Pomeriggio

Un esempio di Comparative Effectiveness Research in Italia: lo studio OUTPUL

Chair: *Francesco Lapi, Riccardo Pistelli*

14.00	**Introduzione**	*Riccardo Pistelli*
14.15	**Lo studio OUTPUL: overview**	*Nera Agabiti*
14.30	**Popolazione in studio: analisi descrittive delle tre regioni**	*Claudio Voci, Silvia Cascini*
14.40	**Lo studio di validazione**	*Lisa Bauleo*
14.50	**Lo studio di farmacoutilizzazione nel Lazio**	*Mirko Di Martino*
15.00	**Efficacia e sicurezza dei cortisonici inalatori**	*Mirko Di Martino, Valeria Belleudi, Silvia Cascini*
15.45	**Efficacia e sicurezza del tiotropio**	*Ursula Kirchmayer, Giulio Formoso, Eliana Ferroni*
16.15	**Conclusioni**	*Francesco Lapi*
16.30	**Chiusura dei lavori**	

Introduzione

I motivi di uno studio visti da un clinico

Riccardo Pistelli

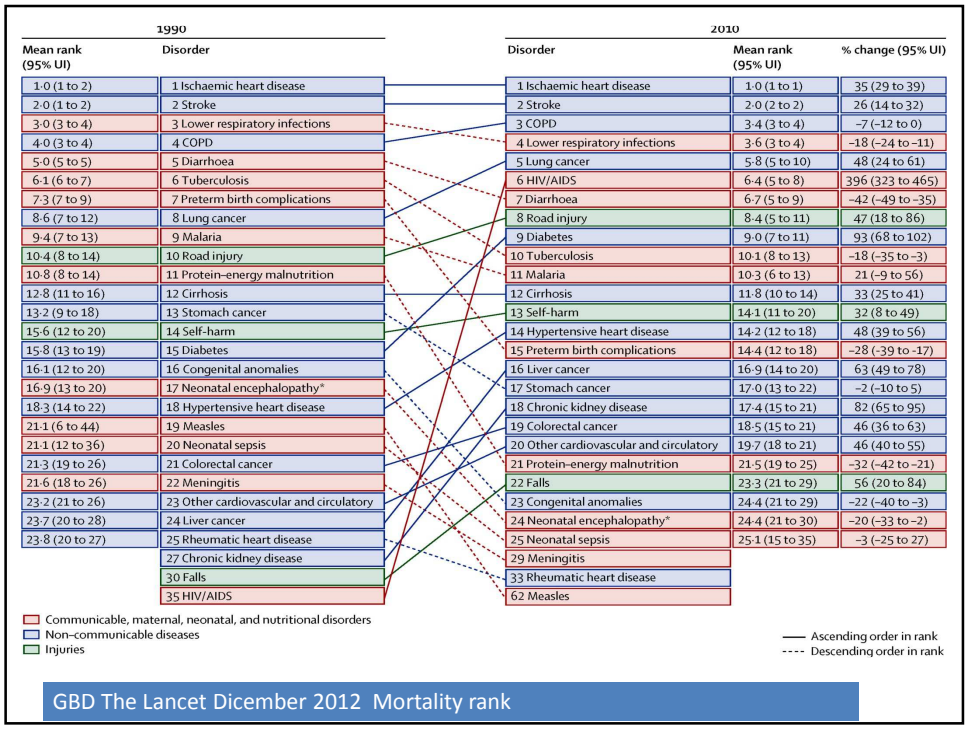
Università Cattolica - Roma

WORKSHOP

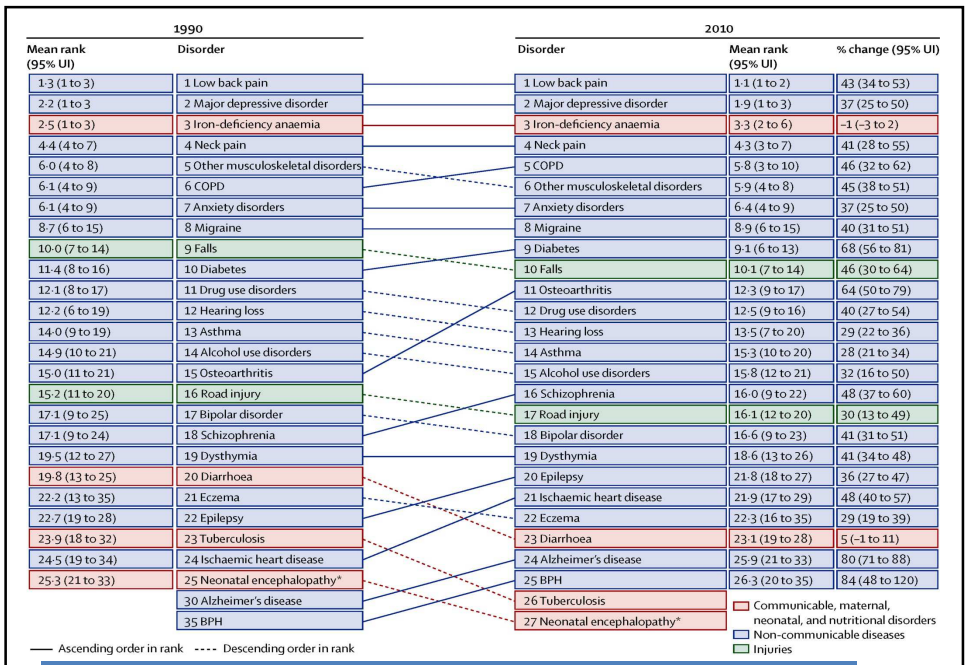
VALUTAZIONE COMPARATIVA DI EFFICACIA E SICUREZZA TRA FARMACI

Il ruolo degli studi osservazionali

outpul



GBD The Lancet Dicember 2012 Mortality rank



GBD The Lancet Dicember 2012 YLDs

COPD: Mean Cost (MC)/patient/y

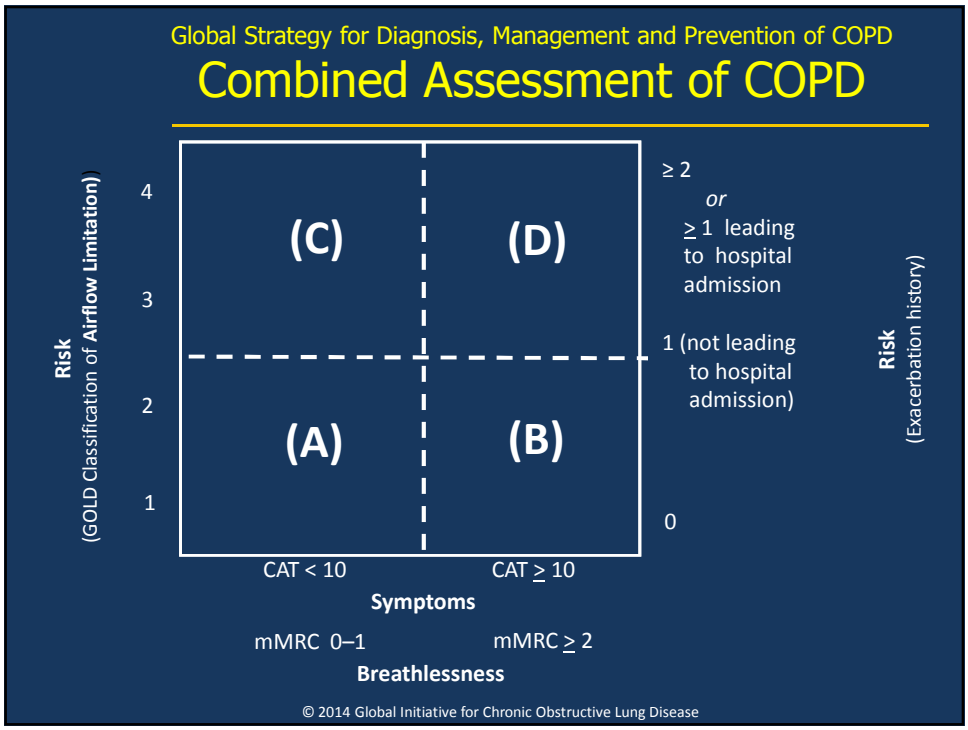
Dal Negro R. et al., SIRIO study, 2006.

