SỬ DỤNG BETA-BLOCKER & BETA 2-AGONIST Ở BỆNH NHÂN ĐỒNG MẮC TIM MẠCH & HEN/COPD

TS.BS. NGUYỄN NGỌC PHƯƠNGTHƯ

TRƯỜNG ĐHYK PHẠM NGỌC THẠCH

HEN DỊ ỨNG
TP. HCM
MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

NỘI DUNG

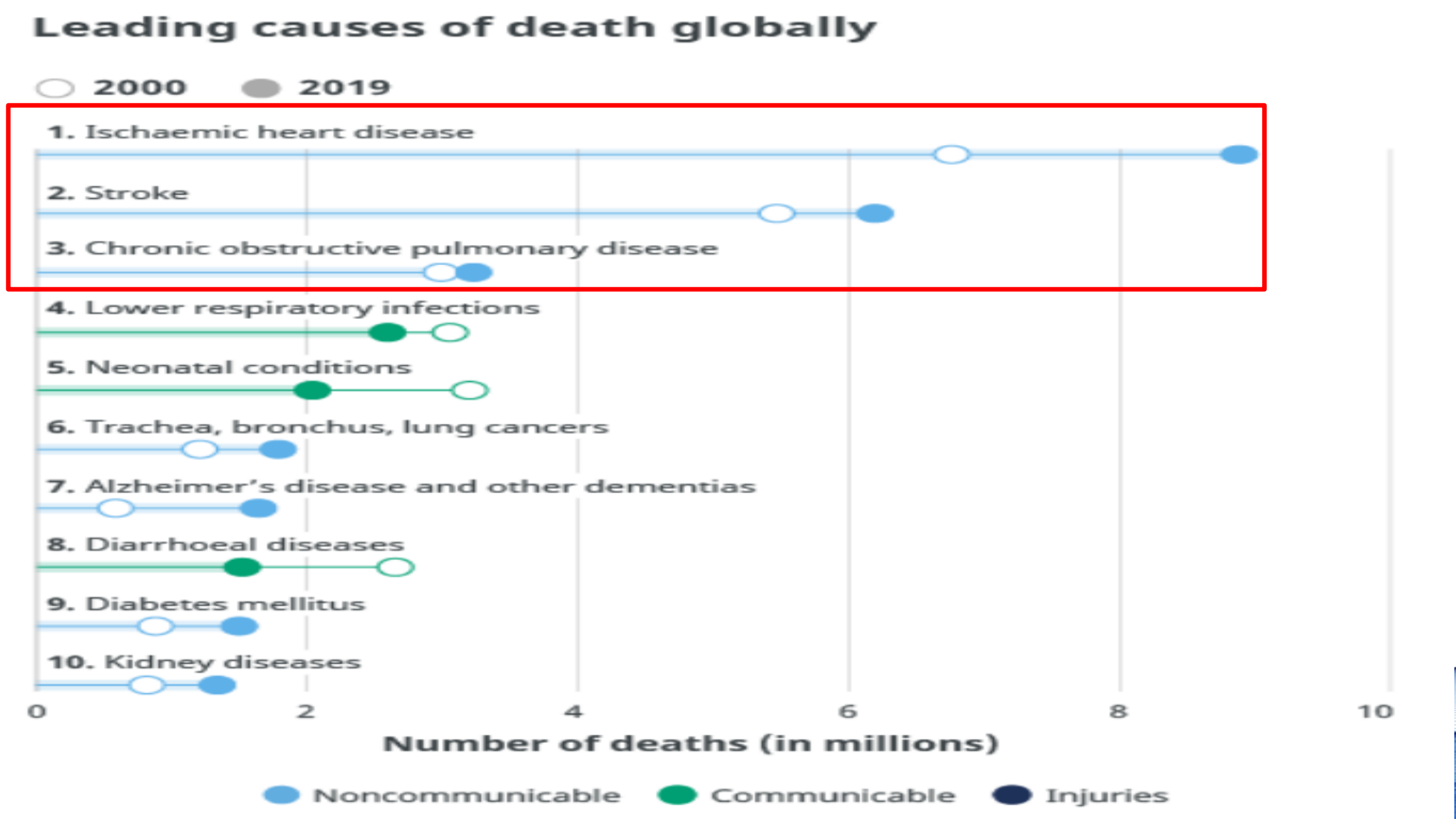
1. Tại sao cần quan tâm Beta-blocker và đồng vận Beta-2 ở BN đồng mắc tim mạch và hen hoặc COPD

2. Sử dụng Beta-blocker cho BN đồng mắc tim mạch và hen hoặc COPD

3. Sử dụng đồng vận Beta-2 cho BN đồng mắc tim mạch và hen hoặc COPD

HEN DỊ ỨNG
TP. HCM
MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

Tại sao cần quan tâm beta-blocker và đồng vận beta-2 ở BN đồng mắc tim mạch và hen hoặc COPD

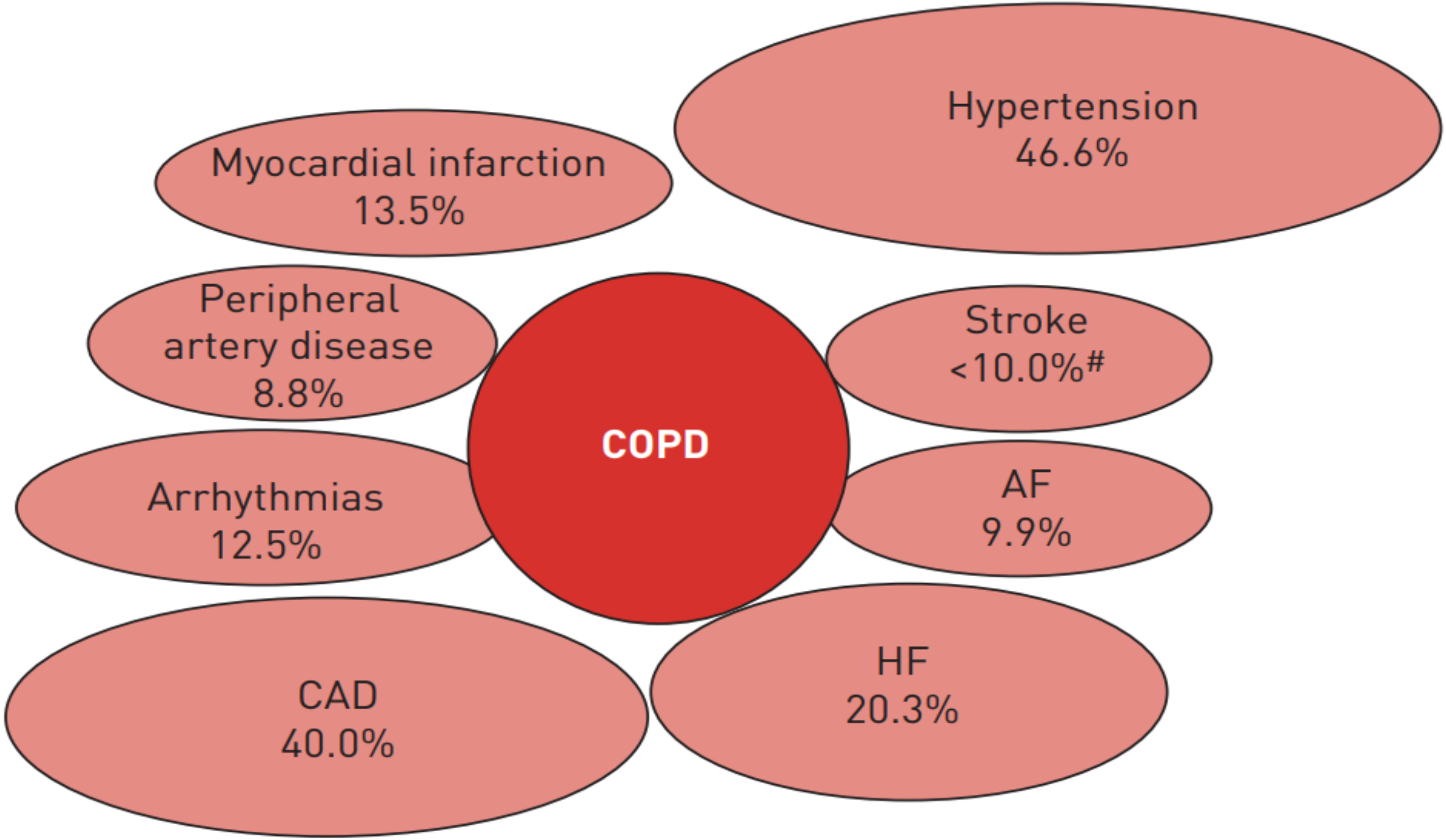

Leading causes of death globally
2000
2019
1. Ischaemic heart disease
2. Stroke
3. Chronic obstructive pulmonary disease
4. Lower respiratory infections
5. Neonatal conditions
6. Trachea, bronchus, lung cancers
7. Alzheimer's disease and other dementias
8. Diarrhoeal diseases
9. Diabetes mellitus
10. Kidney diseases
0
2
4
6
8
10
Number of deaths (in millions)
Noncommunicable
Communicable
Injuries

