SABATO 9 OTTOBRE

Certezze che crollano: i betabloccanti non peggiorano la broncopneumopatia cronica ostruttiva

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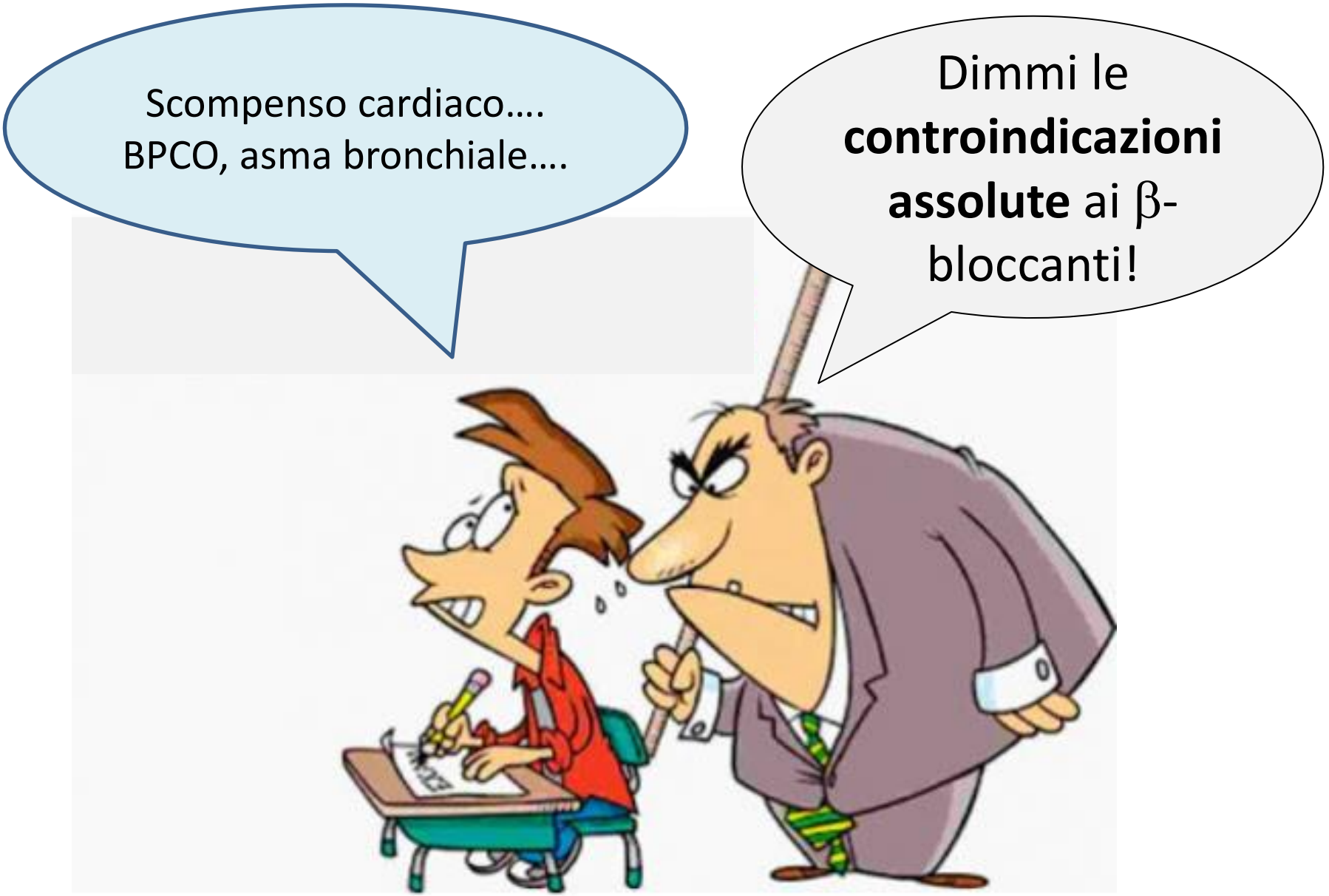
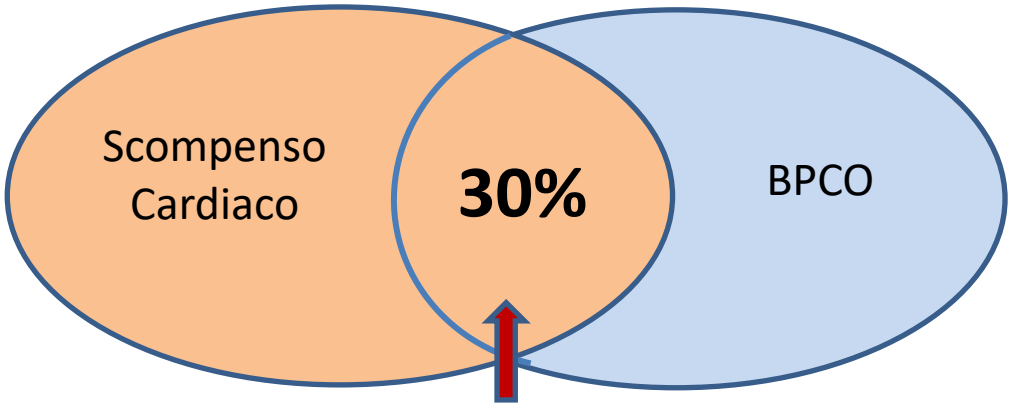
Conflitti di interesse in relazione con la presente lettura:

Nessuno



Quando studiavamo noi…

Aveva ragione il professore?



