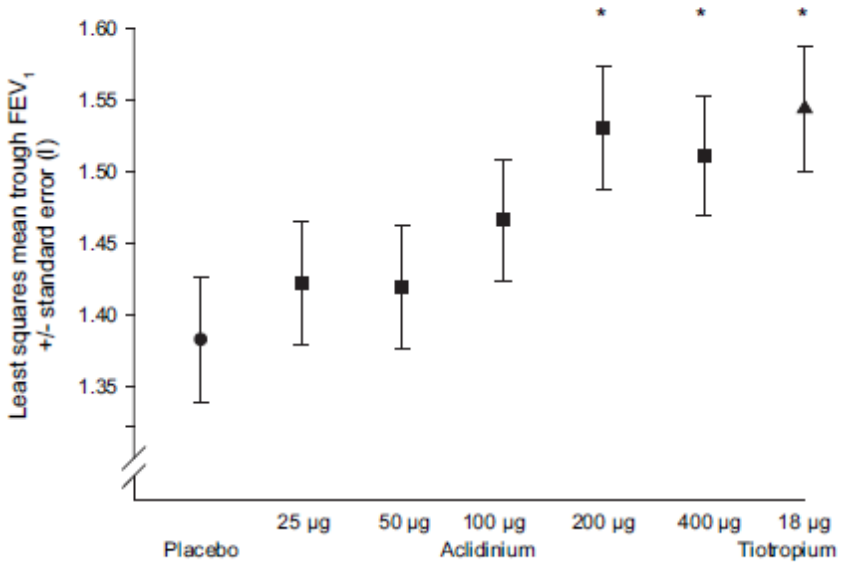
Lo studio Attain conferma l'efficacia

(Jones PW et al. Eur Respir J 2012; 40: 830)



Già alla dose di 200 mcg b i d

(Chanez P et al. Pulm Pharmacol Ther 2010; 23: 15)



* p<0.05 versus placebo on day 29

Fig. 2. Trough FEV_1 values on day 29 (intent-to-treat population).

Efficace sulla tolleranza all'esercizio

(Maltais F et al. Respir Med 2011; 105: 580)

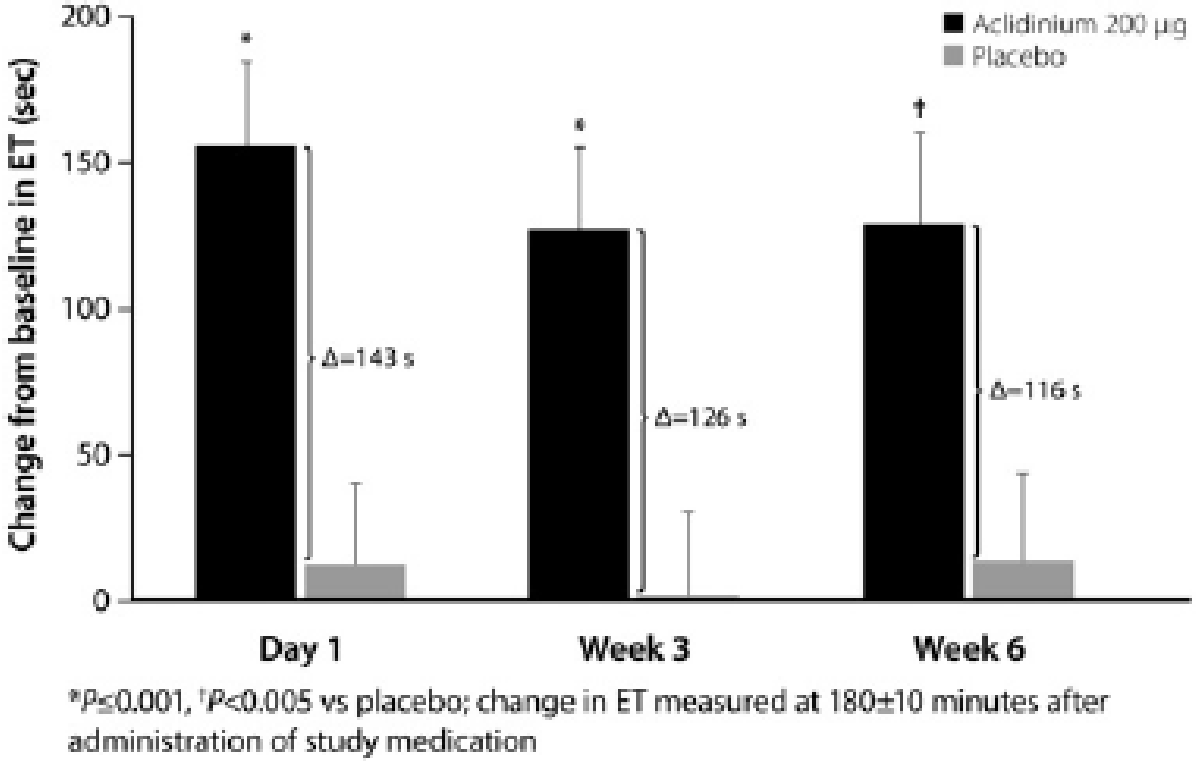
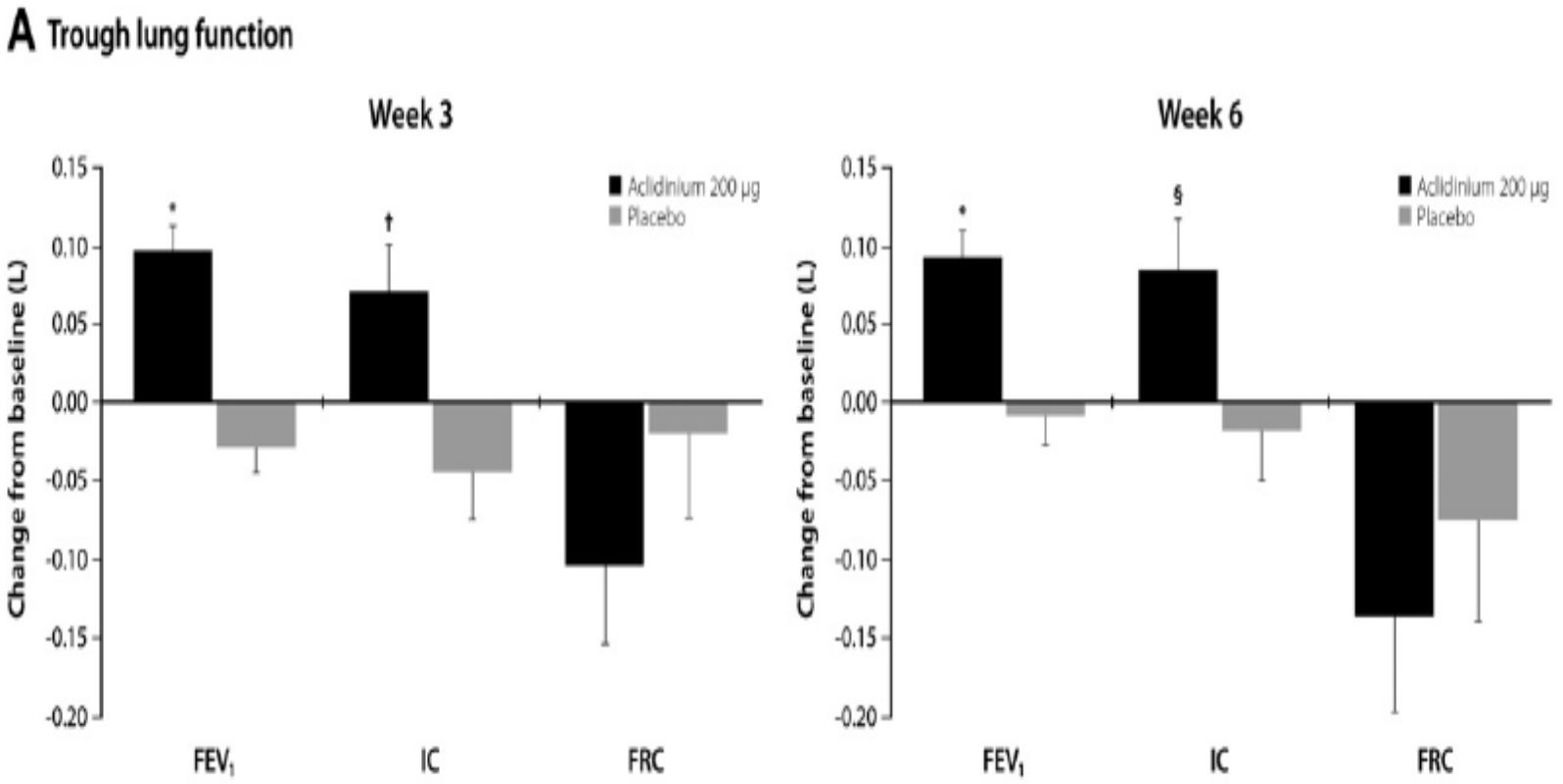


Figure 2 Adjusted mean (SE) change from baseline in endurance time (ET) throughout the study.