HEN & BỆNH ĐỒNG MẮC

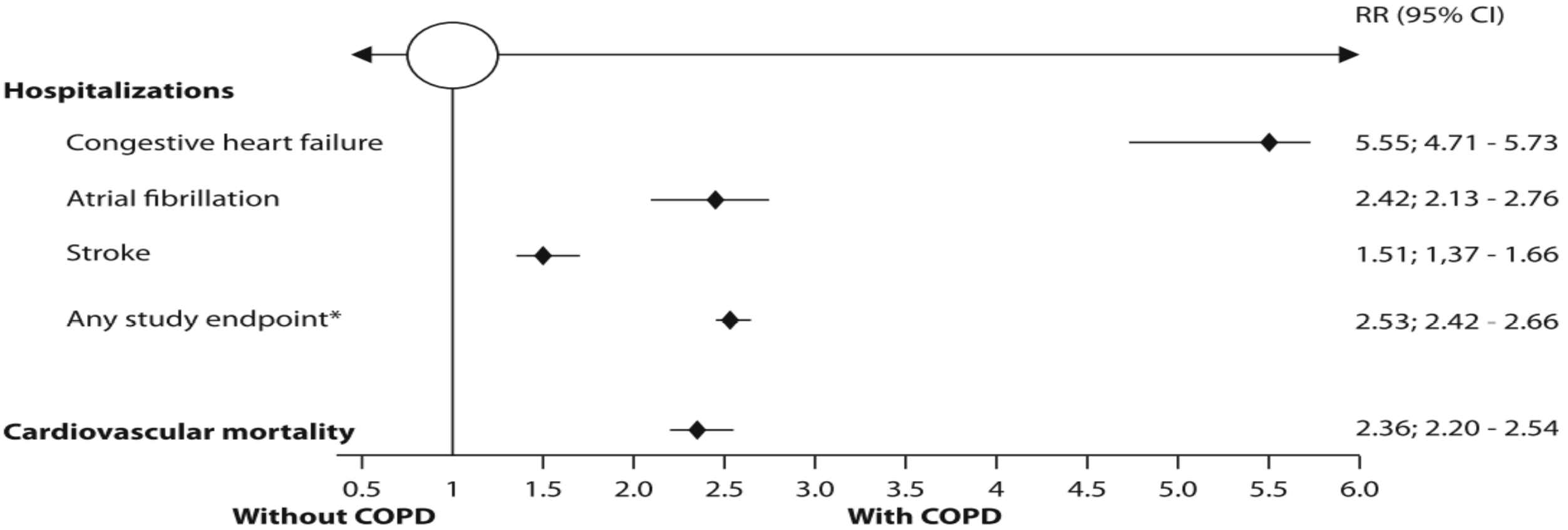
Health condition	OR (95% CI)*	OR (95% CI)†	OR (95% CI)‡
Diabetes mellitus	1.80 (1.48 to 2.18)	1.58 (1.29 to 1.94)	1.31 (1.06 to 1.63)
Hypertension	1.76 (1.56 to 1.98)	1.63 (1.42 to 1.86)	1.47 (1.28 to 1.69)
Coronary heart disease	2.46 (2.06 to 2.94)	2.34 (1.93 to 2.83)	2.14 (1.76 to 2.60)
Chronic heart failure	3.22 (2.54 to 4.09)	2.84 (2.22 to 3.64)	2.74 (2.13 to 3.52)
Stroke	2.48 (1.82 to 3.39)	2.16 (1.57 to 2.97)	2.12 (1.54 to 2.91)
Cancer (any)	1.50 (1.22 to 1.84)	1.28 (1.04 to 1.58)	1.21 (0.98 to 1.50)
Osteoarthritis	1.85 (1.63 to 2.10)	1.63 (1.42 to 1.87)	1.55 (1.35 to 1.79)
Depression	2.27 (1.93 to 2.68)	2.18 (1.85 to 2.58)	2.06 (1.74 to 2.45)

Odds ratio (OR) and 95% confidence interval (CI) obtained from multivariable logistic regression analyses: *Crude OR. †OR adjusted for age group and gender. ‡OR adjusted for age group, gender, body mass index categories, educational attainment, and smoking status.

Prim Care Respir J. 2014 Mar; 23(1): 22–29


Hypertension
46.6%
Myocardial infarction
13.5%
Peripheral
artery disease
8.8%
Stroke
<10.0%#
COPD
Arrhythmias
12.5%
AF
9.9%
CAD
40.0%
HF
20.3%

COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program



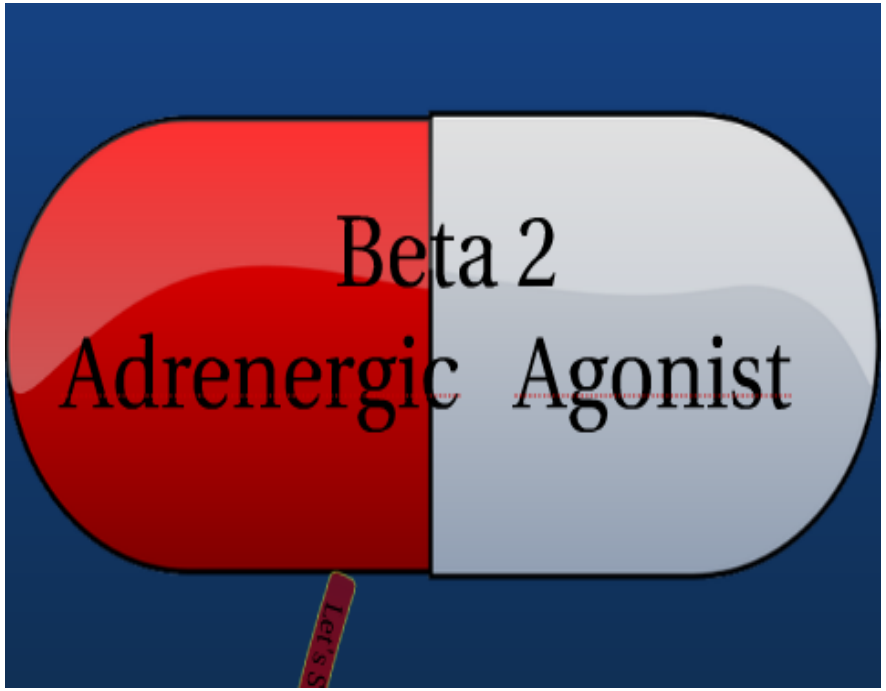
Đoàn hệ hồi cứu ghép cặp, n = 45.966
Bắc California
Theo dõi 4 năm

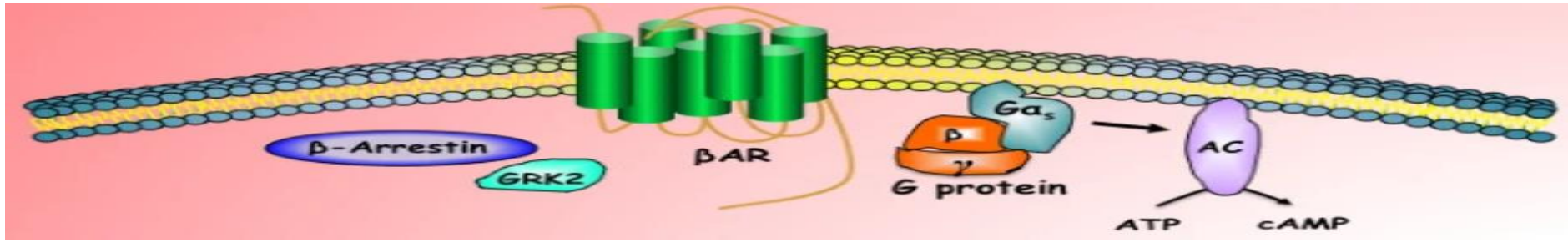
> 1/4

Morgan et al (2018)
Ther Adv RespirDis.