La **coesistenza di scompenso cardiaco e BPCO** (30% dei pazienti con scompenso o BPCO) **aumenta del 20-30% il rischio di ospedalizzazione e di mortalità** rispetto alla loro non coesistenza.

- ✓ **Nei primi giorni di esacerbazione di BPCO**, aumentato rischio di infarto miocardico (2x), morte (4x), scompenso cardiaco (6x) e ictus cerebrale (1,3x).

Da considerare: fattori di rischio comuni (es. fumo, età, inattività fisica...), stato infiammatorio cronico, sottoutilizzo dei β-bloccanti, β-stimolanti nella BPCO etc...).

Ma, attenzione: la diagnosi può essere inesatta!

- ✓ Molti **sintomi/segni sono simili** (dispnea, astenia, intolleranza allo sforzo).
- ✓ **La spirometria**, formalmente richiesta dalle L.G. per fare diagnosi di BPCO, **viene eseguita raramente** nei pazienti con scompenso **e** BPCO (solo nel 30%).

FEV_1/FVC

<0.70 (basso) ← **FEV_1/FVC** → **≥0.70**

<0.70 (basso)

Pattern ostruttivo

FVC ≥80% del predetto

Pattern Combinato Ostruttivo/Restrittivo Vs. Iperinflazione

Necessari ulteriori tests polmonari

FVC <80% del predetto ('basso')

Pattern Ostruttivo

Come è il FEV_1?

- FEV_1 ≥80% del predetto → Lieve
- FEV_1 50-79% del predetto → Moderato
- FEV_1 30-49% del predetto → Severo
- **FEV_1 <30% del predetto** → Molto severo

Necessari ulteriori tests polmonari

BPCO
Ridotta capacità di diffusione del monossido di carbonio

Asma bronchiale
↑FEV_1 >12% (200 ml) 10-15 min dopo broncodilatatore

≥0.70

Pattern non ostruttivo

FVC ≥80% del predetto

Spirometria Normale

FVC <80% del predetto ('basso')

Pattern Restrittivo

Necessari ulteriori tests polmonari

1. **L'interpretazione della spirometria è identica in presenza di HFrEF e HFpEF.**
2. **Durante fasi di riacutizzazione, con sovraccarico di liquidi, la spirometria è poco attendibile (↓FVC, ↓FEV_1).**
3. **Nella PAH può essere presente ostruzione vie aeree, male differenziabile dalla BPCO.**

β-bloccanti in pazienti con BPCO….. Perché?

1. Per prevenire le esacerbazioni della BPCO
2. Per trattare correttamente pazienti con BPCO ed indicazioni ai β-bloccanti (**scompenso cardiaco, cardiopatia ischemica cronica**). I β-bloccanti sono pericolosi in questi pazienti?

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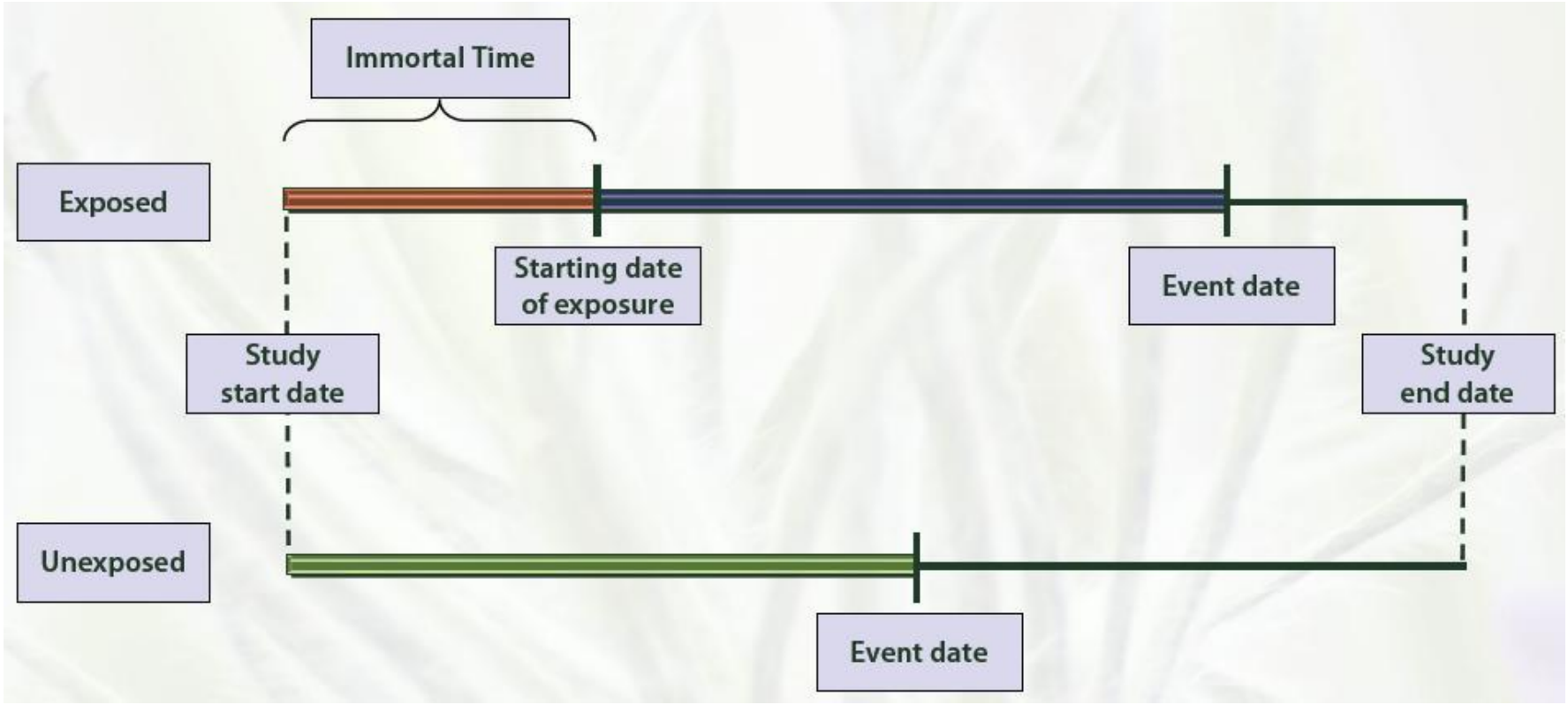
I β-bloccanti sembrano ridurre non solo il rischio di esacerbazioni della BPCO, ma anche la mortalità associata a tali esacerbazioni.