Parameters	val. in €	%
principal pharmacological treat.	347.23	12.7
concomitant pharmacological treat.	186.82	6.9
Hospitalisations	1519.67	55.8
Day Hospital	88.68	3.3
E.D. visits	7.62	0.3
Medical Visits	150.59	5.5
Diagnostic tests	162.68	6.0
Tests due to adverse events	0.70	0.0
Envir. Prophil.& domestic aids	3.07	0.1
Non conventional therapies	39.77	1.5
Total Direct Costs	2506.84	92.0
Total Indirect Costs	216.84	8.0
Total Cost	2723.68	100.0

Ricoveri ospedalieri per BPCO

Anni	Ricoveri totali (A)	Ricoveri BPCO+IR (B)	B/A*100
2007	7872567	206000	2.61
2008	7721883	208000	2.69
2009	7585269	207000	2.72
2010	7374765	202000	2.73
2011	7046481	200000	2.84

Ministero della salute, sito WEB


Global Strategy for Diagnosis, Management and Prevention of COPD
Combined Assessment of COPD
Risk
(GOLD Classification of Airflow Limitation))
4
3
2
1
(C)
(D)
(A)
(B)
≥ 2
or
≥ 1 leading to hospital admission
1 (not leading to hospital admission)
0
Risk
(Exacerbation history)
CAT < 10
CAT ≥ 10
Symptoms
mMRC 0–1
mMRC ≥ 2
Breathlessness
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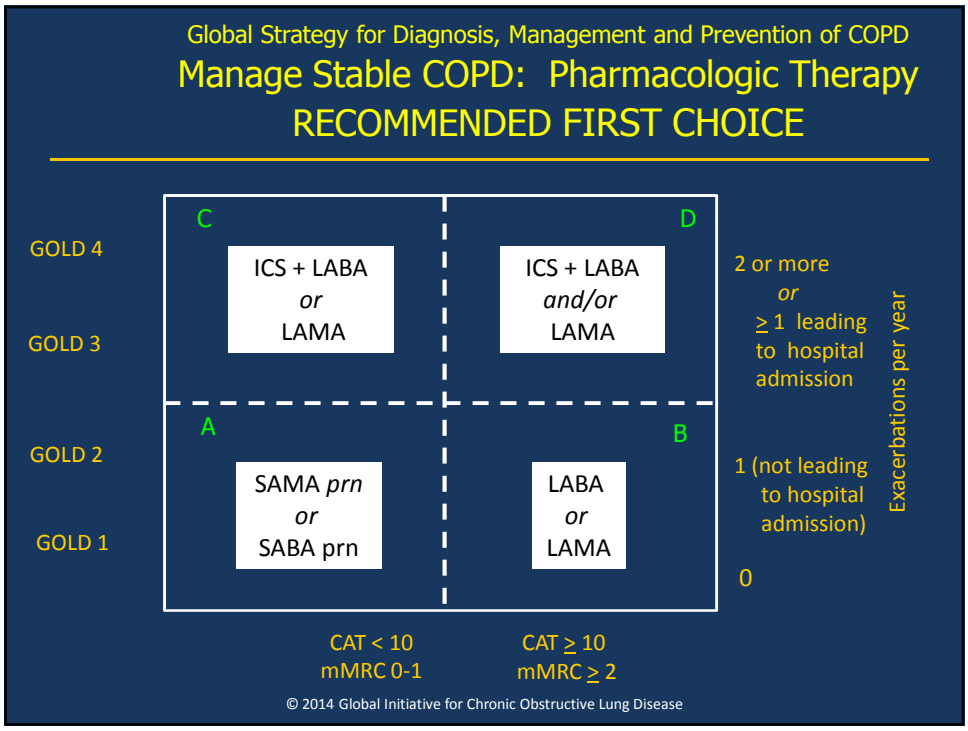
Global Strategy for Diagnosis, Management and Prevention of COPD
Manage Stable COPD: Pharmacologic Therapy
RECOMMENDED FIRST CHOICE
GOLD 4
GOLD 3
GOLD 2
GOLD 1
C
ICS + LABA
or
LAMA
D
ICS + LABA
and/or
LAMA
A
SAMA prn
or
SABA prn
B
LABA
or
LAMA
2 or more
or
≥ 1 leading to hospital admission
1 (not leading to hospital admission)
0
Exacerbations per year
CAT < 10
mMRC 0-1
CAT ≥ 10
mMRC ≥ 2
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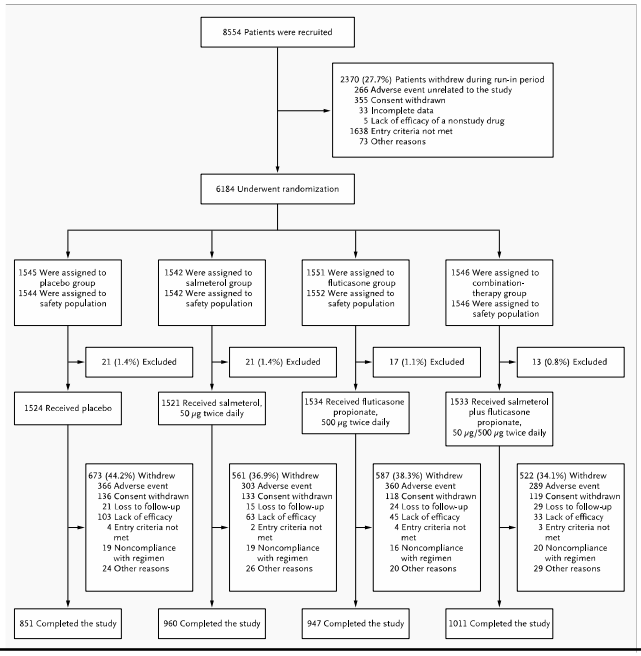
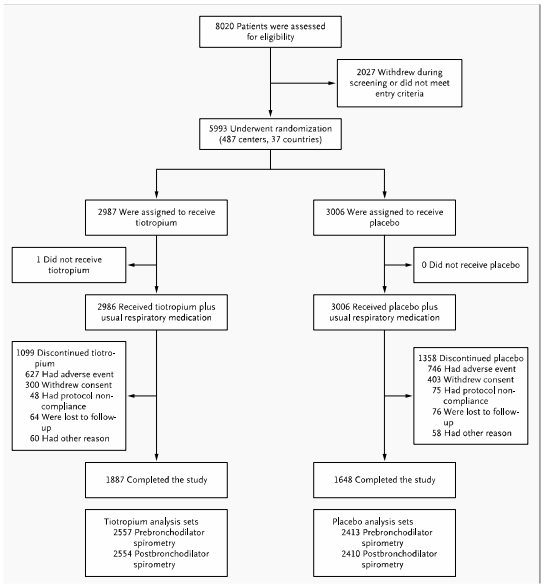
I tre mega RCT in tema di BPCO

- TORCH (2007): 6112 pazienti, età media 65
- UPLIFT (2008): 5993 pazienti, età media 65
- POET (2011) 7376 pazienti, età media 63