Sidney S et al (2005). Chest. 2005;128(4):2068–75.


Beta
Blockers


Beta 2
Adrenergic Agonist


β-Arrestin
GRK2
βAR
Gαs
β
γ
G protein
AC
ATP
cAMP

A case of fatal asthma induced by timolol eye-drop

M Taniguchi, H Kino, M Mori… - The Japanese journal of …, 1990 - jstage.jst.go.jp

抄録 症例は 74 歳, 男性, 1972 年以来気管支喘息発作があり, アミノフィリン, 交感神経刺激剤, 副腎皮質ステロイド剤の投与を受けていた. 本年 1 月急性緑内障を併発, マレイン酸チモロール点眼液の投与後呼吸困難が急速に進行, 死亡した. 剖検では典型的な気管支喘息重積発作の所見を認めた. 本例はチモロールの点眼により喘息発作が誘発され, 死亡した可能性が極めて高く, チモロール点眼による死亡例としては本邦初例である. 高齢者ではチモロールなど β 遮断剤を主成分とする点眼剤を使用する場合, 気管支喘息の既往がないことを十分確認し …

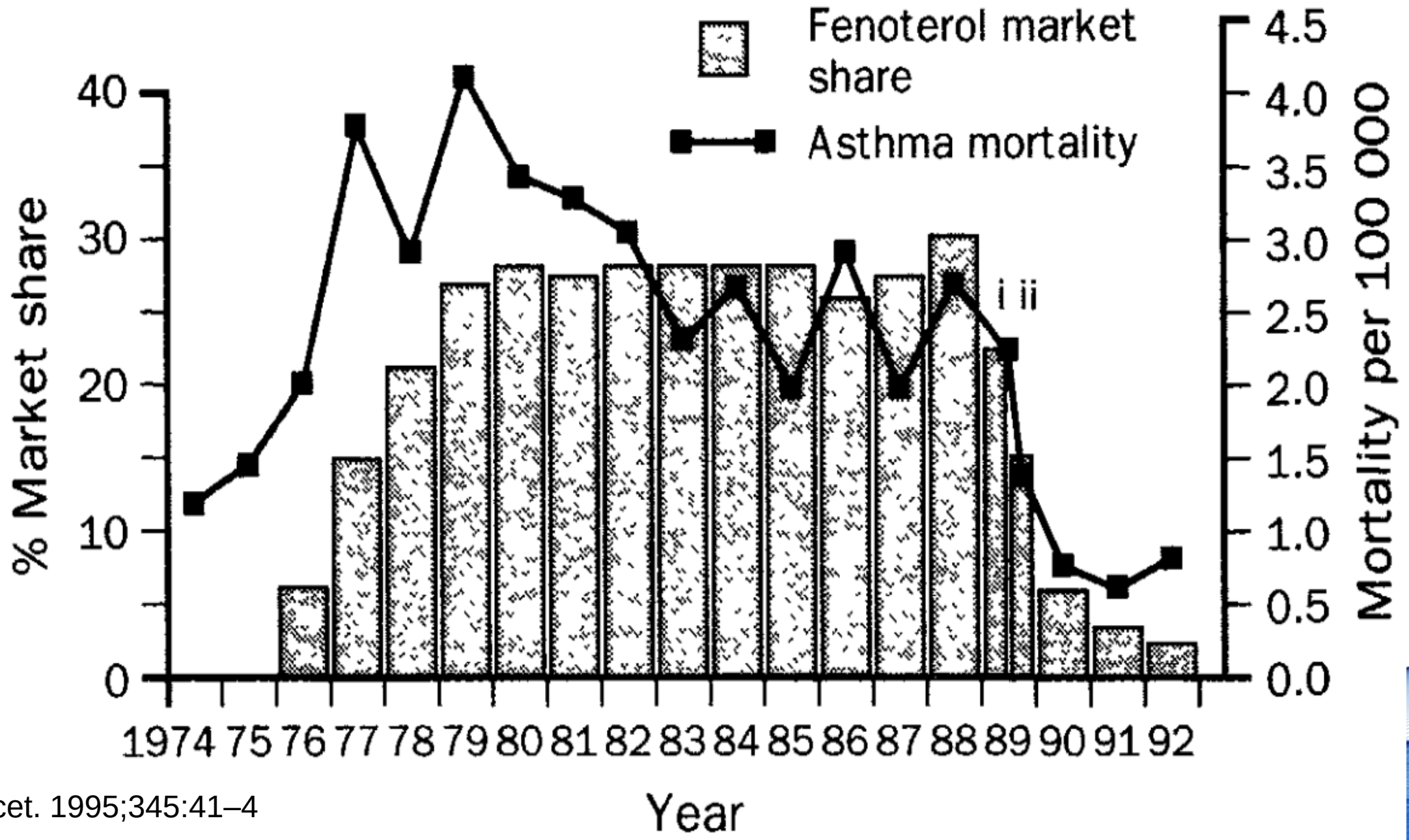
Respiratory Effects of Timolol

F. T. Fraunfelder, Alan F. Barker

Ophthalmology, Pulmonary & Critical Care Medicine

65
Scopus citations

Research output: Contribution to journal › Letter › peer-review



Pearce et al. Lancet. 1995;345:41–4

MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

Thực trạng sử dụng beta-blocker ở BN đồng mắc tim mạch & Hen/COPD

- NMCT & COPD đồng mắc: < 40% dùng beta blocker

(BMJ 2013; 347:f6650)

- Suy tim & COPD đồng mắc: COPD là lý do không dùng beta blocker

(Clin Res Cardiol 2014;103: 733 –741)

- Tại thời điểm xuất viện: BN COPD ít được kê các thuốc suy tim theo khuyến cáo, gồm beta-blocker

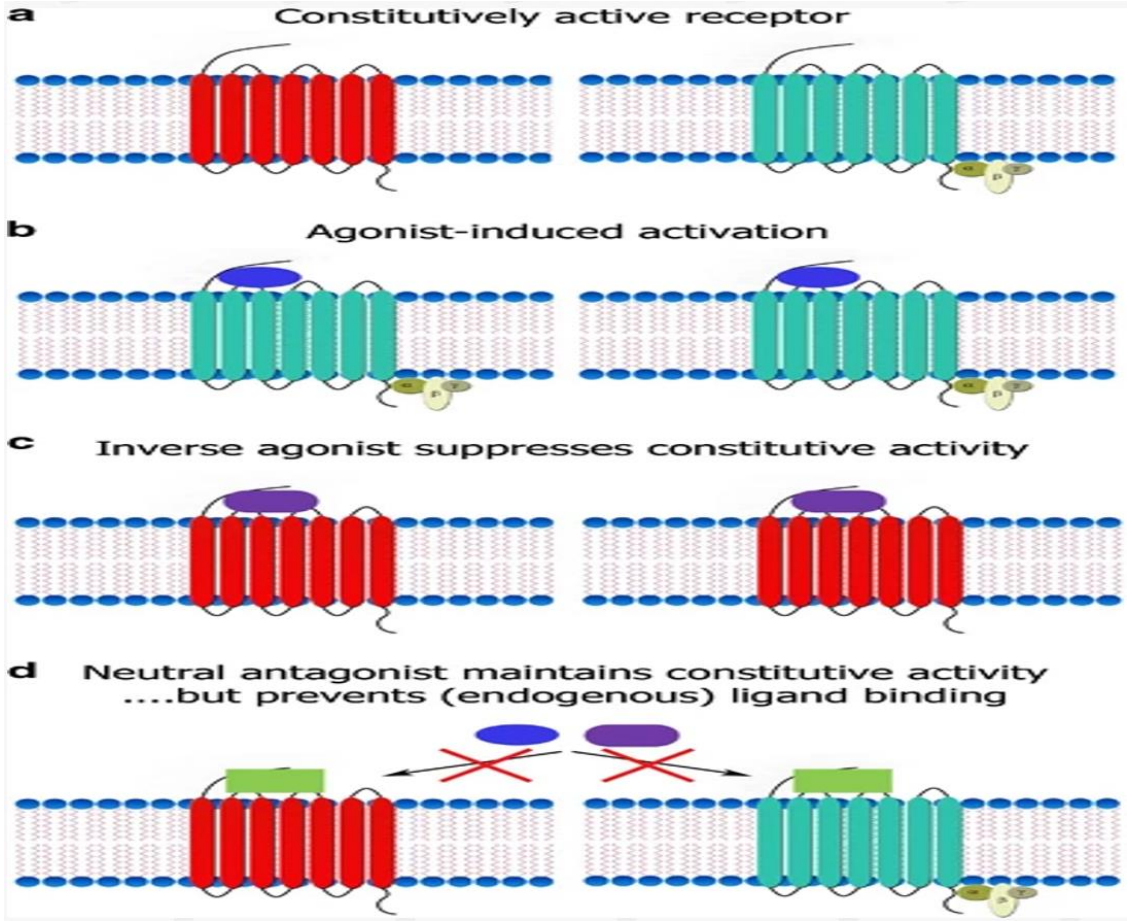
(Chest 2015;147:637 –645)