- ✓ Bhatt SP, Wells JM, Kinney GL, et al. β-Blockers are associated with a reduction in COPD exacerbations. Thorax 2016; 71: 8-14.
- ✓ Etminan M, Jafari S, Carleton B, FitzGerald JM. Beta-blocker use and COPD mortality: a systematic review and meta-analysis. BMC Pulm Med 2012; 12: 48.
- ✓ Du Q, Sun Y, Ding N, Lu L, Chen Y. Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: a meta-analysis of observational studies. PLoS One 2014; 9(11): e113048.
- ✓ Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. J Am Coll Cardiol 2006; 47: 2554-60.

‘Immortal Time’ Bias



Immortal time bias: a distortion that modifies an association between an exposure and an outcome, caused when a cohort study is designed so that **follow-up includes a period of time where participants in the exposed group cannot experience the outcome and thus they are essentially 'immortal'.**

ESC European Society of Cardiology
European Heart Journal (2020) 00, 1–8
doi:10.1093/eurheartj/ehaa793

CLINICAL RESEARCH
Heart failure

Association of β-blocker use with survival and pulmonary function in patients with chronic obstructive pulmonary and cardiovascular disease: a systematic review and meta-analysis

Yan-Li Yang[1], Zi-Jian Xiang[2], Jing-Hua Yang[2], Wen-Jie Wang[2], Zhi-Chun Xu[2], and Ruo-Lan Xiang[3]*

Limitations (Ferrari R et al. Eur Heart J 2020):

1) Only 12 RCTs, and **37 observational studies.**

2) 'Wide' definition of cardiovascular disease (hypertension, HF, MI, effort angina).

3) Data on CV mortality missing, preventing discrimination whether benefits are driven by reduction of cardiac complications (arrhythmias, MI, HF progression, etc.) or COPD improvement.

Title

Association of β-Blocker Use with Survival and Pulmonary Function in Patients with COPD and CVD

Summary

To clarify the effect of BBs on respiratory function and survival in COPD patients with CVD as well as the difference between the effects of cardioselective and noncardioselective BBs.

Data sources

Results

Outcome	Samples	Number of Studies included	Comparison	Patients	HR [95% CI]
COPD exacerbation	183685	17	BB vs no BB	COPD+CVD	0.77 [0.67, 0.89]
	17834	7	selective BB vs no BB	COPD+CVD	0.72 [0.56, 0.94]
	17455	5	nonselective BB vs no BB	COPD+CVD	0.98 [0.71, 1.34]
	41183	4	selective BB vs nonselective B	COPD+CVD	1.00 [0.91, 1.10]
	20252	4	BB vs no BB	COPD+CHF	0.83 [0.56, 1.23]
Hospital mortality	108459	5	BB vs no BB	COPD+CVD	0.67 [0.46, 0.99]
All-cause mortality	335419	22	BB vs no BB	COPD+CVD	0.69 [0.58, 0.81]
	44775	8	selective BB vs no BB	COPD+CVD	0.60 [0.48, 0.76]
	17624	4	nonselective BB vs no BB	COPD+CVD	0.72 [0.58, 0.91]
	30691	6	BB vs no BB	COPD+CHF	0.62 [0.53, 0.74]
	33067	4	BB vs no BB	COPD+MI	0.87 [0.82, 0.91]