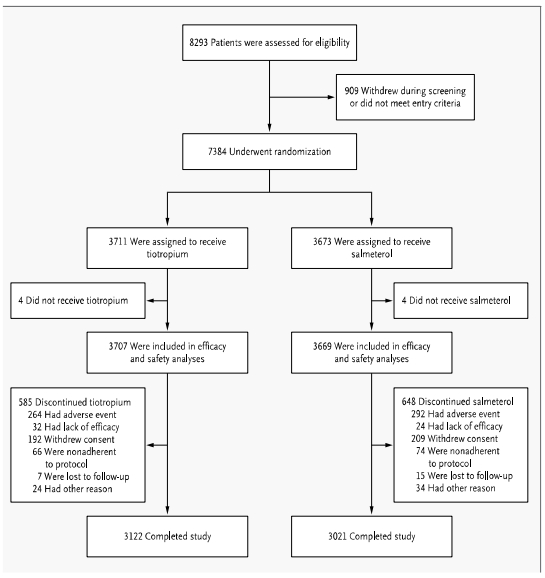
La flow-chart dello studio TORCH



La flow-chart dello studio UPLIFT



La flow-chart dello studio POET



Criteri di esclusione del RCT TORCH

1. In the opinion of the investigator, there is a current diagnosis of asthma
2. Current respiratory disorders other than COPD (e.g., lung cancer, sarcoidosis, tuberculosis, lung fibrosis)
3. Chest X-ray indicating diagnosis other than COPD that might interfere with the study (chest X-ray to be taken up to 6 months before entry to the treatment period)
4. Had lung-volume reduction surgery and/or a lung transplant
5. Requirement for long term oxygen therapy (LTOT is defined as oxygen therapy prescribed for 12 hours or more per day) at start of study
6. Receiving long-term oral corticosteroid therapy (Defined as continuous use for greater than 6 weeks. Courses of oral corticosteroids separated by a period of less than 7 days will be considered as continuous use).
7. Serious, uncontrolled disease (including serious psychological disorders) likely to interfere with the study and/or likely to cause death within the 3-year study duration
8. Received any other investigational drugs in the last 4 weeks before entry to Visit 1. NOTE: Subjects previously enrolled into TRISTAN (SFCB3024) may be recruited to this trial 4 weeks after stopping their previous study medication.
9. Have, in the opinion of the investigator, evidence of alcohol, drug or solvent abuse
10. Known or suspected hypersensitivity to inhaled corticosteroids, bronchodilators or lactose
11. Known deficiency of α-1antitrypsin
12. Previously been enrolled into the Run-in Period

Criteri di esclusione nel RCT UPLIFT

1. Significant diseases other than COPD which, in the opinion of the investigator, may either put the patient at risk because of participation in the study or a disease which may influence the results of the study or the patient's ability to participate in the study.
2. A recent history (*i.e.,* six months or less) of myocardial infarction.
3. Any unstable or life threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy within the past year.
4. Hospitalization for heart failure (NYHA Class III or IV) within the past year.
5. Known active tuberculosis.
6. A history of asthma, cystic fibrosis, bronchiectasis, interstitial lung disease, or pulmonary thromboembolic disease.
7. A history of thoracotomy with pulmonary resection. Patients with a history of thoracotomy for other reasons should be evaluated as per Exclusion 1.
8. Patients planning to undergo lung transplant or lung volume reduction surgery (LVRS).
9. Malignancy for which patient has undergone resection, radiation therapy or chemotherapy within the last 5 years. Patients with treated basal cell carcinoma are allowed.
10. A respiratory infection or exacerbation of COPD in the four weeks prior to the Screening Visit (Visit 1) or during the baseline period (between Visit 1 and Visit 2). If a patient experiences an exacerbation between Visits 1 and 2 the patient must be stable for 6 weeks prior to Visit 2.
11. A known hypersensitivity to anticholinergic drugs, lactose or any other components of the inhalation capsule delivery system.
12. Patients with known moderate to severe renal impairment.
13. Patients with known narrow-angle glaucoma.
14. Patients with significant symptomatic prostatic hyperplasia or bladder-neck obstruction. Patients whose symptoms are controlled on treatment may be included.
15. Use of oral corticosteroid medication at unstable doses (*i.e.*, less than six weeks on a stable dose) or at doses ≥ 10 mg/day.
16. Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception (i.e. oral contraceptives, intrauterine devices, diaphragm or subdermal implants e.g.: Norplant®) for at least three months prior to and for the duration of the trial.
17. Significant alcohol or drug abuse within the past 12 months.
18. Patients requiring the use of supplemental oxygen therapy for >12 hours per day.
19. Participation in another trial with an investigational drug within one month or six half lives (whichever is greater) prior to Screening Visit (Visit 1).