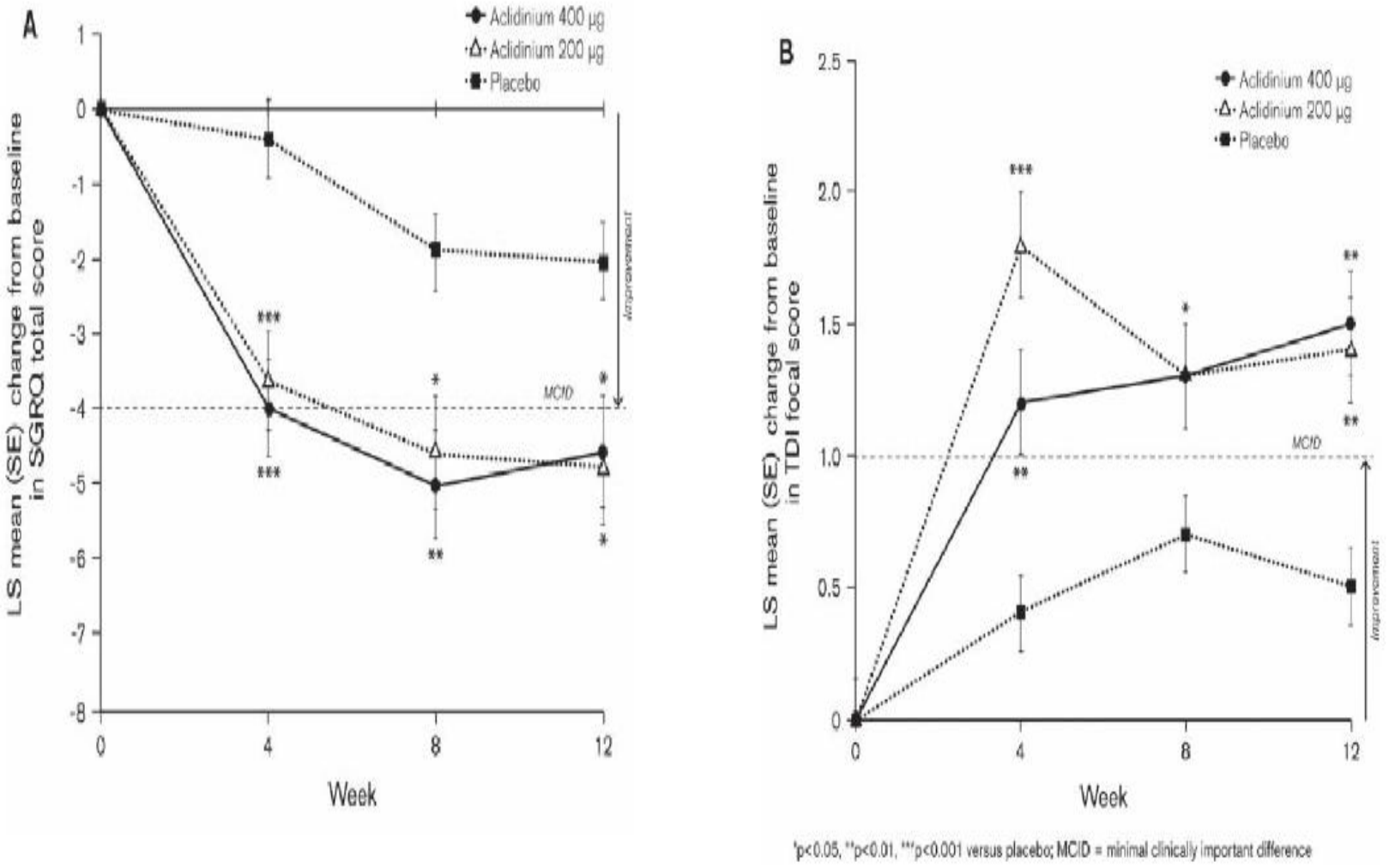
…e sull'air trapping

(Maltais F et al. Respir Med 2011; 105: 580)

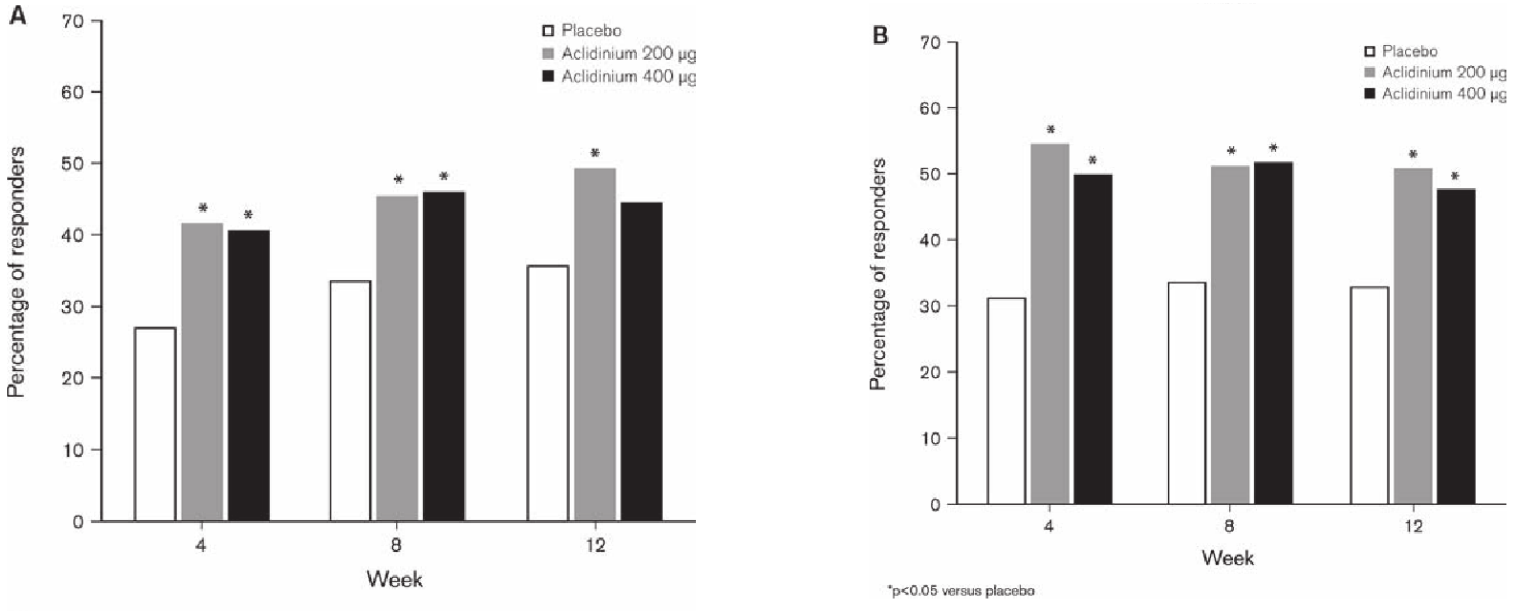


Efficace su stato di salute e dispnea

(Kerwin ED et al. COPD; 2012; 9: 90)

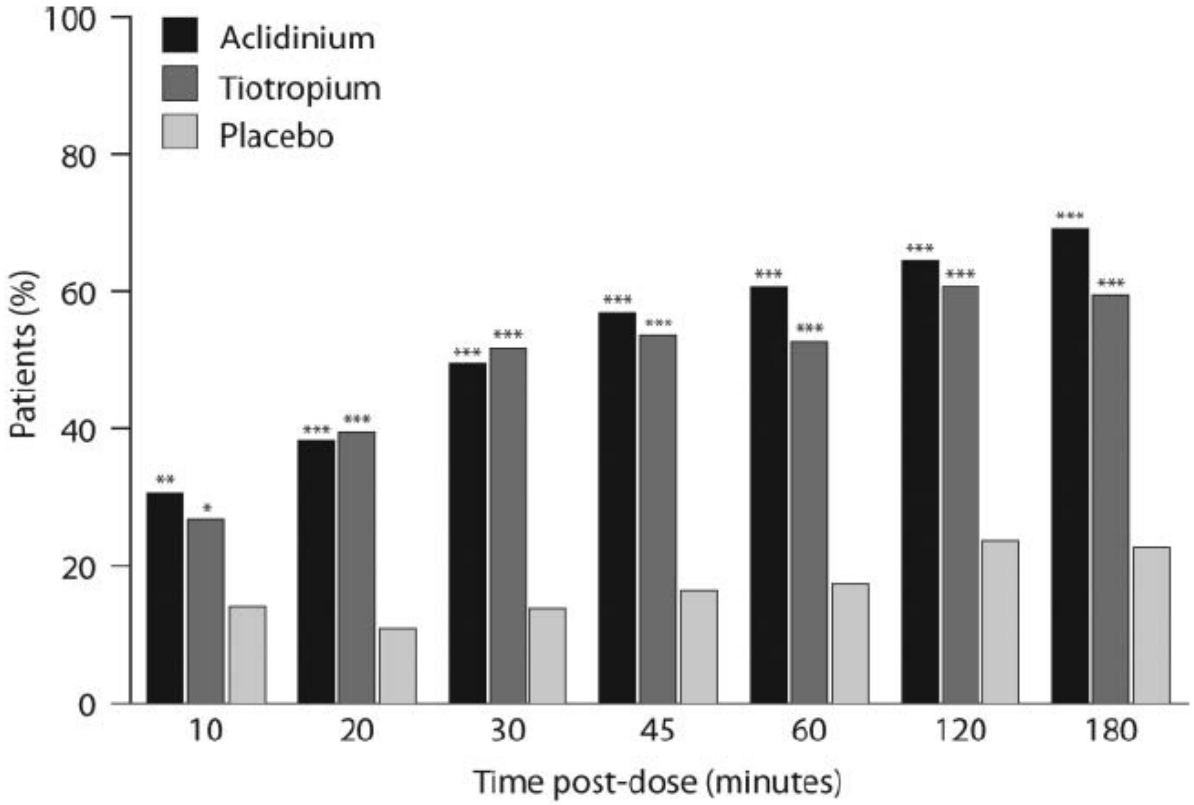


…ma, come per ogni farmaco, non tutti rispondono (Kerwin ED et al. COPD; 2012; 9: 90)