Outcome	Samples	Number of Studies included	Comparison	Patients	MD [95% CI]
Heart rate	5473	5	BB vs no BB	COPD+CVD	-7.87 [-11.12, -4.62]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

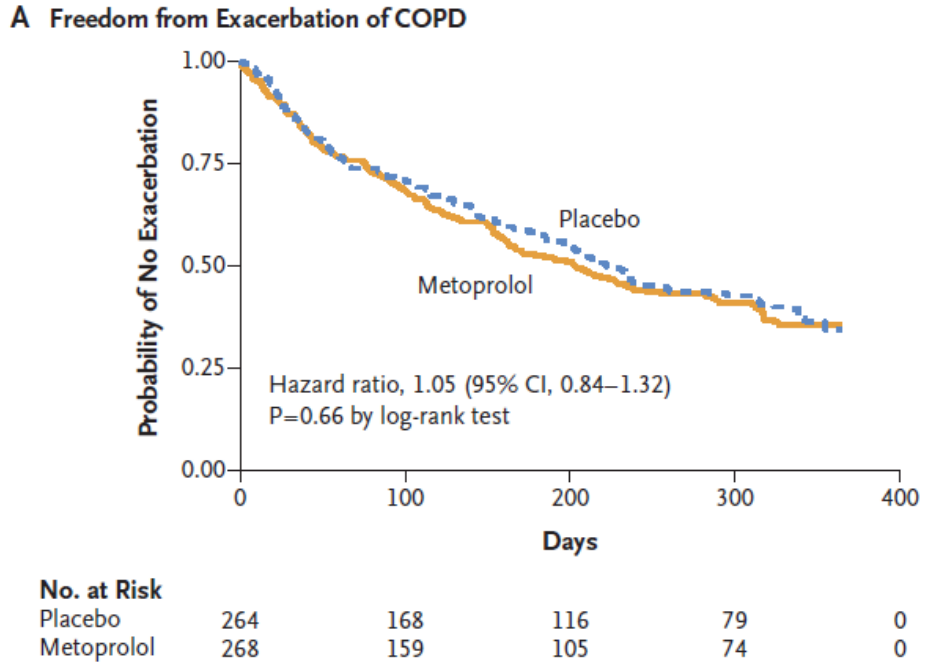
Metoprolol for the Prevention of Acute Exacerbations of COPD

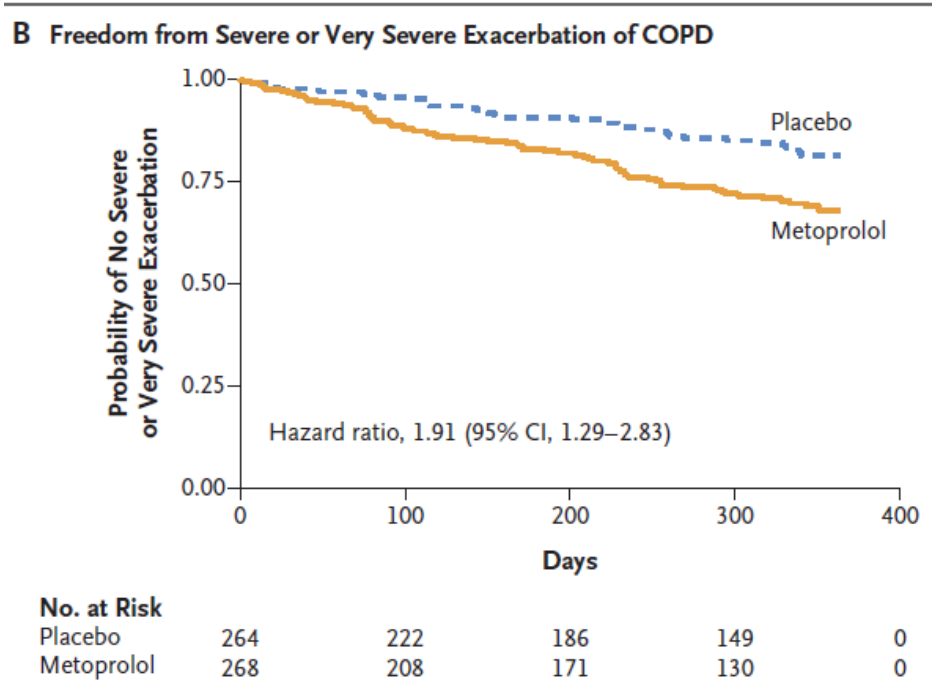
M.T. Dransfield, H. Voelker, S.P. Bhatt, K. Brenner, R. Casaburi, C.E. Come, J.A.D. Cooper, G.J. Criner, J.L. Curtis, M.L.K. Han, U. Hatipoğlu, E.S. Helgeson, V.V. Jain, R. Kalhan, D. Kaminsky, R. Kaner, K.M. Kunisaki, A.A. Lambert, M.R. Lammi, S. Lindberg, B.J. Make, F.J. Martinez, C. McEvoy, R.J. Panos, R.M. Reed, P.D. Scanlon, F.C. Sciurba, A. Smith, P.S. Sriram, W.W. Stringer, J.A. Weingarten, J.M. Wells, E. Westfall, S.C. Lazarus, and J.E. Connett, for the BLOCK COPD Trial Group*

CONCLUSIONS

Among patients with **moderate or severe COPD** who **did not have an established indication for beta-blocker use**, the time until the first COPD exacerbation was similar in the metoprolol group and the placebo group. **Hospitalization for severe, or very severe (intubation), exacerbation was more common among the patients treated with metoprolol**.