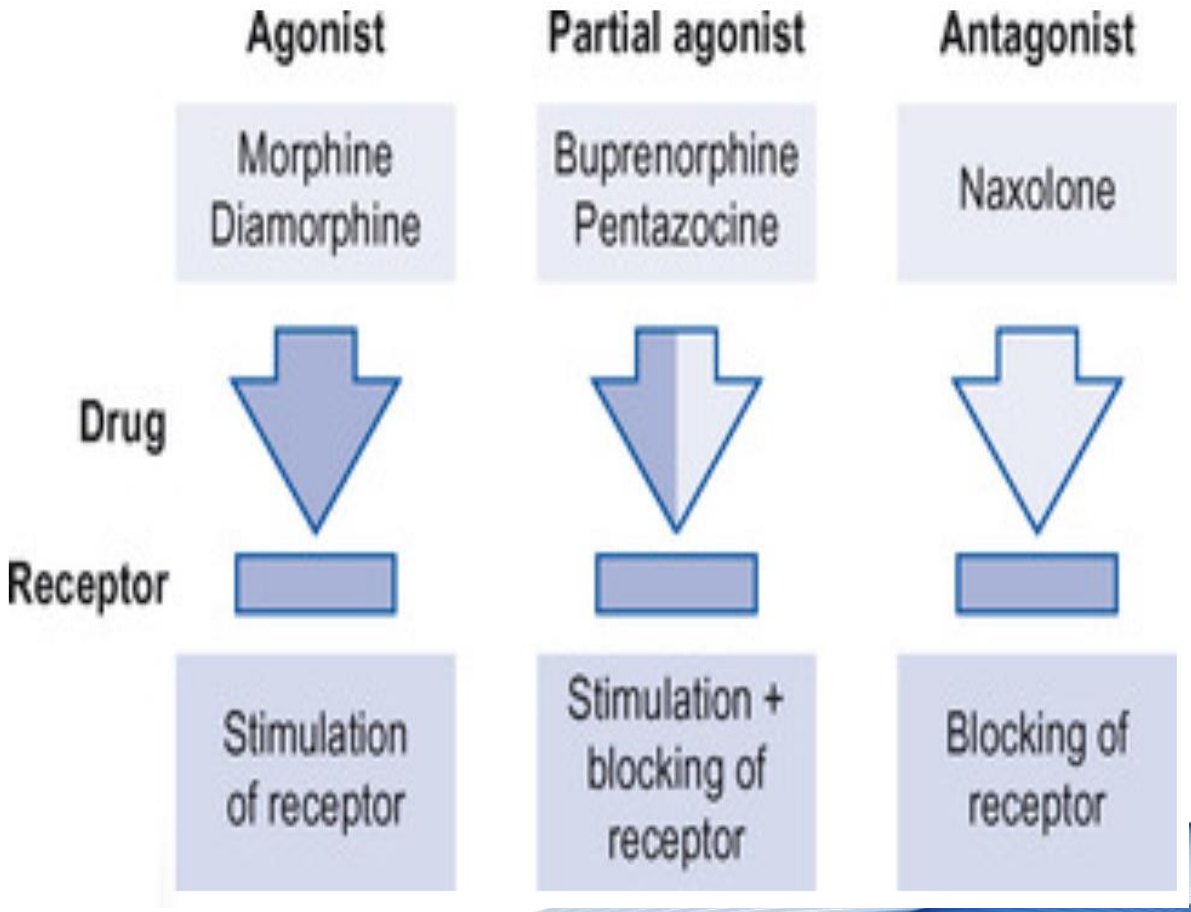
- Trong 35.502 CVD và Hen: 14,1% và 1,2% có dùng beta-blocker chọn lọc & không chọn lọc tim (BMC Med. 2017; 15: 18.)

HEN DỊ ỨNG
TP. HCM
MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

Sử dụng Beta blocker cho BN đồng mắc tim mạch & Hen/COPD

CÁC TRẠNG THÁI HOẠT ĐỘNG CỦA BETA RECEPTOR





The vital role of constitutive GPCR activity in the mesolimbic dopamine system. Translational Psychiatry (nature.com)

PHÂN LOẠI BETA-BLOCKER

	Cardioselective β_1-blockers (relative selectivity of β_1 *versus* β_2)	Nonselective β-blockers (relative selectivity of β_1 *versus* β_2)
Partial agonist/ISA	Acebutolol (2.4#) Practolol (>14.1#)	Labetalol (2.5#) Alprenolol (16.2#)
Inverse agonist	Metoprolol (2.3#, 6.0¶) Atenolol (4.7#, 5.7¶) Bisoprolol (13.5#, 19.6¶) Nebivolol (40.6¶)	Carvedilol (4.5#) Propranolol (8.3#) Sotalol (12.0#) Nadolol (23.4#) Timolol (25.7#)

MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

CHỈ ĐỊNH, LIỀU, ĐƯỜNG THẢI TRỪ CỦA BETA-BLOCKER

Drug	Indications in CVD (other than hypertension[a])	Daily dose (mg/day)	Half-life (h)	Route of excretion
Acebutolol	Chronic stable angina; tachyarrhythmia	200–1200	3–4	Renal 30–40%; non-renal 50–60%
Atenolol	Chronic stable angina; following MI; cardiac arrhythmia	50–100	6–7	Mainly renal
Bisoprolol	HF with reduced EF	1.25–10	9–12	Renal 50%; non-renal 50%
Carvedilol	Mild to severe HF; chronic stable angina; following MI	3.125–100	6–10	Mainly non-renal
Metoprolol	HF; chronic stable angina; following MI; tachyarrhythmia;	50–450	3–9	Mainly renal
Nadolol	Chronic stable angina; tachyarrhythmia; thyrotoxicosis	20–240	20–24	Mainly renal
Nebivolol	Mild to moderate HF	2.5–20	12–19	38–67% renal; 13–48% non-renal
Propranolol	Chronic stable angina; following MI; cardiac arrhythmias; thyrotoxicosis	10–320	3–6	10% renal; 90% non-renal