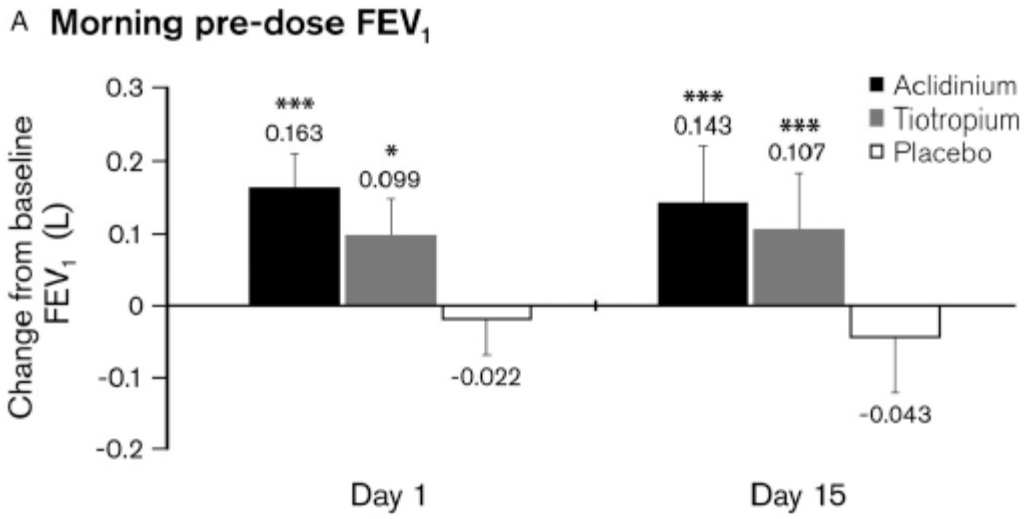
Prevalenza di responders ad aclidinio e tiotropio

(Vestbo J et al. *J COPD 2010;* 7:331)



*p<0.05 vs placebo; **p<0.01 vs placebo; ***p<0.0001 vs placebo
Differences between aclidinium and tiotropium were not statistically significant

Più efficace del tiotropio sull'ostruzione al risveglio in una popolazione adulta (Fuhr R et al. CHEST 2012; 1417 45–752)



Più efficace del tiotropio sui sintomi in una popolazione adulta (Fuhr R et al. CHEST 2012; 1417 45–752)

Table 4—*Change From Baseline in COPD Symptom Scores on Day 15 (Intention-to-Treat Population)*

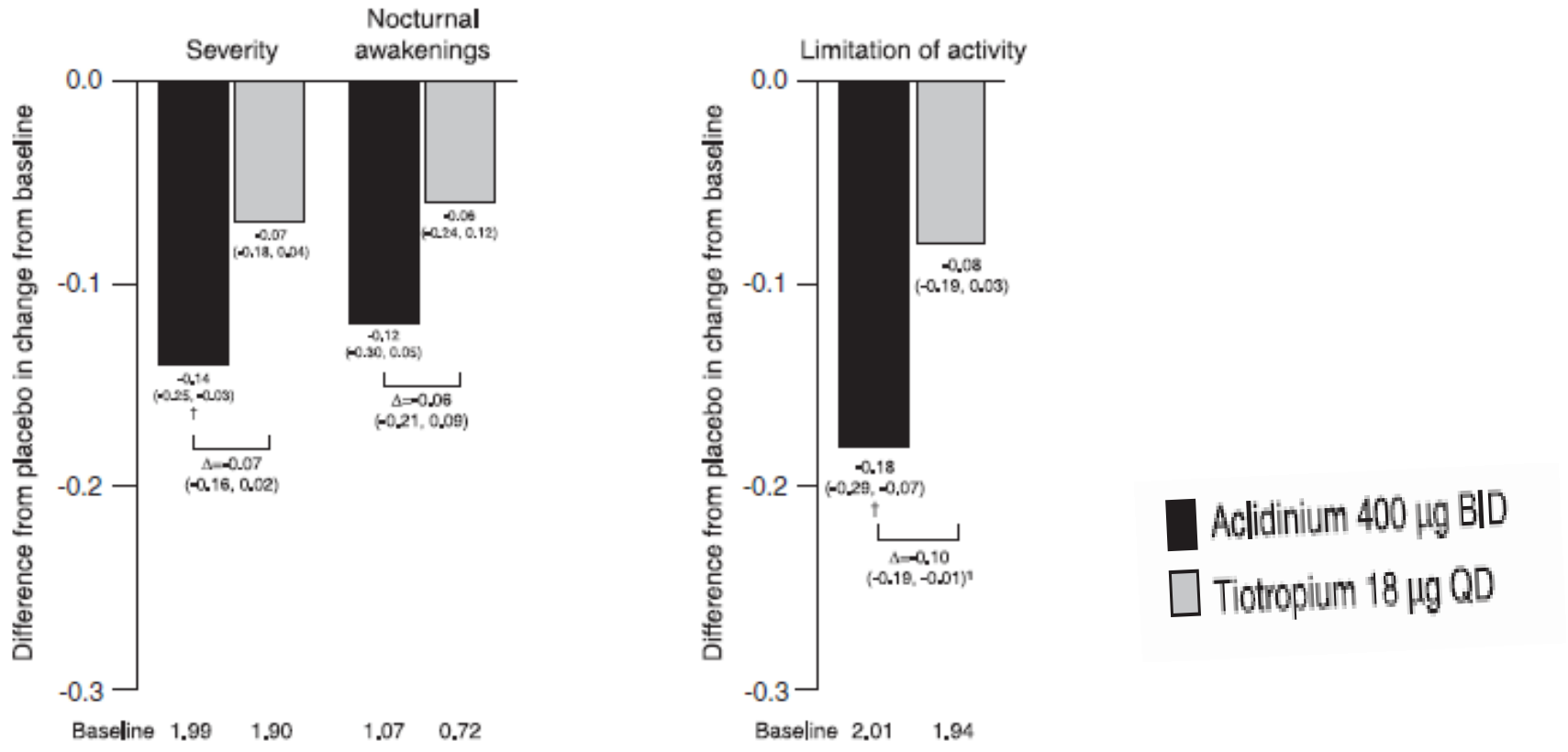
	Aclidinium (n = 29)	Tiotropium (n = 28)	Placebo (n = 30)
Breathlessness	−0.289 ± 0.126[a]	−0.197 ± 0.128	0.020 ± 0.124
Cough	−0.147 ± 0.118[a]	−0.016 ± 0.120	0.138 ± 0.117
Sputum[b]	−0.013 ± 0.082	0.126 ± 0.084	0.032 ± 0.081
Nighttime symptoms	−0.123 ± 0.089[a]	−0.011 ± 0.091	0.061 ± 0.088

Data are presented as mean ± SE. COPD symptom scores scale is from 0 (none) to 4 (severe), unless otherwise indicated.

[a]$P < .05$ vs placebo.

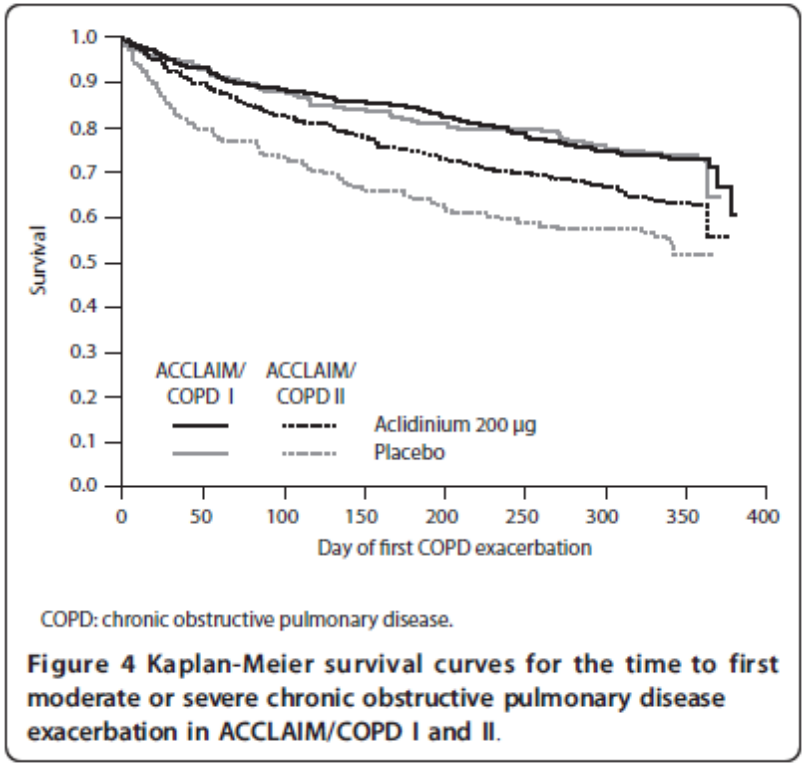
[b]Scale is from 0 (none) to 3 (> 1 Tbsp).