(Funded by the Department of Defense; BLOCK COPD ClinicalTrials.gov number, NCT02587351.)



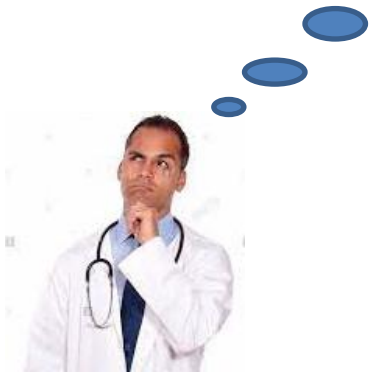


Quindi:

Se non c'è una chiara indicazione al β-bloccante, questo non appare indicato in presenza di BPCO (con lo scopo di prevenire le esacerbazioni della malattia e/o le complicanze cardiovascolari associate a tali esacerbazioni).

β-bloccanti in pazienti con BPCO….. Perché?

1. Per prevenire le esacerbazioni della BPCO
2. Per trattare correttamente pazienti con BPCO ed indicazioni ai β-bloccanti (**scompenso cardiaco, cardiopatia ischemica cronica**). I β-bloccanti sono pericolosi in questi pazienti?



ESC
European Society of Cardiology
European Heart Journal (2021) **42**, 3599–3726
doi:10.1093/eurheartj/ehab368

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

13.8 Lung disease, sleep-disordered breathing

Treatment of HF is generally well tolerated in COPD.[800] Beta-blockers can worsen pulmonary function in individual patients but are not contraindicated in either COPD or asthma, as stated in the Global initiative for chronic Obstructive Lung Disease (GOLD) and the Global INitiative for Asthma (GINA), respectively.[801,802] GINA states that asthma should not be regarded as an absolute contraindication to the use of cardioselective beta-blockers (bisoprolol, metoprolol succinate, or nebivolol) with consideration of relative risks and benefits. In clinical practice, starting with low doses of cardioselective beta-blockers combined with close monitoring for signs of airway obstruction (wheezing, shortness of breath with lengthening of the expiration) should be encouraged. Although not tested in HF patients, inhaled corticosteroids and beta-adrenergic agonists do not seem to increase CV events, including HF, in patients at high risk.[803,804] Moreover, optimal COPD management can improve cardiac function.[805]

The contraindication to beta-blockers in asthma, as mentioned on pharmacy leaflets, is based on small case series published in the 1980s and late 1990s with very high initial dosages in young patients with severe asthma.

Eppure, nonostante le indicazioni delle Linee Guida…

I β-bloccanti restano **ampiamente sottoutilizzati** in pazienti con chiare indicazioni (scompenso cardiaco, cardiopatia ischemica cronica), spesso solo per ‘supposta’ BPCO.

TABLE 2 Data From Large Heart Failure Registries Reporting Differences in the Use of Beta-Blockers in Patients With Versus Those Without Chronic Obstructive Pulmonary Disease

	Sample Characteristics	Overall Sample	COPD Sample	Diagnosis of COPD	BB Use in COPD Vs. Non-COPD	β_1-Selective BB Use in COPD Vs. Non-COPD (BB Users Only)
European registry 2011-2013 (3)	Ambulatory HFrEF (~70%) and HFpEF (~30%)	9,409	1,322 (14.1%)	Clinical	81.6% vs. 89.8%	65.6% vs. 56.6%
Asian regions 2010-2015 (52)	Ambulatory HFrEF	5,232	434 (8.3%)	Clinical	66.3% vs. 79.9%	48.3% vs. 23.2%
European registry 2011-2013 (3)	Hospitalized HFrEF (~60%) and HFpEF (~40%)	6,920	1,334 (19.3%)	Clinical	At admission: 51.0% vs. 56.3% At discharge: 62.8% vs. 76.9%	At admission: 60.0% vs. 66.3% At discharge: 66.9% vs. 66.9% (p = NS)
OPTIMIZE-HF registry (U.S.) 2003-2004 (19)	Hospitalized HFrEF	20,118	5,057 (25.1%)	Clinical	At admission: 52.0% vs. 57.1% At discharge: 65.9% vs. 75.4%	39% vs. 41% (p = NS) (in a subset of 2,670 patients, 722 [27%] with COPD, with available data)
Worcester Heart Failure Study 1995-2004 (18)	Hospitalized HFrEF (~30%) and HFpEF (~70%)	9,748	3,500 (35.9%)	Clinical	At discharge: 39.4% vs. 55.9% (45.4% vs. 59% in HFrEF only, 57.5% vs. 72.9% in 2004 only)	Not available

HFpEF and HFrEF were differentiated using the 40% cutoff recommended in the guidelines. All comparisons were statistically significant, except as indicated.