Am J Cardiovasc Drugs (2017) 17:361–373

Adverse Respiratory Effect of Acute β-blocker Exposure in Asthma

Study or Subgroup	Beta-blocker Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Nicolaescu 1972	-8.63	4.96	10	0.07	8.64	10	5.3%	-8.70 [-14.87, -2.53]	1972
Nicolaescu 1973	-4.13	5.66	10	-1.87	6.22	10	6.7%	-2.26 [-7.47, 2.95]	1973
Thiringer 1976	-7.51	4.39	24	-2.88	4.39	8	10.6%	-4.63 [-8.14, -1.12]	1976
Boye 1977	-14.39	11.4	10	-0.73	11.63	10	2.4%	-13.66 [-23.75, -3.57]	1977
Benson 1978	-5.54	11.4	24	1.92	11.4	12	3.6%	-7.46 [-15.36, 0.44]	1978
Ellis 1981	-12.97	11.43	30	-2.83	11.43	10	3.4%	-10.14 [-18.32, -1.96]	1981
Suzuki 1981	-10.66	11.95	24	-6.35	11.95	24	4.6%	-4.31 [-11.07, 2.45]	1981
Lofdhal 1981	-8.04	7.03	16	2.31	7.2	8	5.5%	-10.35 [-16.41, -4.29]	1981
Nair 1981	-17.61	14.83	10	-2.82	14.83	10	1.5%	-14.79 [-27.79, -1.79]	1981
Larsson 1982	-9.5	7.01	14	-3.9	5.04	13	8.0%	-5.60 [-10.18, -1.02]	1982
Lawrence 1982	-9.22	9.06	28	3.63	9.06	14	5.8%	-12.85 [-18.66, -7.04]	1982
Jackson 1983	-16.18	11.61	11	-6.18	16.35	11	1.8%	-10.00 [-21.85, 1.85]	1983
Ellis 1984	-8.47	12.87	16	2.4	12.87	8	2.1%	-10.87 [-21.79, 0.05]	1984
Lammers 1985	-21.87	22.79	16	-2.75	22.79	8	0.7%	-19.12 [-38.46, 0.22]	1985
Chatterjee 1986	-5.75	13.02	36	1.15	13.02	12	3.2%	-6.90 [-15.41, 1.61]	1986
Falliers 1986	-5.8	10.92	18	1.8	10.92	18	4.3%	-7.60 [-14.73, -0.47]	1986
Doshan 1986 A	3.03	17.1	45	3.7	11.23	15	3.9%	-0.67 [-8.24, 6.90]	1986
Doshan 1986 B	3.4	12.27	102	5.48	10.37	34	8.8%	-2.08 [-6.30, 2.14]	1986
Repsher 1986	-7.28	10.69	31	3.03	10.69	18	5.3%	-10.31 [-16.52, -4.10]	1986
Chodosh 1988	-10.01	12.18	32	-1.59	12.18	16	4.1%	-8.42 [-15.73, -1.11]	1988
Fogari 1990	-4.3	8.27	20	0	8.27	10	5.2%	-4.30 [-10.58, 1.98]	1990
Tantucci 1990	-13.55	15.52	24	-1.12	15.52	12	2.1%	-12.43 [-23.18, -1.68]	1990
Dal Negro 2002	-2.3	18.62	12	-2.33	15.92	12	1.3%	0.03 [-13.83, 13.89]	2002
Total (95% CI)			563			303	100.0%	-6.88 [-8.53, -5.23]	

Heterogeneity: Tau² = 3.46; Chi² = 28.50, df = 22 (P = 0.16); I² = 23%
Test for overall effect: Z = 8.16 (P < 0.00001)

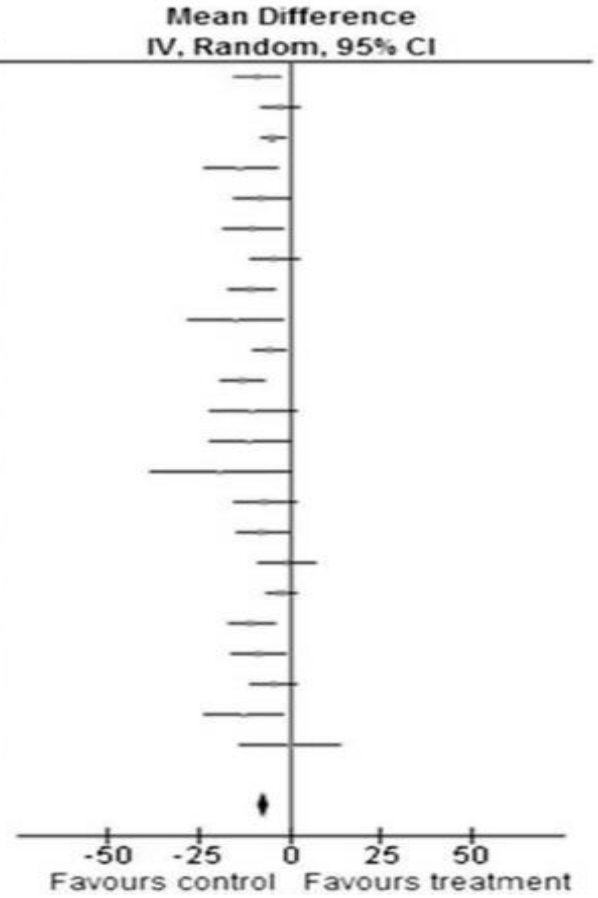
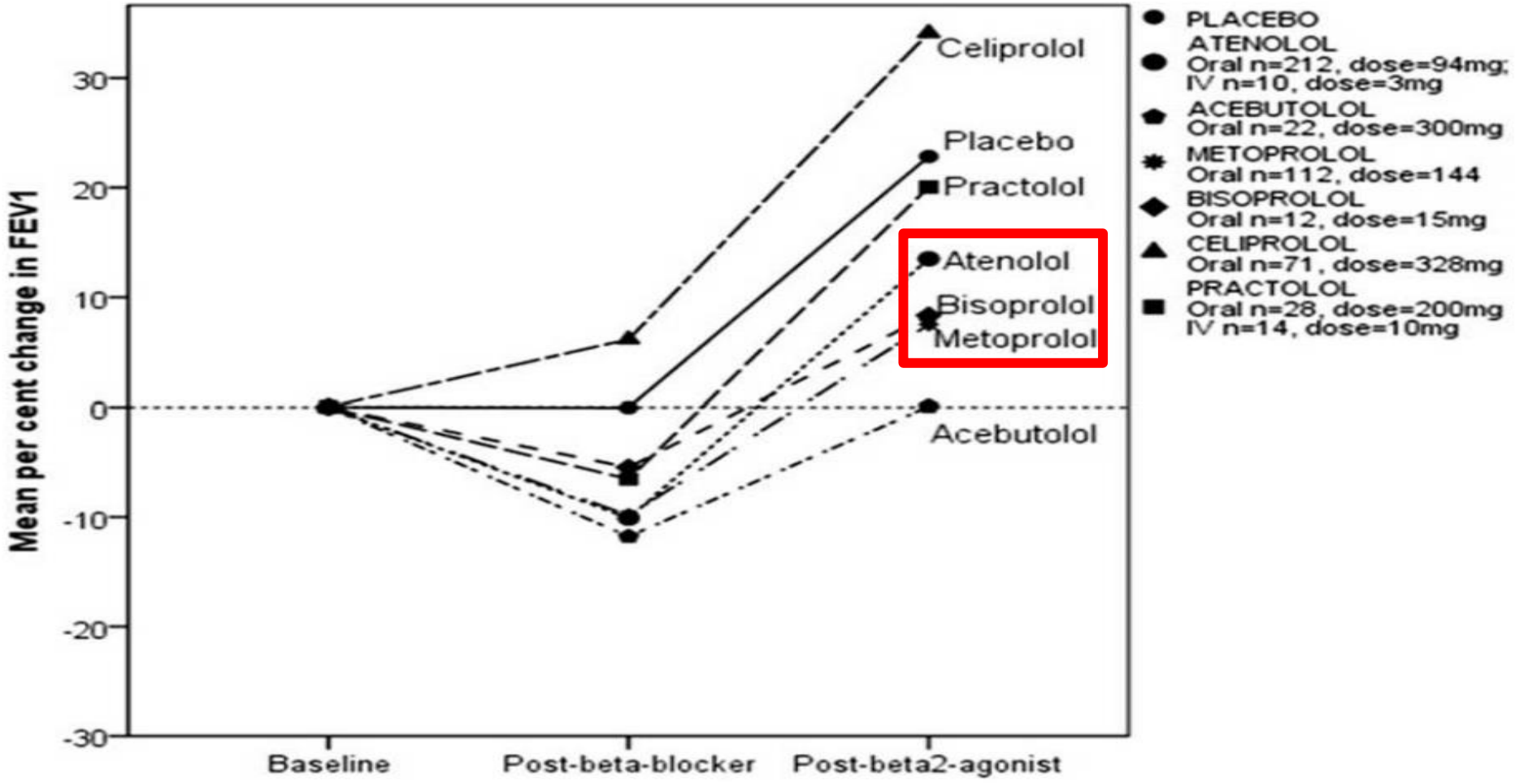


FIGURE 2. Mean change in FEV_1 following acute selective β-blocker exposure. df = degrees of freedom.