I criteri di esclusione del RCT POET

1. Significant diseases other than COPD, i.e. disease or condition which, in the opinion of the investigator, may have put the patient at risk because of participation in the study or may have influenced either the results of the study or the patients' ability to participate in the study
2. Patients with a diagnosis of asthma
3. Patients with a life-threatening pulmonary obstruction, or a history of cystic fibrosis
4. Patients with known active tuberculosis
5. Patients with a known symptomatic prostatic hyperplasia or bladder neck obstruction
6. Patients with symptomatically-controlled prostatic hyperplasia on medication might have been included and should have continued their medication.
7. Patients with known narrow-angle glaucoma
8. Patients with a history of myocardial infarction within the year prior to Visit 1
9. Patients with a history of hospital admission for heart failure within the year prior to Visit 1
10. Patients with cardiac arrhythmia that required medical or surgical treatment
11. Patients with severe cardiovascular disorders
12. Patients with a known hypersensitivity to anticholinergic drugs, beta-adrenergics, lactose or any other component of the medication delivery system
13. Patients with known moderate or severe renal insufficiency (known creatinine clearance of ≤50 mL/min)
14. Patients with untreated known hypokalaemia
15. Patients with untreated known thyrotoxicosis
16. Patients with brittle/unstable diabetes mellitus
17. Patients with a history of and/or active significant alcohol or drug abuse. See exclusion criterion 1
18. Patients who had taken an investigational drug within 30 days or 6 half-lives (whichever is greater) prior to Visit 1
19. Use of systemic corticosteroid medication at unstable doses (i.e., less than 6 weeks on stable dose) or at doses in excess of the equivalent of 10 mg prednisolone per day or 20 mg every other day
20. Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception (i.e., oral contraceptives, intrauterine devices, diaphragm or subdermal implants such as Norplant) for at least 3 months prior to, and for the duration of the trial
21. Previous participation (receipt of randomized treatment) in this study
22. Patients who were participating at the same time in another study
23. Patients with any respiratory infection or COPD exacerbation in the 4 weeks prior to Visit 1 or during the run-in period should have been postponed. In the case of a respiratory infection or COPD exacerbation during the run-in period, the run-in period could have been extended up to 4 weeks

Pazienti della regione Lazio inclusi nello studio OUTPUL

Table 1. Demographic patient's characteristics

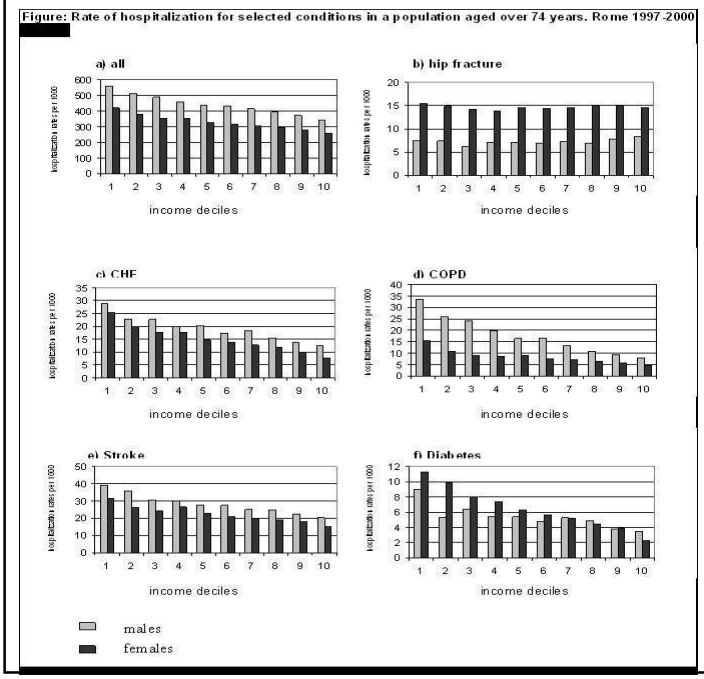
	MALE		FEMALE		TOTAL	
	N	%	N	%	N	%
	11402		9742		21144	
45-54	409	3,6	330	3,4	739	3,5
55-64	1318	11,6	868	8,9	2186	10,3
65-74	3349	29,4	2319	23,8	5668	26,8
75-84	4822	42,3	4026	41,3	8848	41,8
85+	1504	13,2	2199	22,6	3703	17,5
Mean age (SD)	74,6 (9,6)		76,8 (10,1)		75,9 (9,8)	