BB = beta-blocker; COPD = chronic obstructive pulmonary disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

Canepa M et al. JACC Heart Failure 2019;7:823-33

Underuse of beta-blockers by patients with COPD and co-morbid acute coronary syndrome: A nationwide follow-up study in New Zealand

LIANNE PARKIN,[1,2*] JOSHUA QUON,[3*] KATRINA SHARPLES,[1,4,5] DAVID BARSON[1,2] AND JACK DUMMER[1,4]

Results: **The study cohort included 83 435 patients aged ≥45 years, with 290 400 person-years of follow-up. Among 2637 patients with ≥1 ACS admission during follow-up, only 56.6% received a beta-blocker in the 6 months following the first admission, while 87.7% and 81%, respectively, received aspirin and a statin. Patients with higher COPD severity were less likely to receive a beta-blocker than those with lower severity, as were those with no history of previous ACS and/or heart failure.**

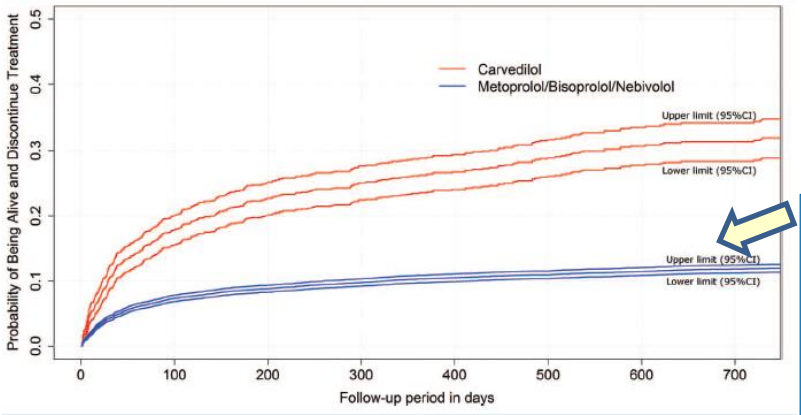
Conclusion: **Use of beta-blockers following an ACS admission was much lower than expected based on the findings of general audits of ACS management in New Zealand. Along with the higher proportions using aspirin and statins, and the differences in beta-blocker dispensing by COPD severity, this suggests a particular reluctance to prescribe beta-blockers to patients with COPD.**

Parkin L et al. Respirology 2019;25:173-82

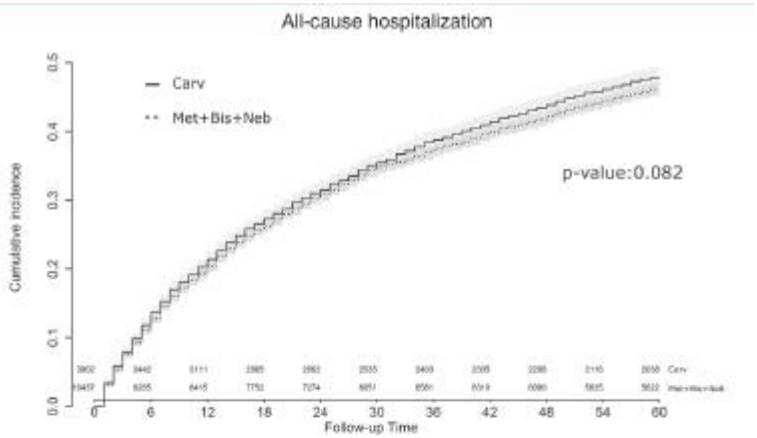
Relationship between heart failure, concurrer chronic obstructive pulmonary disease and beta-blocker use: a Danish nationwide cohort study

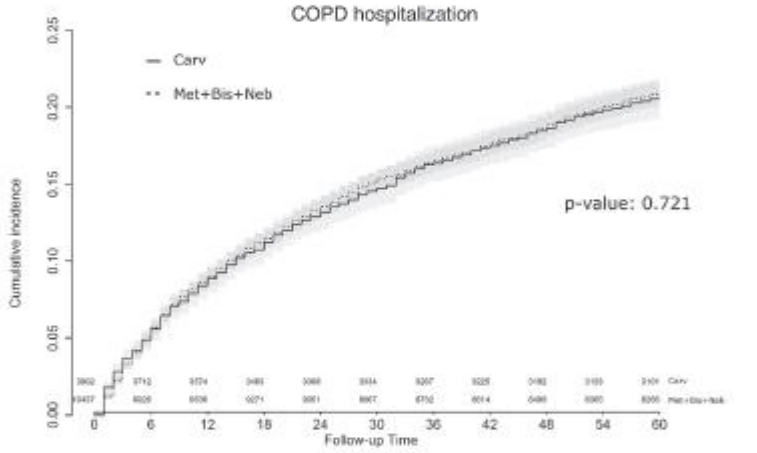
Maurizio Sessa[1,2*†], Annamaria Mascolo[1†], Rikke Nørmark Mortensen[2], Mikkel Porsborg Andersen[3], Giuseppe Massimo Claudio Rosano[4,5], Annalisa Capuano[1], Francesco Rossi[1], Gunnar Gislason[6,7,8], Henrik Enghusen-Poulsen[9], and Christian Torp-Pedersen[2,3]