La conferma in un RCT (Beier G et al. *COPD, 00:1–12, 2013)*



Efficacia nel prevenire le riacutizzazioni: da precisare

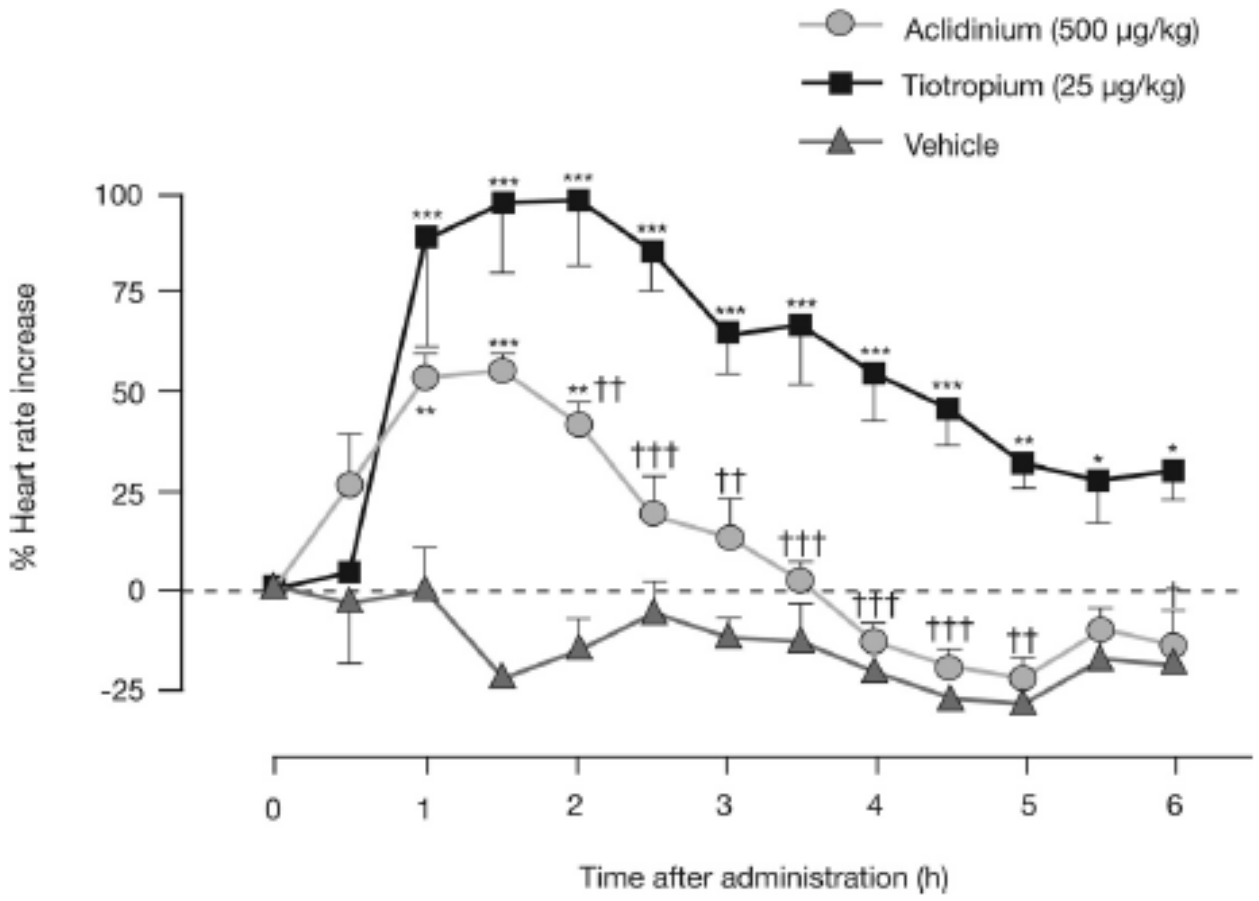
(Jones PW et al. Respir Res 2011, 12:55)



COPD: chronic obstructive pulmonary disease.

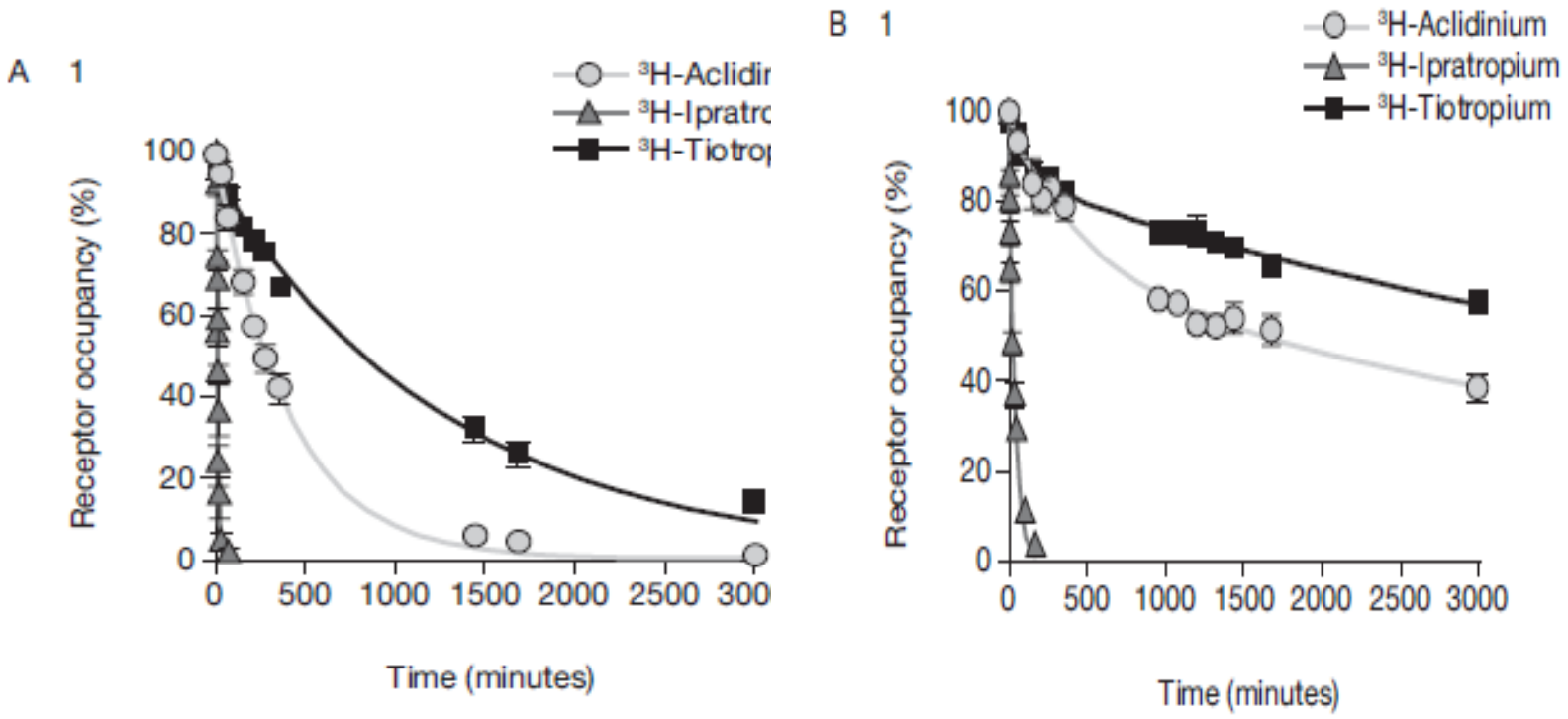
Figure 4 Kaplan-Meier survival curves for the time to first moderate or severe chronic obstructive pulmonary disease exacerbation in ACCLAIM/COPD I and II.