Table 3. Distribution of comorbidities by gender

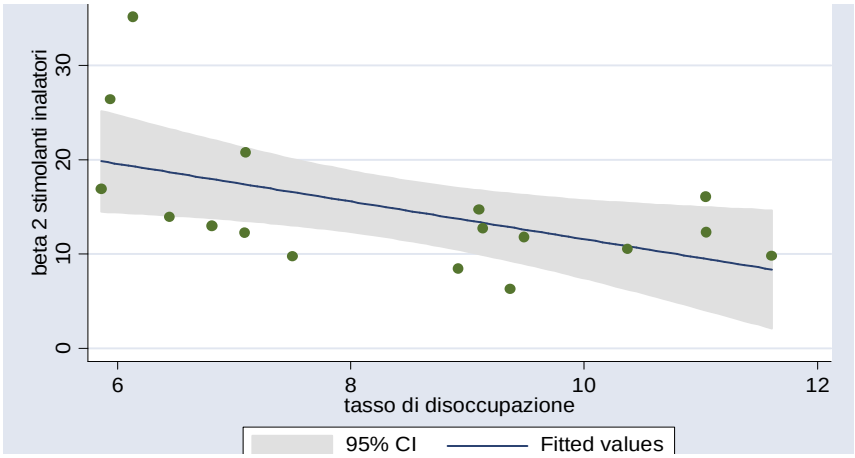
	MALE		FEMALE		TOTAL	
	N	%	N	%	N	%
	11402		9742		21144	
Asthma	121	1,1	213	2,2	334	1,6
Chronic respiratory disease	518	4,5	327	3,4	845	4,0
Pulmonary infections	1368	12,0	809	8,3	2177	10,3
Pulmonary symptoms	338	3,0	262	2,7	600	2,8
Diabetes	2325	20,4	1984	20,4	4309	20,4
Hypertension	2784	24,4	2467	25,3	5251	24,8
Ischemic heart disease	1644	14,4	1110	11,4	2754	13,0
Heart failure	1469	12,9	1194	12,3	2663	12,6
Other chronic heart diseases	1078	9,5	931	9,6	2009	9,5
Arrhythmia	1424	12,5	1174	12,1	2598	12,3
Cerebrovascular diseases	1114	9,8	893	9,2	2007	9,5
Peripheral vascular diseases	631	5,5	303	3,1	934	4,4
Obesity – dyslipidemia	577	5,1	629	6,5	1206	5,7
Liver disease	374	3,3	212	2,2	586	2,8
Chronic digestive disease (excluding liver)	147	1,3	110	1,1	257	1,2
Chronic renal diseases	670	5,9	472	4,8	1142	5,4
Neurological and muscle disease	325	2,9	247	2,5	572	2,7
Anemia and coagulation disorders	361	3,2	392	4,0	753	3,6
Thyroid disease	229	2,0	509	5,2	738	3,5
Depression	108	0,9	220	2,3	328	1,6
Psychiatric disease	137	1,2	186	1,9	323	1,5
Peptic ulcer and gastroesophageal reflux disease	123	1,1	82	0,8	205	1,0
Rheumatological and connective tissue disease	31	0,3	89	0,9	120	0,6
HIV and disorders of the immune system	17	0,1	10	0,1	27	0,1

Ricoveri ospedalieri e reddito, Roma 1998-2000

Figure: Rate of hospitalization for selected conditions in a population aged over 74 years. Rome 1997-2000