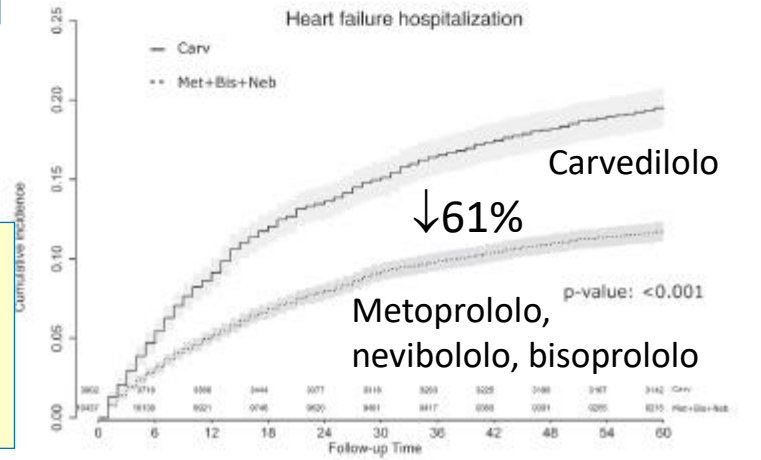
- ✓ 24.999 pazienti con **BPCO e scompenso**. **Solo il 57% di questi pazienti ha ricevuto β-bloccanti.**
- ✓ Tra questi: carvedilolo nel 27% e β-bloccanti β_1-selettivi (metoprolo, bisoprololo, nevibololo) nel rimanente 73%).
- ✓ Quelli trattati con **carvedilolo** hanno presentato un **maggior rischio di ospedalizzazioni per scompenso cardiaco** [HR 1.61; 95% CI 1.52–1.70], ma non di ospedalizzazioni per BPCO o per tutte le cause.



Ed anche un minor rischio di sospensione del trattamento







I β-bloccanti β_1 selettivi inducono:

1) Una minore riduzione del FEV_1 rispetto ai non-selettivi.

- Jabbour A, Macdonald PS, Keogh AM, et al. Differences between betablockers in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized crossover trial. J Am Coll Cardiol 2010; 55:1780–1787.
- Ni Y, Shi G, Wan H. Use of cardioselective beta-blockers in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized, placebo-controlled, blinded trials. J Int Med Res 2012; 40:2051–2065.
- Neef PA, Burrell LM, McDonald CF, et al. Commencement of cardioselective beta-blockers during hospitalisation for acute exacerbations of chronic obstructive pulmonary disease. Intern Med J 2017; 47:1043–1050.

2) Una maggiore risposta broncodilatatrice ai farmaci β_2 stimolanti rispetto ai non-selettivi.

- Maltais F, Buhl R, Koch A, et al. Beta-blockers in COPD: a cohort study from the TONADO Research Program. Chest 2018; 153:1315–1325.
- Dransfield MT, McAllister DA, Anderson JA, et al. Beta-blocker therapy and clinical outcomes in patients with moderate chronic obstructive pulmonary disease and heightened cardiovascular risk. An Observational Substudy of SUMMIT. Ann Am Thorac Soc 2018; 15:608–614.

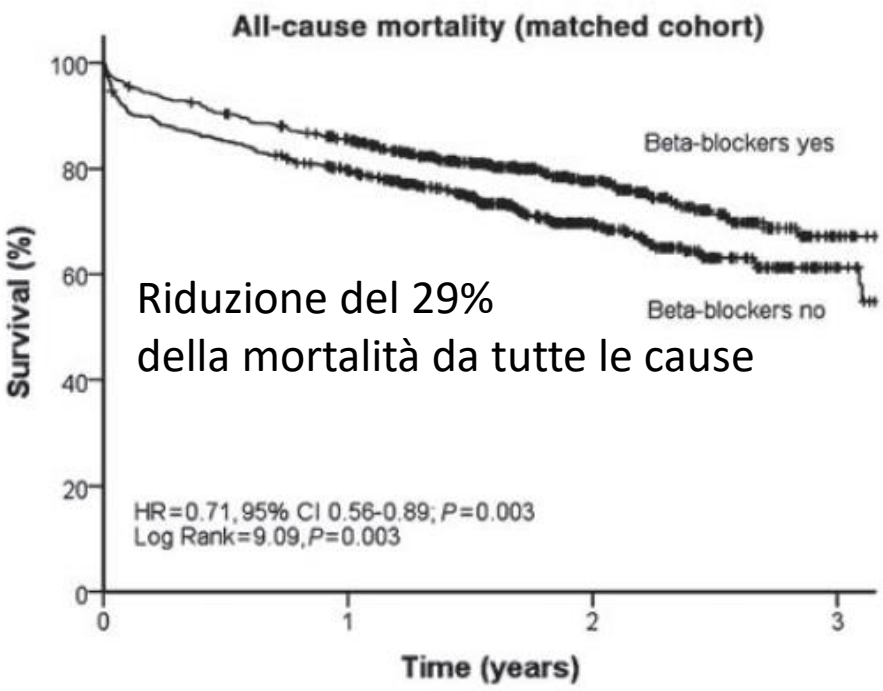
European Journal of Heart Failure (2017) 19, 271–279
doi:10.1002/ejhf.647