Effetto cronotropo positivo minore del tiotropio (Gavaldà A et al JPET 2009; 331:740)



Elevata affinità M3: % occupazione recettori M2 (A) e M3 (B)

(Gavaldà A et al JPET 2009; 331:740)



Aclidinio, un farmaco sicuro: studio Accord

(D'Urzo A et al. COPD 2013; 10: 500)

Table 3. Treatment-emergent cardiac adverse events reported by ≥2 patients in the total population (number [%]; safety population)

	Aclidinium 200 µg			*Aclidinium 400 µg*			
	Prior treatment in lead-in study			Prior treatment in lead-in study			
Preferred term	Placebo n = 44	Aclidinium 200 µg n = 93	Total n = 137	Placebo n = 46	Aclidinium 400 µg n = 106	Total n = 152	Total N = 289
Any cardiac TEAE	6 (13.6)	10 (10.8)	16 (11.7)	1 (2.2)	9 (8.5)	10 (6.6)	26 (9.0)
Left/right bundle branch block	3 (6.8)	5 (5.4)	8 (5.8)	0 (0)	3 (2.8)	3 (2.0)	11 (3.8)
Atrioventricular block first degree	1 (2.3)	2 (2.2)	3 (2.2)	1 (2.2)	1 (0.9)	2 (1.3)	5 (1.7)
Coronary artery disease	1 (2.3)	0	1 (0.7)	0	1 (0.9)	1 (0.7)	2 (0.7)
Congestive cardiac failure	2 (4.5)	0	2 (1.5)	0	1 (0.9)	1 (0.7)	3 (1.0)
Ventricular extrasystoles	1 (2.3)	1 (1.1)	2 (1.5)	0	0	0	2 (0.7)

Aclidinio un farmaco sicuro: studio Attain

(Jones PW et al. Eur Respir J 2012; 40: 830)

TABLE 3 Adverse events reported by ⩾2% of patients in any treatment group (safety population)

Preferred term	Patients		
	Placebo[#]	Aclidinium 200 µg *b.i.d.*[¶]	Aclidinium 400 µg *b.i.d.*[+]
COPD exacerbations	56 (20.5)	44 (15.9)	38 (14.1)
Headache	22 (8.1)	30 (10.8)	33 (12.3)
Nasopharyngitis	23 (8.4)	32 (11.6)	30 (11.2)
Rhinitis	7 (2.6)	4 (1.4)	9 (3.3)
Diarrhoea	3 (1.1)	5 (1.8)	8 (3.0)
Bronchitis	6 (2.2)	1 (0.4)	7 (2.6)
Hypertension	9 (3.3)	5 (1.8)	7 (2.6)
Cough	5 (1.8)	7 (2.5)	7 (2.6)
Toothache	1 (0.4)	3 (1.1)	6 (2.2)
Back pain	10 (3.7)	12 (4.3)	5 (1.9)
Influenza	6 (2.2)	3 (1.1)	5 (1.9)
Arthralgia	6 (2.2)	5 (1.8)	3 (1.1)
Urinary tract infection	2 (0.7)	6 (2.2)	2 (0.7)
Dyspepsia	6 (2.2)	5 (1.8)	1 (0.4)

Data are presented as n (%). COPD: chronic obstructive pulmonary disease. [#]: n=273; [¶]: n=277; [+]: n=269.

Particolarmente sicuro a livello cardiovascolare

Table 3 Treatment-emergent cardiac adverse events reported by ≥2 patients in the total population (safety population).

Preferred term	Aclidinium 200 μg $n = 311$	Aclidinium 400 μg $n = 291$	Total $N = 602$
Any cardiac TEAE	24 (7.7)	12 (4.1)	36 (6.0)
Coronary artery disease	5 (1.6)	0 (0)	5 (0.8)
Acute myocardial infarction	2 (0.6)	2 (0.7)	4 (0.7)
Atrial fibrillation	2 (0.6)	2 (0.7)	4 (0.7)
Tachycardia	3 (1.0)	0	3 (0.5)
Angina pectoris	1 (0.3)	2 (0.7)	3 (0.5)
Left/right bundle branch block	1 (0.3)	2 (0.7)	3 (0.5)
Ventricular extrasystoles	1 (0.3)	2 (0.7)	3 (0.5)
Sinus bradycardia	2 (0.6)	0 (0)	2 (0.3)
Palpitations	1 (0.3)	1 (0.3)	2 (0.3)
Myocardial infarction	2 (0.6)	0 (0)	2 (0.3)
Extrasystoles	1 (0.3)	1 (0.3)	2 (0.3)

Data reported as *n* (%).

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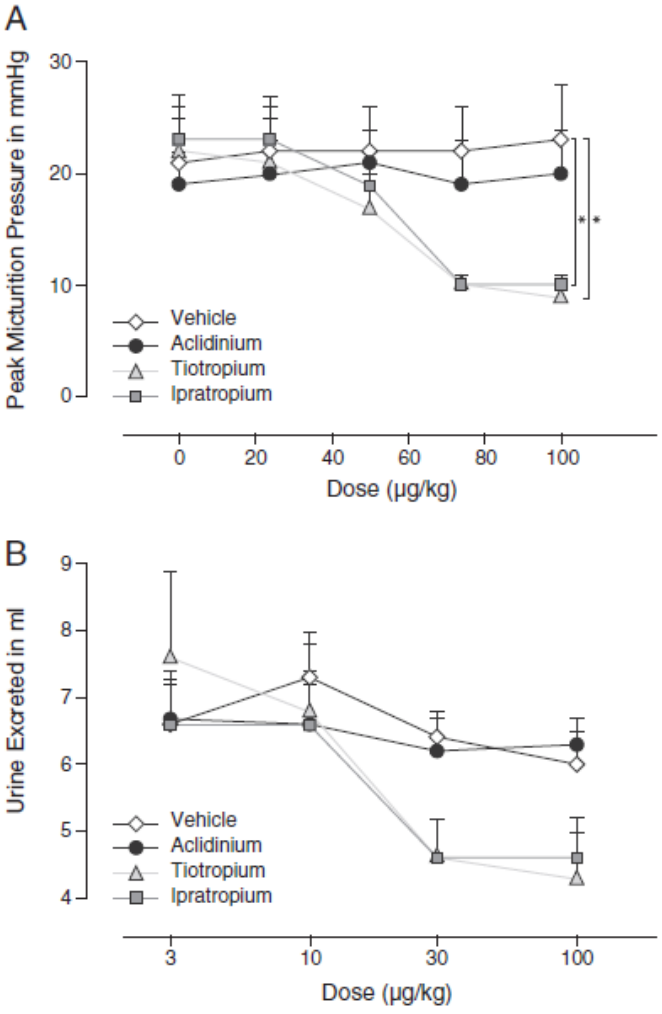
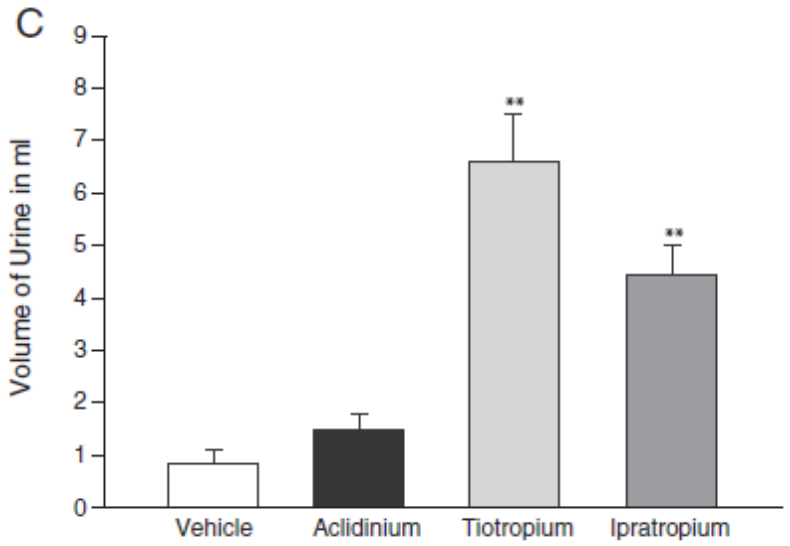
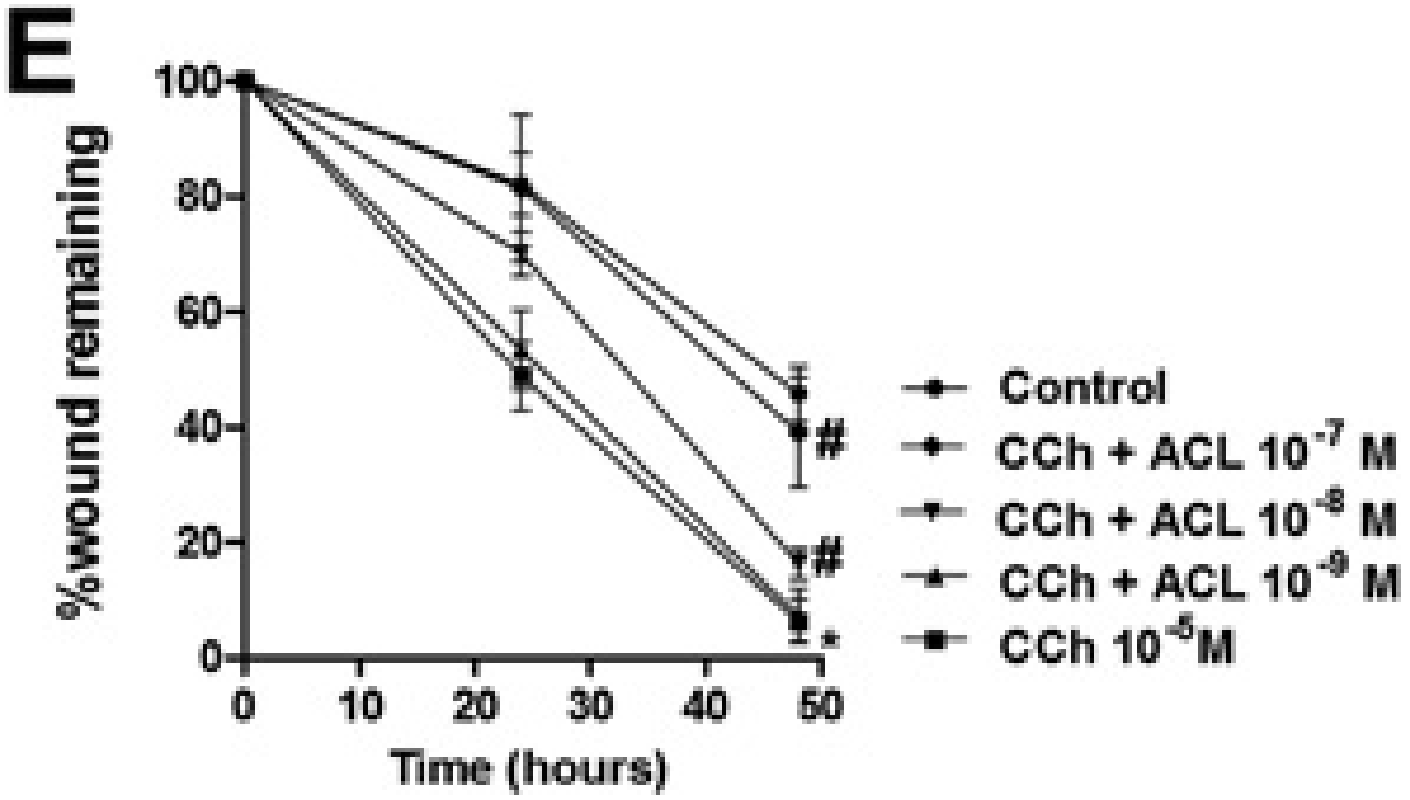
L’evidenza sperimentale nel ratto: nessun effetto sui parametri urologici