Morales et al, Chest 2014; 145(4):779–786

Adverse Respiratory Effect of Acute β-blocker Exposure in Asthma



Morales et al, Chest 2014; 145(4):779–786

Specialist initiation and monitoring of beta blockers in patients with chronic heart failure and concomitant obstructive airways disease

Variable	Initiation (pre-nebivolol mean [95% CI])	Final visit (maximum dosage mean [95% CI])	p-value
FEV1 (litres)			
Total cohort (n = 36)	1.64 [1.45–1.83]	1.61 [1.40–1.81]	p = 0.624
Asthma (n = 13)	2.02 [1.71–2.34]	1.99 [1.64–2.34]	p = 0.793
COPD (n = 23)	1.44 [1.24–1.65]	1.42 [1.18–1.65]	p = 0.686
Mild reversibility (n = 24)	1.66 [1.41–1.91]	1.67 [1.40–1.95]	p = 0.872
Moderate reversibility (n = 4)	1.59 [1.26–1.91]	1.37 [0.96–1.79]	p = 0.033
Moderate GOLD classification (n = 10)	1.57 [1.37–1.78]	1.53 [1.26–1.80]	p = 0.662
Severe GOLD classification (n = 5)	0.89 [0.69–1.09]	0.88 [0.66–1.11]	p = 0.941
PEFR (≤2 episodes ≥15% diurnal variation/week, n = 14)	1.79 [1.46–2.11]	1.86 [1.49–2.22]	p = 0.505
PEFR (>2 episodes ≥15% diurnal variation/week, n = 18)	1.53 [1.24–1.82]	1.40 [1.13–1.67]	p = 0.011

Critchley, Int J Cardiol 2013

MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

Respiratory effect of beta-blockers in people with asthma and cardiovascular disease: population-based nested case control study

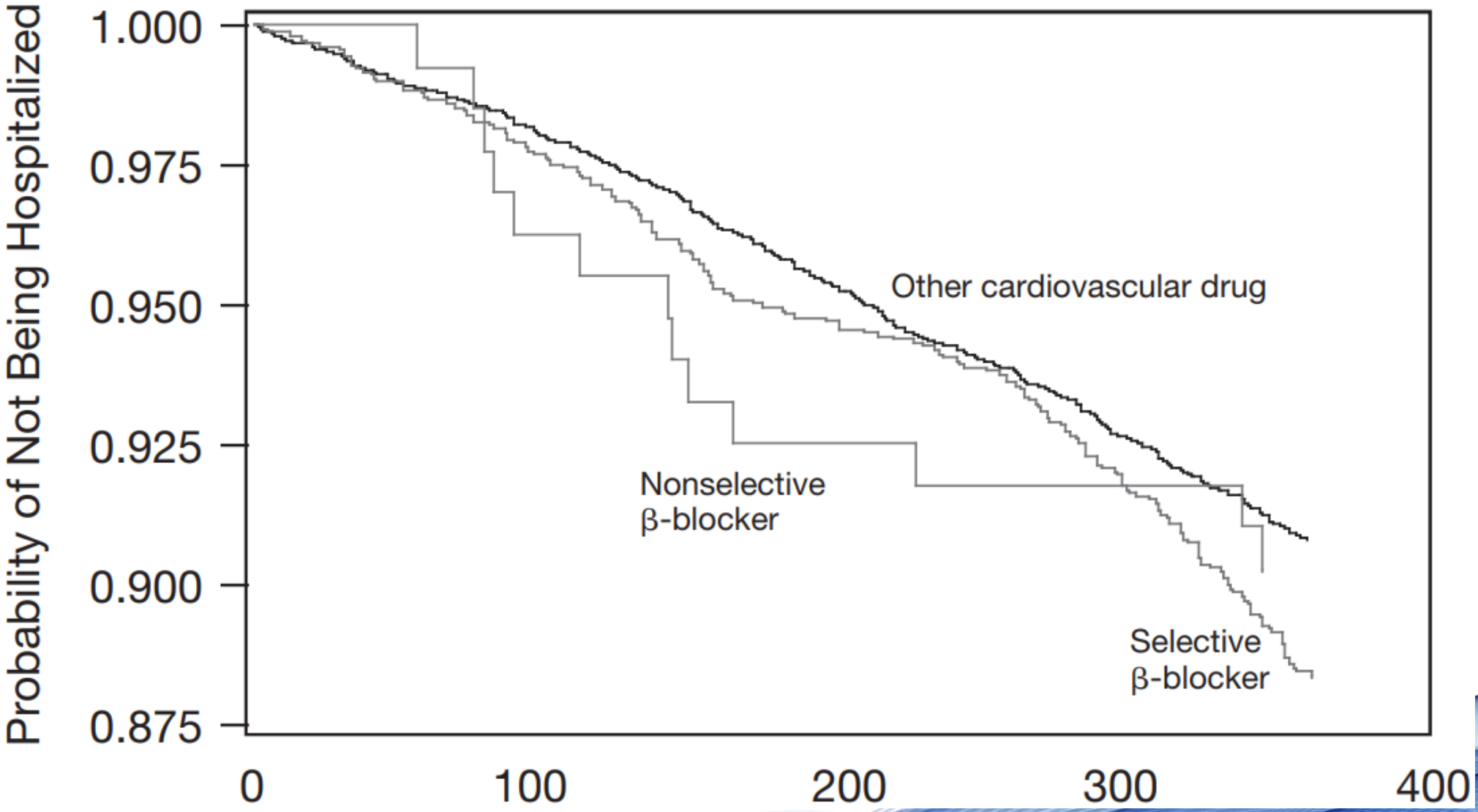
35.502 pts with active asthma and CVD, of which 14.1% and 1.2% were selective and non-selective beta-blockers

	Cardioselective beta-blockers						Non-selective beta-blockers					
	Exposed cases[a]	Exposed controls[a]	Crude IRR	Adjusted IRR	95% CI	*P* value	Exposed cases[a]	Exposed controls[a]	Crude IRR	Adjusted IRR	95% CI	*P* value
Any exposure												
Severe exacerbation	27	466	0.72	0.87	0.57–1.35	0.540	9	51	1.29	1.66	0.53–5.35	0.398
Moderate exacerbation	357	3956	0.89	0.97	0.85–1.11	0.658	35	309	1.33	1.41	0.95–2.08	0.088
Low dose												
Severe exacerbation	23	388	0.70	0.85	0.53–1.36	0.501	8	44	1.04	1.19	0.31–4.53	0.799
Moderate exacerbation	283	3256	0.87	0.96	0.83–1.10	0.544	29	271	1.19	1.24	0.80–1.91	0.336
High dose												
Severe exacerbation	4	82	0.85	0.96	0.33–2.84	0.943	1	7	5.00	12.11	1.02–144.11	0.048
Moderate exacerbation	79	733	0.99	1.08	0.82–1.42	0.600	6	39	2.50	2.67	1.08–6.62	0.034

Morales, DR, BMC Med. 2017, 15, 18

MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

β-Blocker Therapy in Veterans with Asthma or Chronic Obstructive Pulmonary Disease



Barnett et al, Pharmacotherapy 2005;25(11):1550–1559

MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

Beta-blocker use and COPD mortality: a systematic review and meta-analysis

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Au 2004	-0.56	0.225	5.3%	0.57 [0.37, 0.89]
Chen 2001	-0.155	0.079	14.0%	0.86 [0.73, 1.00]
Dransfield 2007	-0.95	0.48	1.5%	0.39 [0.15, 0.99]
Gottlieb 1998	-0.51	0.022	17.9%	0.60 [0.58, 0.63]
Hawkins 2009	-0.3	0.04	17.0%	0.74 [0.68, 0.80]
Rutten 2007	-0.39	0.105	11.9%	0.68 [0.55, 0.83]
Short 2011	-0.244	0.08	13.9%	0.78 [0.67, 0.92]
Staszewsky 2007	-0.59	0.2	6.2%	0.55 [0.37, 0.82]
Van Gestel 2008	-0.32	0.1	12.3%	0.73 [0.60, 0.88]
Total (95% CI)			**100.0%**	**0.69 [0.62, 0.78]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 44.80$, $df = 8$ ($P < 0.00001$); $I^2 = 82\%$
Test for overall effect: $Z = 5.94$ ($P < 0.00001$)