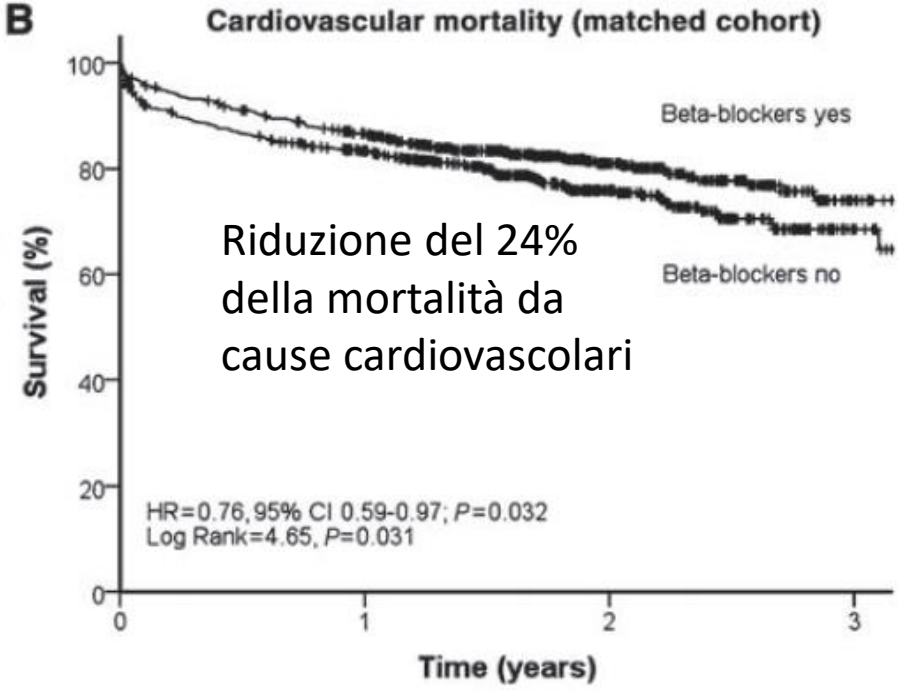
RESEARCH ARTICLE

Association of beta-blocker treatment with mortality following myocardial infarction in patients with chronic obstructive pulmonary disease and heart failure or left ventricular dysfunction: a propensity matched-cohort analysis from the High-Risk Myocardial Infarction Database Initiative

Stefano Coiro[1,2,3], Nicolas Girerd[1,2], Patrick Rossignol[1,2], João Pedro Ferreira[1,2,4], Aldo Maggioni[5], Bertram Pitt[6], Isabella Tritto[3], Giuseppe Ambrosio[3], Kenneth Dickstein[7], and Faiez Zannad[1,2]*

Methods and Results. Among 28 771 patients from the High-Risk MI Database Initiative, 1573 had a baseline history of COPD.
After adjustment for confounding, including 24 baseline covariates, **COPD patients still benefited from β-blockers for all-cause mortality and CV mortality**.
Conclusions. In the specific setting of a well-treated cohort of high-risk MI survivors, β-blockers were associated with better outcomes in patients with COPD.





Coiro S et al. Eur J Heart Fail 2017;19:271-79

Beta-bloccanti Raccomandati nello Scompenso Cardiaco a Funzione Sistolica Ridotta

Farmaco	Blocco recettori	Dose iniziale	Dose target
Carvedilolo	α_1, β_1, β_2	3,125 mg b.i.d.	25-50 mg b.i.d.
Bisoprololo	β_1	1,25 mg o.d.	10 mg o.d.
Metoprololo	β_1	12,5-25 mg o.d.	200 mg o.d.
Nevibololo*	β_1	1,25 mg o.d.	10 mg o.d.

*Non ancora autorizzato negli USA. Ha effetti vasodilatatori mediati dalla stimolazione dei recettori β_3, con conseguente rilascio di ossido nitrico. È quello con più elevato rapporto di blocco $\beta1/\beta2$ (45:1), contro metoprololo (2:1) e bisoprololo (14:1).

Modificata da: Canepa M et al. JACC Heart Failure 2019;7:823-33

Quindi:

Nei pazienti con BPCO e **chiare indicazioni ai β-bloccanti** (scompenso cardiaco, cardiopatia ischemica cronica), i β-bloccanti:

- ✓ **Non sono pericolosi**, soprattutto se usiamo quelli β1-selettivi, iniziando a basse dosi.
- ✓ **Non alterano l'effetto broncodilatatore dei farmaci β_2-stimolanti**.

Stiamo comunque attenti ad eventuali episodi di broncospasmo, peraltro rari nei soggetti anziani (come quelli che vediamo di solito).

Vi ringrazio
per l'attenzione