Residuo urinario post dose nel ratto (Gavaldà A et al. Life Sciences 2012; 90: 301)

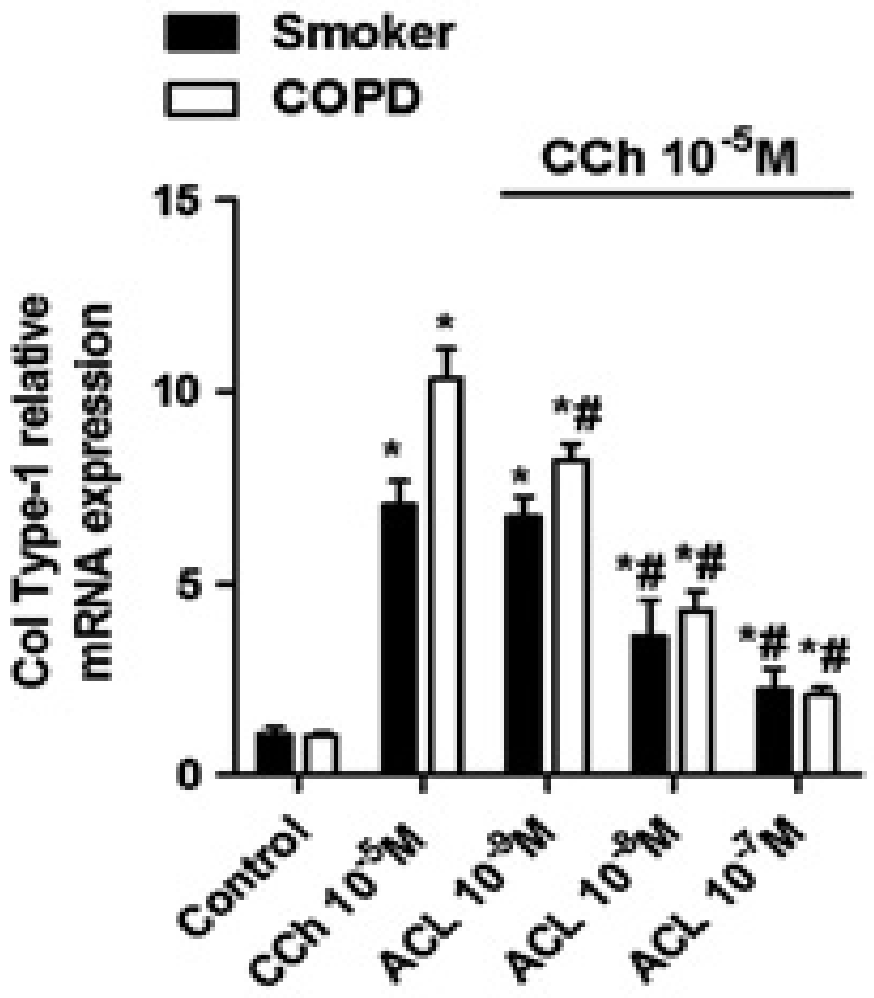


Inibizione dell'attività fibroblastica: dimostrata solo per l'aclidinio (Milara J et al. Thorax 2012; 67:229)

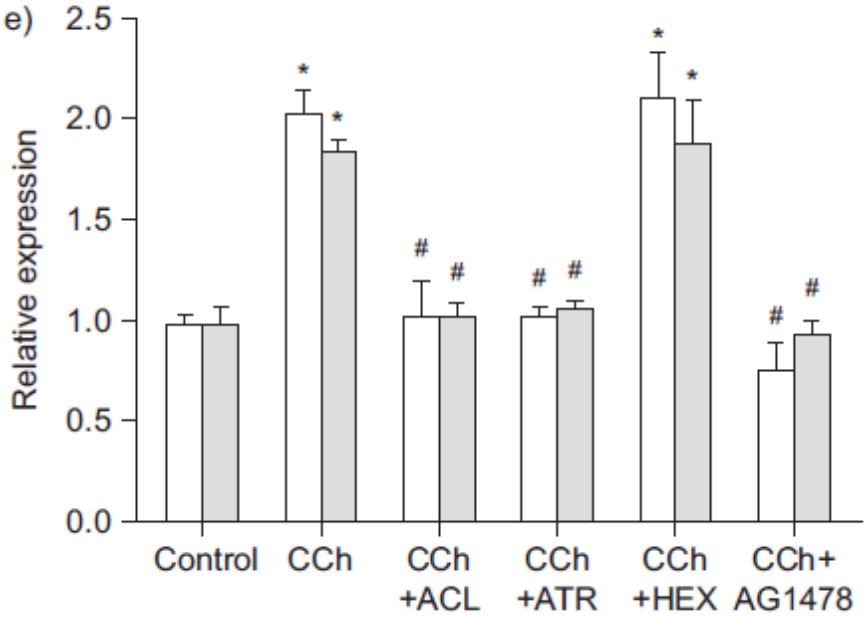


Relativa anche all'effetto del fumo

(Milara J et al. Thorax 2012; 67:229)



Nonché all'induzione della secrezione mucosa (Cortijo J et al. Eur Respir J 2011; 37: 244)



LE 1 Potency values of aclidinium as antagonist of carbachol- and cigarette smoke-induced augmentation of the expressi of mucin MUC5AC mRNA and protein expression in human isolated bronchial tissue and human airway epithelial ce cultured in air–liquid interface system

	Potency values as inhibitor of	
	MUC5AC mRNA expression	**MUC5AC protein express**
chol in human isolated bronchial tissues		
inium	9.17±0.14	8.81±0.16
ine	8.61±0.08	8.78±0.09
chol in human cultured airway epithelial cells		
inium	9.13±0.12	8.95±0.09
ine	8.69±0.05	8.60±0.06
tte smoke in human cultured airway epithelial cells		
inium	8.80±0.12	8.67±0.11
ine	8.29±0.14	8.24±0.13

e presented as mean±SEM of 3–5 independent experiments. The corresponding values for atropine are also given for comparison. Potency values are given as $_{50}$ values calculated from the concentration-dependent inhibition of the carbachol 100 μM and cigarette smoke 10%-induced overexpression of MUC5AC mR otein obtained in the presence of aclidinium (0.1, 1, 10 and 100 nM) and atropine (1, 10, 100 and 1000 nM) under the experimental conditions described in ls section.