Utilizzazione di farmaci ATC R03 Roma 2005



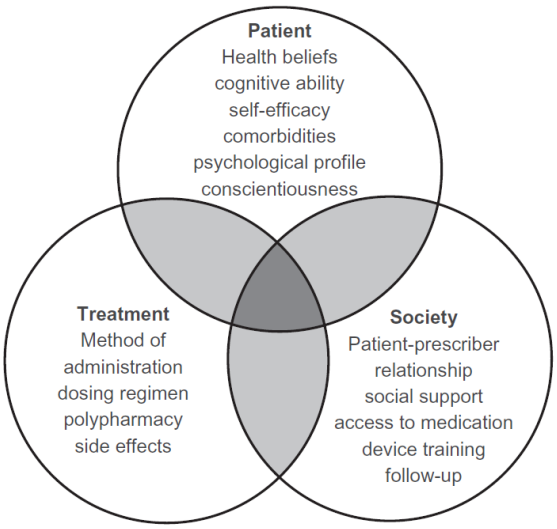


Figure 1 Patient adherence in chronic obstructive pulmonary disease is multifactorial and is influenced by the patient, the clinician, and society.

Bourbeau J, Bartlett SJ. Patient adherence in COPD. *Thorax*. 2008;63:831–838.[19]

Trial clinico ed eventi avversi

- Il trial clinico è uno strumento affetto da un errore casuale di sottostima degli eventi avversi:
  - La dimensione campionaria è stimata sulla base dell'evento desiderato (terapeutico) che, di norma, è più frequente dell'evento avverso.

Trial clinico ed eventi avversi

- Il trial clinico è uno strumento affetto da un errore sistematico di sottostima degli eventi avversi:
  - Selezione dei pazienti
  - Assenza di molte terapie concomitanti
  - Attenzione alla somministrazione del farmaco

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*

ABSTRACT

BACKGROUND

Tiotropium delivered at a dose of 5 μg with the Respimat inhaler showed efficacy similar to that of 18 μg of tiotropium delivered with the HandiHaler inhalation device in placebo-controlled trials involving patients with chronic obstructive pulmonary disease (COPD). Although tiotropium HandiHaler was associated with reduced mortality, as compared with placebo, more deaths were reported with tiotropium Respimat than with placebo.

METHODS

In this randomized, double-blind, parallel-group trial involving 17,135 patients with COPD, we evaluated the safety and efficacy of tiotropium Respimat at a once-daily dose of 2.5 μg or 5 μg, as compared with tiotropium HandiHaler at a once-daily dose of 18 μg. Primary end points were the risk of death (noninferiority study, Respimat at a dose of 5 μg or 2.5 μg vs. HandiHaler) and the risk of the first COPD exacerbation (superiority study, Respimat at a dose of 5 μg vs. HandiHaler). We also assessed cardiovascular safety, including safety in patients with stable cardiac disease.

RESULTS

During a mean follow-up of 2.3 years, Respimat was noninferior to HandiHaler with respect to the risk of death (Respimat at a dose of 5 μg vs. HandiHaler: hazard ratio, 0.96; 95% confidence interval [CI], 0.84 to 1.09; Respimat at a dose of 2.5 μg vs. HandiHaler: hazard ratio, 1.00; 95% CI, 0.87 to 1.14) and not superior to HandiHaler with respect to the risk of the first exacerbation (Respimat at a dose of 5 μg vs. HandiHaler: hazard ratio, 0.98; 95% CI, 0.93 to 1.03). Causes of death and incidences of major cardiovascular adverse events were similar in the three groups.

CONCLUSIONS

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. (Funded by Boehringer Ingelheim; TIOSPIR ClinicalTrials.gov number, NCT01126437.)

From Johns Hopkins University School of Medicine, Baltimore (R.A.W.); University of Texas Health Science Center and South Texas Veterans Health Care System, San Antonio (A.A.), and private practice, Hamilton (G.P.) — both in Texas; Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (D.C., T.D., E.J.); Odense University Hospital, Odense, Denmark (R.D.); Boehringer Ingelheim, Ingelheim, Germany (B.D., S.K., M.K.-B.); Service de Pneumologie Hôpital Cochin, Assistance Publique—Hôpitaux de Paris, Université Paris Descartes, Sorbonne Paris Cité, Paris (D.D.); and Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, United Kingdom (P.C.). Address reprint requests to Dr. Wise at Johns Hopkins University School of Medicine, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, or at rwise@jhmi.edu.

*Investigators in the Tiotropium Safety and Performance in Respimat (TIOSPIR) study are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on August 30, 2013, at NEJM.org.

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1303942

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