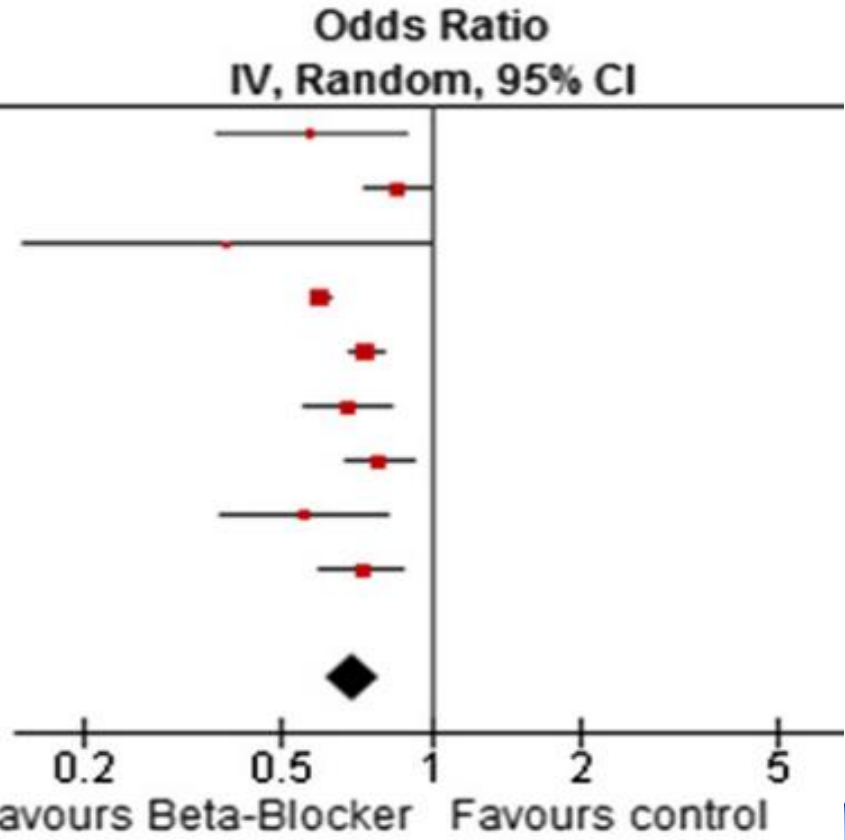


Figure 2 Forest plot of association between beta-blockers and COPD mortality.

Etminan et al. BMC Pulmonary Medicine 2012

TABLE 3 Summary of VigiBase total and fatal reports for cardioselective β_1-blockers with asthma or bronchospasm as reported suspected adverse reactions from start to December 2019

Cardioselective β_1-blockers	Reactions coded as asthma		Reactions coded as bronchospasm	
	Total	Of which were fatal	Total	Of which were fatal
Metoprolol	286	4	322	6
Atenolol	141	1	385	3
Bisoprolol	95	0	108	1
Nebivolol	29	0	32	0
Betaxolol	18	0	86	0
Acebutolol	5	1	30	0
Celiprolol	6	0	41	1
Landiolol	1	0	0	0
Esmolol	1	0	11	1
Esatenolol	1	0	0	0

MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

BETA1- BLOCKER VÀ HEN

Avoidance of medications that may make asthma worse	• Always ask about asthma before prescribing NSAIDs, and advise patients to stop using them if asthma worsens.	D
	• Always ask people with asthma about concomitant medications.	D
	• Aspirin and NSAIDs (non-steroidal anti-inflammatory drugs) are not generally contraindicated unless there is a history of previous reactions to these agents (see p.102).	A
	• Decide about prescription of oral or ophthalmic beta-blockers on a case-by-case basis. Initiate treatment under close medical supervision by a specialist.	D
	• If cardioselective beta-blockers are indicated for acute coronary events, asthma is not an absolute contra-indication, but the relative risks/benefits should be considered.	D

GINA guideline 2023

MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

BETA1- BLOCKER VÀ COPD

Cardiovascular diseases (CVD)

Heart failure

- The prevalence of systolic or diastolic heart failure in COPD patients ranges from 20% to 70%,[14] and its annual incidence is between 3-4%. Incident heart failure is a significant and independent predictor of all-cause mortality.

- Unrecognized heart failure may mimic or accompany acute COPD; 40% of COPD patients that are mechanically ventilated because of hypercapnic respiratory failure have evidence of left ventricular dysfunction.[15,16]

- Treatment with β_1-blockers improves survival in heart failure and is recommended in patients with heart failure who also have COPD. Selective β_1-blockers should be used, and only used, to treat people with COPD for approved cardiovascular indications; not solely for the purpose of preventing exacerbations of COPD.[17]

GOLD guideline 2023

MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

Sử dụng beta-blocker ở BN đồng mắc tim mạch & Hen/COPD

- Chống chỉ định beta-blocker không chọn lọc tim ở BN Hen/COPD
- Sử dụng loại chọn lọc tim cao và ISA (-)
- Nebivolol, Bisoprolol
- Khởi đầu: bệnh ổn định, liều thấp, BS chuyên khoa tim mạch
- BN nặng, khi khởi đầu điều trị, nên theo dõi trong bệnh viện 24 giờ

HEN DỊ ỨNG TP. HCM
MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

Sử dụng beta-blocker ở BN đồng mắc tim mạch & Hen/COPD

- Tăng liều sau > 2 tuần
- Duy trì tần số tim khi nghỉ: 60 – 70 lần/phút
- Theo dõi sát trong 4 tuần đầu bởi bác sĩ chuyên khoa
- Có thể phối hợp LAMA lúc khởi đầu

HEN DỊ ỨNG
TP. HCM
MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

Sử dụng đồng vận Beta-2 cho BN đồng mắc tim mạch & Hen/COPD

Ảnh hưởng tim mạch của đồng vận Beta-2

- Tần số tim
- Sức co bóp cơ tim
- Kháng lực mạch ngoại biên
- Kali và Mg máu
- QT

MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

Safety of SABA Monotherapy in Asthma Management: a Systematic Review and Meta-analysis

Introduction: SABA reliever overuse is common in asthma, despite availability of ICS-based maintenance therapies, and may be associated with increased risk of AEs. This systematic literature review (SLR) and meta analysis aimed to investigate the safety and tolerability of SABA reliever monotherapy for adults and adolescents with asthma, through analysis of randomized controlled trials (RCTs) and real-world evidence.

Results: No other treatment-related deaths were reported. SAE and DAE rates were \ 4%. DAEs were reported more frequently in the SABA treatment groups than with ICS, potentially owing to worsening asthma symptoms being classified as an AE. SAE risk was comparable between SABA and ICS treatments

Conclusions: Meta-analysis of data from RCTs showed that deaths were rare with SABA reliever monotherapy, and rates of SAEs and DAEs were comparable between SABA reliever and ICS treatment groups. When used appropriately within prescribed limits as reliever therapy, SABA does not contribute to excess rates of mortality, SAEs, or DAEs.

Sriprasart et al (2023). Adv Ther (2023) 40:133–158

Table 1 – Randomized trials reporting adverse cardiovascular events with LABA and LAMA use for COPD management.

Reference	Design	Follow-up time	Subjects	Exclusion for CVD	Intervention arms	Primary outcomes	Secondary CVD outcomes	CVD related results
Calverley et al. (2007) [17]	Randomized double-blind, placebo controlled study	3 years	Moderate-to-severe COPD patients aged between 40 and 8 years	Diseases that could interfere with the study outcome, including fatal cardiovascular events	Salmeterol 50 μg (n = 1542) vs. Fluticasone 500 μg (n = 1552) vs. Salmeterol + Fluticasone 50/500 μg n = 1533) vs. Placebo (n = 1524)	All-cause mortality	Any adverse cardiovascular events	No excess of cardiac disorders among patients treated with the combination regimen or salmeterol alone.
Tashkin et al. (2008) [18]	Randomized, double-blind, placebo-controlled study	4 years	Moderate-to-severe COPD patients aged ≧40 years	Prior history of MI, any unstable or life threatening cardiac arrhythmia and HF	Tiotropium 18 μg (n = 2987) vs. Placebo (n = 3006)	Annual rates of decline in FEV_1 and FVC	Cardiac disorders of MI, stroke, HF, AF	16% reduced risk of CVD with tiotropium vs. placebo.
Donohue et al. (2010) [34]	Randomized, double-blind, placebo- controlled study	26 weeks	Moderate-to-severe COPD patients aged ≧40 years	Not mentioned	Indacaterol 150 μg (n = 416) vs. Indacaterol 300 μg (n = 416) vs. Tiotropium 18 μg (n = 415) vs. Placebo (n = 418)	Spirometry data, dyspnea by TDI score and COPD exacerbations	ECG and general cardiac disorders	5.7% cardiac disorders for the two indacaterol doses combined and 5.6% for tiotropium group, compared with 3.8% for placebo.
Dahl et al. (2010) [33]	Randomized, double-blind, double-dummy, placebo- controlled study.	52 weeks	Moderate-to-severe COPD patients aged ≧40 years	Not mentioned	Indacaterol 300 μg (n = 437) vs. Indacaterol 600 μg (n = 425) vs. Formoterol 12 μg (n = 425) vs. Placebo (n = 432)	Spirometry FEV1	ECG assessment, blood pressure and pulse rate measurements	No observed CVD events.
Jones et al. (2012) [36]	Randomized double-blind, placebo- controlled study	24 weeks	Moderate-to-severe COPD patients aged ≧40 years	Unstable cardiac conditions, including MI	Aclidinium 400 μg (n = 272) vs. Aclidinium 200 μg (n = 280) vs. Placebo (n = 276)	Spirometric measurements, health status using SGRQ, dyspnea with BDI and TDI score and COPD exacerbations	Any CVD events and 12-lead ECG	Two cardiovascular deaths in the two aclidinium treatment groups. No clinically relevant changes in the primary outcome measurements.