Genuair: di per sé farmaco

- Feedback acustico/visivo
- Prevenzione doppia dose
- Indicatore di dose
- Lock out (impedisce l'uso di un device scarico)
- Efficace sistema di deagglomerazione della polvere
- Elevata riproducibilità dell'aerosol
- Sufficiente Fli>35 l/min

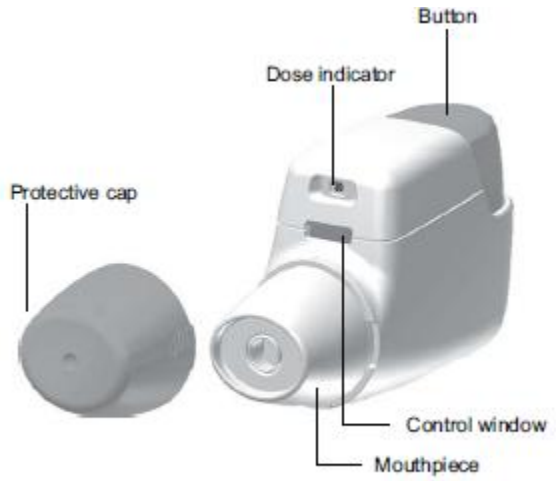


Figure 1 The Genuair® inhaler.

Sistemi di erogazione a confronto

	Vantaggi	Svantaggi
MDI	Elevata riproducibilità da dose a dose	Necessità di coordinare il respiro con l'attivazione dell'inalatore
DPI	Attivato dal respiro, non richiede collaborazione	Può essere difficoltoso per le persone con deficit cognitivo. Richiede un maggior sforzo respiratorio
Aerosol	Elevata riproducibilità da dose a dose	Richiede maggior tempo e (spesso) assistenza per la preparazione

Gooneratne et al. J Am Geriatr Soc 2010; 58:1153-1162.

Declino della pressione inspiratoria con l'età

		Entire Cohort				Healthy Subjects			
Age Group (*yr*)	Gender	No.	Mean Age (Range) (*yr*)	Mean MIP ± SD ($cm\ H_2O$)	Mean FEV_1% Predicted ± SD	No.	Mean Age (Range) (*yr*)	Mean MIP ± SD ($cm\ H_2O$)	Mean FEV_1% Predicted ± SD
Age < 39.9	Men	56	30.5 (22–39)	117.6 ± 28.8	96.5 ± 14.6	38	30.4 (23–39)	120.5 ± 26.9	100.3 ± 9.9
	Women	68	29.9 (20–39)	79.5 ± 20.4	98.6 ± 10.5	40	29.6 (20–39)	79.7 ± 17.6	98.0 ± 10.3
40 < Age < 54.9	Men	89	46.4 (40–54)	107.4 ± 23.7	95.8 ± 11.9	40	46.4 (40–53)	111.6 ± 22.6	97.1 ± 22.6
	Women	89	47.0 (40–54)	73.7 ± 20.3	99.9 ± 12.8	50	46.9 (40–53)	75.8 ± 23.1	105.7 ± 11.7
55 < Age < 64.9	Men	72	60.0 (55–64)	94.4 ± 27.3	92.4 ± 14.1	22	60.2 (55–64)	91.7 ± 23.4	91.7 ± 12.0
	Women	46	59.2 (55–64)	64.6 ± 17.9	101.3 ± 15.7	17	57.8 (55–63)	68.3 ± 20.9	102.9 ± 17.3
65 < Age < 74.9	Men	95	68.9 (65–74)	81.9 ± 21.4	92.2 ± 14.9	24	69.3 (65–74)	84.1 ± 19.9	96.5 ± 12.9
	Women	45	69.5 (65–74)	55.7 ± 17.4	100.3 ± 17.9	11	67.1 (65–72)	60.8 ± 16.5	101.1 ± 18.8
Age > 74.9	Men	69	80.1 (75–90)	66.0 ± 19.4	89.6 ± 23.2	15	80.3 (75–90)	65.4 ± 19.4	105.7 ± 20.0
	Women	39	80.0 (75–90)	45.5 ± 17.5	99.5 ± 16.4	10	78.6 (75–83)	46.0 ± 20.0	99.5 ± 20.0

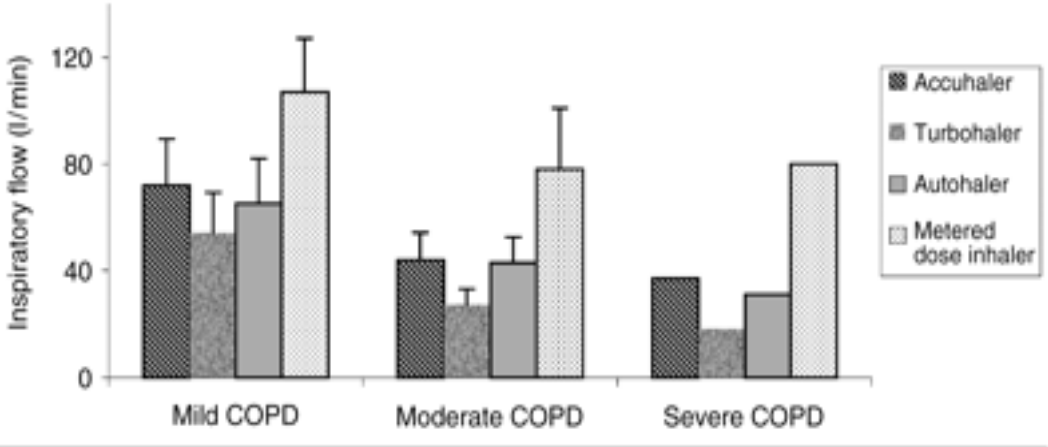
Harik-Khan R et al. Am J Respir Crit Care Med 1998; 158:1459–1464.

Flussi necessari per attivare gli inalatori

- In genere gli MDI richiedono un flusso di 25 L/min per essere efficaci (Goodman DE et al. J Am Respir Crit Care Med 1994; 150:1256-1261);
- La maggior parte dei DPI richiede un flusso di 30 – 60 L/min, e 60 L/min è considerata la soglia per il costo/beneficio (Payne N et al. NICE 2000);
- Il picco di flusso espiratorio in persone anziane con BPCO, misurato contro resistenza di 60 L/min, è di (Jarvis S et al. Age Ageing 2007; 36:213-218):
    - 54 L/min nella BPCO lieve
    - 27 L/min nella BPCO moderata
    - 18 L/min nella BPCO grave

Flussi inspiratori in pazienti con BPCO

Table 1. Inspiratory flow in elderly COPD patients according to different degrees of resistance

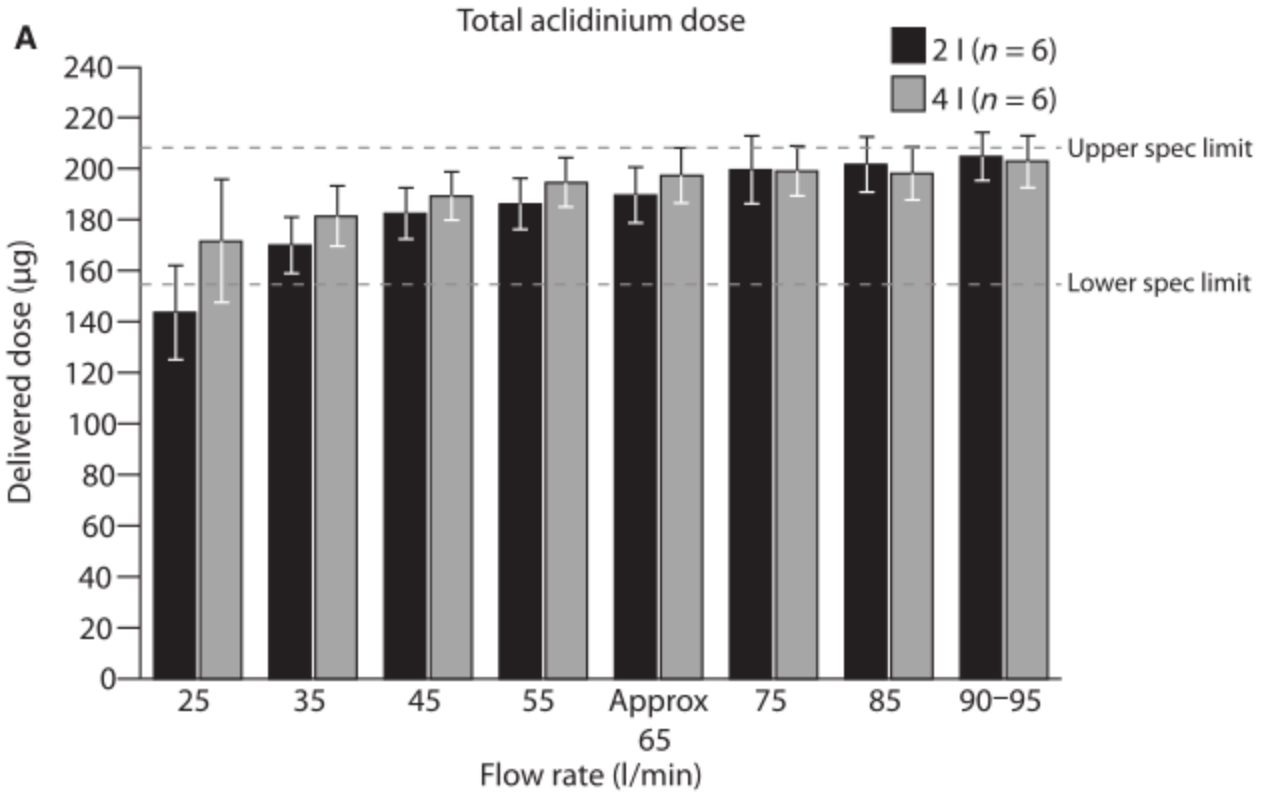


	Accuhaler* (l/min)	Turbohaler* (l/min)	Autohaler* (l/min)	pMDI* (l/min)
Mild	72 ± 17	54 ± 15	65 ± 16	107 ± 20
Moderate	44 ± 10	27 ± 6	43 ± 10	78 ± 22
Severe	37	18	31	80
All Patients	63 ± 20	44 ±19	58 ± 18	98 ±25

* Minimum required inspiratory flow rate: MDI, 25 l/min; Autohaler, 301 l/min; Accuhaler, 30 l/min; Turbohaler, 60 1/min

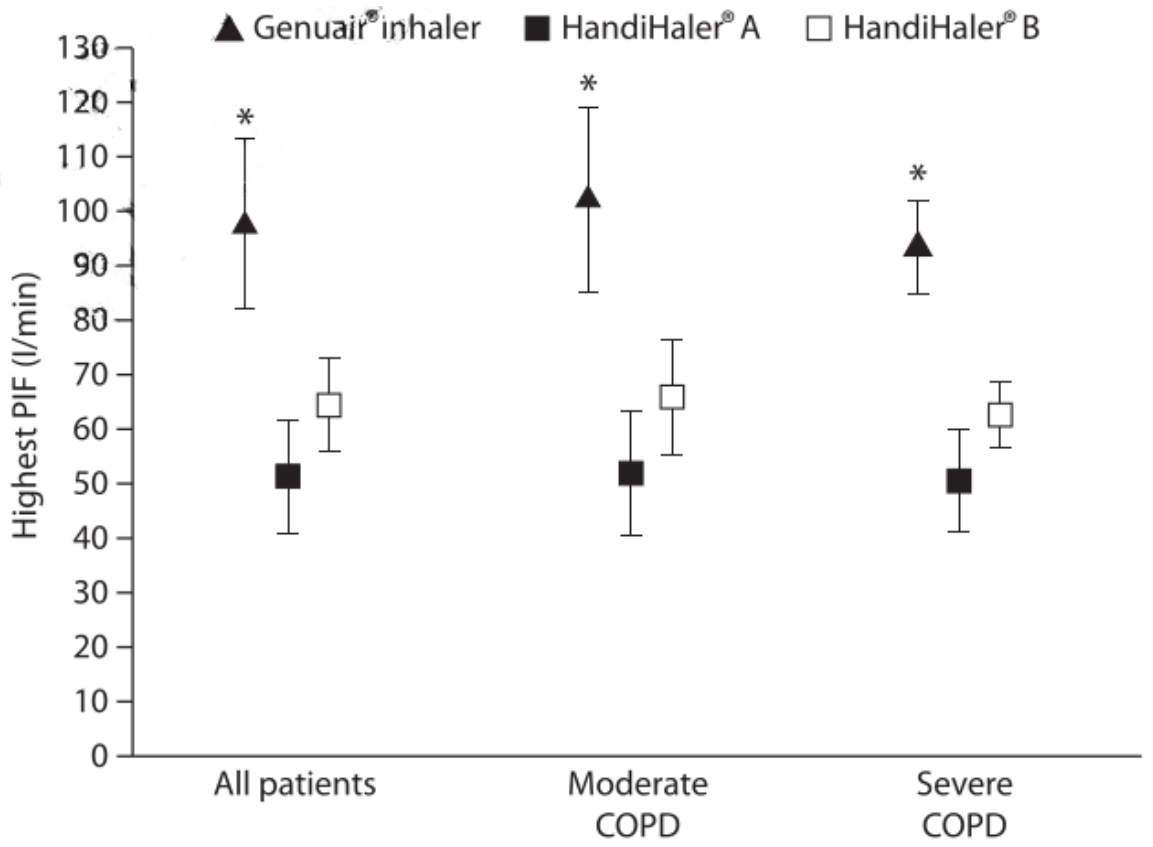
Jarvis S et al. Age Ageing 2007; 36:213-218

Ottima dose rilasciata anche per bassi flussi generati (Chrystyn H et al. Int J Clin Pract 2012; 66: 309)



PIF generati da Genuair e Handihaler A e B

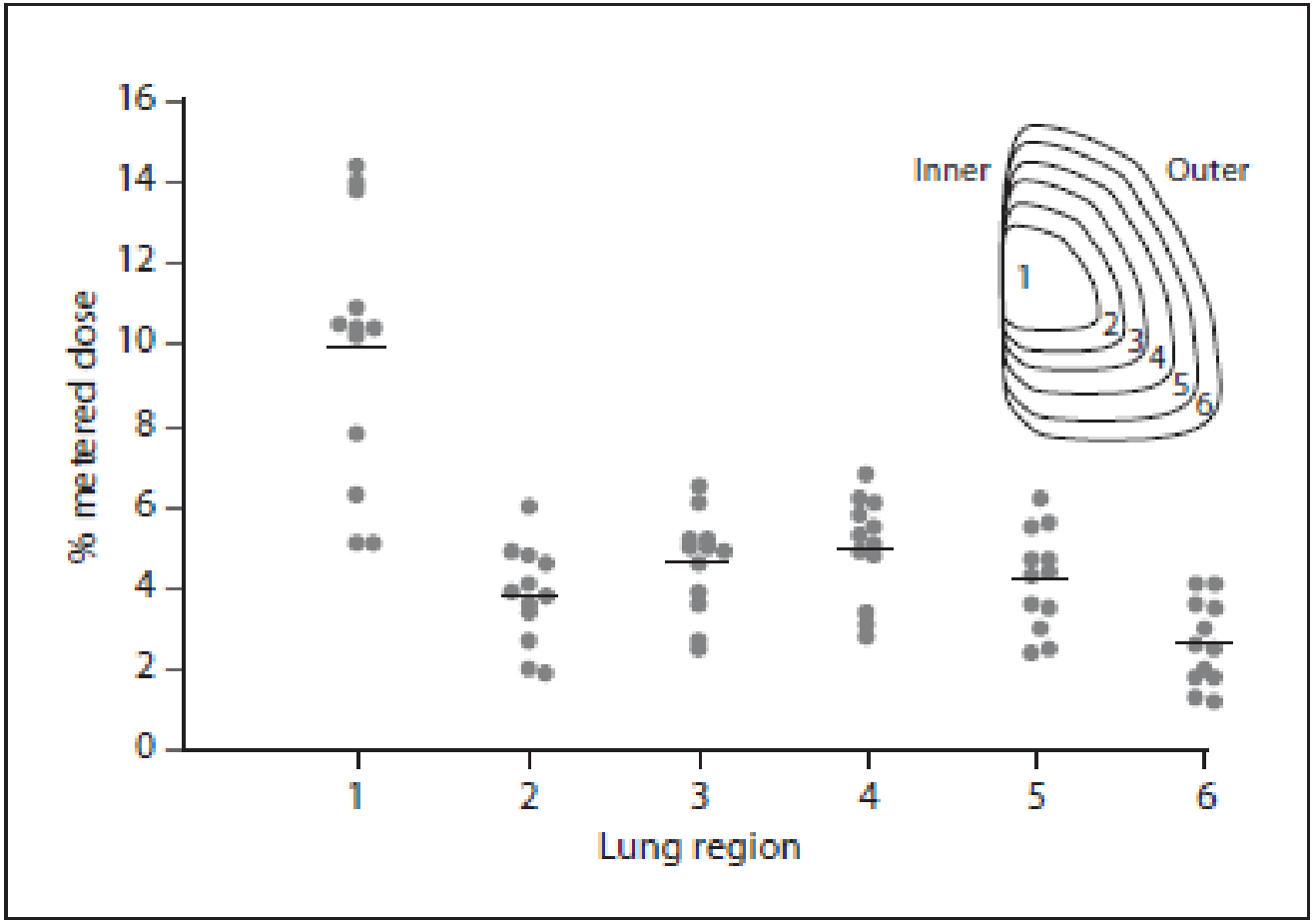
(Chrystyn H et al. Int J Clin Pract 2012; 66: 309)



*P < 0.001 vs. HandiHaler® A and HandiHaler® B.
COPD, chronic obstructive pulmonary disease; PIF, peak inspiratory flow.

Topografia della deposizione polmonare

(Newman SP et al. Respiration 2009; 78: 322)



L’aclidinio: un LAMA “geriatrico”?

- Facilità d’uso
- Efficacia
- Sicurezza
- Elettiva utilità in presenza di sintomi notturni
- Uso preferenziale se v’è insufficienza renale
- Impiego agevole anche in malati sarcopenici o molto ostruiti