Wang et al (2019). Journal of Food and Drug Analysis Volume 27, Issue 3, July 2019, Pages 657-670

HEN DỊ ỨNG TP. HCM
MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

ĐẶC ĐIỂM RCT AN TOÀN TIM MẠCH CỦA LABA, LABA/LAMA, ICS/LABA

- COPD trung bình đến nặng, theo dõi 6 - 52 tuần
- Kết cục tiên phát: CNHH và tử vong mọi nn
- Kết cục thứ phát: biến cố tim mạch
- FLAME: nhóm IND/GLY tử vong tim tương tự nhóm SAL/FLU
- IMPACT: FLU/UMC/VIL, FLU/VIL, UME/VIL: Không khác biệt CVD

Không tăng nguy cơ CVD do LABA hoặc LABA/LAMA, LABA/ISC

Type of ILAB	OCAE HR (95% CI), *P*	SCAE HR (95% CI), *P*	Arrhythmia HR (95% CI), *P*	Hypertension HR (95% CI), *P*	MI HR (95% CI), *P*	Cardiac Failure HR (95%CI), *P*	Stroke HR (95%CI), *P*	Cardiac ischemia HR (95%CI), *P*
Aclidinium	0.89 (0.38–2.08), 0.278	-	-	0.87 (0.44–1.71), 0.408	-	-	-	-
Acldinium/formoterol	0.7 8(0.41–1.48), 0.000	-	-	0.78 (0.41–1.48), 0.566	-	-	-	-
Formoterol	0.91 (0.67–1.25), 0.056	0.62 (0.30–1.29), 0.475	0.85 (0.60–1.19), 0.319	0.76 (0.50–1.14), 0.408	0.67 (0.22–1.99), 0.221	1.63 (0.50–5.33), 0.103	0.74 (0.12–4.72), 0.236	0.53 (0.32–0.91), 0.676
Glycopyrrolate	0.98 (0.63–1.53), 0.024	0.80 (0.31–2.06), 0.775	1.34 (0.46–3.98), 0.012.	0.68 (0.43–1.07), 0.391	0.49 (0.09–2.68), 0.432	0.96 (0.37–2.45), 0.555	1.99 (0.50–7.92), 0.997	0.56 (0.28–1.10), 0.685
Glycopyrrolate/ formoterol	1.19 (0.23–6.06), 0.005	0.82 (0.14–4.75), 0.845	-	-	-	1.37 (0.54–3.48), 0.314	-	-
Indacaterol	1.03 (0.72–1.47), 0.022	1.07 (0.71–1.60), 0.487	0.94 (0.62–1.43), 0.331	0.61 (0.29–1.28), 0.178	1.02 (0.60–1.72), 0.532	2.06 (0.87–4.88), 0.828	0.68(0.32–1.49), 0.630	-
Indacaterol/ glycopyrrolate	1.63 (0.85–3.15), 0.626	-	-	-	-	-	-	-
Olodaterol	0.65 (0.49–0.88), 0.238	-	1.22 (0.38–3.85), 0.096	0.66 (0.43–1.03), 0.309	-	-	-	-
Salmeterol	1.03 (0.89–1.18), 0.671	0.91 (0.76–1.08), 0.906	1.41 (0.71–2.79), 0.551		-	-	-	1.68 (0.65–4.37), 0.576
Tiotropium	1.01 (0.80–1.28), 0.006	0.92 (0.74–1.15), 0.825	0.73 (0.44–1.22), 0.194	0.83 (0.39–1.75), 0.194	0.81 (0.62–1.05), 0.378	0.90 (0.60–1.35), 0.897	1.04 (0.78–1.39), 0.905	1.13 (0.16–7.93), 0.011
Umeclidinium	1.28 (0.46–3.57), 0.000	0.67 (0.07–6.46), 43	-		-	-	-	-
Vilanterol	0.94 (0.74–1.19), 0.047	0.95 (0.78–1.16), 0.961	-	0.77 (0.06–9.88), 0.095	-	-	-	-
Umeclidinium/ vilanterol	1.12 (0.61–2.06)	0.68 (0.07–6.53)	-	-	-	-	-	-

Li et al, Int J Chron Obstruct Pulmon Dis. 2019; 14: 799–808

- Không xem CVE là kết cục tiên phát => không ghi nhận, bỏ sót số liệu
- Loại trừ BN có tiền căn CVD
- Phần lớn đã dùng LABA trước đó => không quan sát được CVE
- Không đề cập đến nhiễu do các thuốc dùng kèm (Nhóm Placebo dùng nhiều Ventolin vì khó thở cấp hơn) => ↑ CVE

Table 2 — Observational studies evaluating risk of cardiovascular events with LABA and LAMA use in COPD patients.

Reference	Study design	Population	Exclusion for CVD	New-user design (yes/no)	Exposures	Cases or outcome definitions	Results
AU et al. (2000) [12]	Case-control design	Cases: postmenopausal women and hypertensive male aged 30–79 years Controls: patients aged 30–79 years	Excluded prior MI	Yes, but no exclusion of exposure prior to cohort entry.	Any MDI β-agonist prescriptions in the two years before the index/ event date, and new use, defined as β-agonists prescription only filled for one time in the 90 days before the index date.	Incident nonfatal or fatal MI	MDIβ-agonists vs non-use: aOR (95%CI) New use: 1.67 (1.07–2.60)[a]
Grosso et al. (2009) [58]	Self-controlled case-series design	Patients receiving any tiotropium prescription and diagnosed with ≧ 1 stroke event	Excluded carotid endarterectomy > 6 weeks prior to events	No.	Exposure periods in which patients using tiotropium or fluticasone plus salmeterol *vs.* other unexposed observation periods.	First-ever diagnosis of ischaemic, haemorrhagic or unspecified stroke within the study time window	IRR (95%CI) • Tiotropium: 1.5 (0.7–3.1) • ≦ 1 year exposed period of tiotropium: 1.0 (1.0–2.0) • Fluticasone + salmeterol: 1.3 (0.5–3.1)
Wilchesky et al. (2012) - Part 1 [13]	Nested case-control design	Saskatchewan cohort, COPD patients aged ≧55 years with at least one bronchodilator use	No exclusion of CVD	Yes, but no exclusion of exposure of interest preceding cohort entry.	One of the exposures was LABA use. Current use: a LABA prescription in 60 days preceding the index/ event date. Current new use: current use but no prescription in 61–365 days before the index/ event date.	Arrhythmic death or hospital admission with a primary discharge diagnosis of arrhythmia	LABA *vs.* non-use: aOR (95%CI) • Current use: 1.13 (0.53–2.43) • Current new use: 4.55 (1.43–14.45)[a] • No current new use: 0.72 (0.27–1.90)
Wilchesky et al. (2012) - Part2 [14]	Nested case-control design	Quebec Cohort, COPD patients aged ≧67 years with at least one bronchodilator use	No exclusion of CVD	Yes, but no exclusion of LABA use preceding cohort entry	One of the exposures was LABA use. Current use: a LABA prescription in 60 days preceding the index/ event date. Current new use: current use but no prescription in 61–365 days before the index/ event date.	Arrhythmic death or hospital admission with a primary discharge diagnosis of arrhythmia	LABA *vs.* non-use: aOR (95%CI) • Current new use: 1.47 (1.01–2.15)[a] • No current new use: 1.06 (0.88–1.27)

JAMA Internal Medicine

View Article

JAMA Intern Med. 2018 Feb; 178(2): 229–238.

PMCID: PMC5838614

Published online 2018 Jan 2. doi: 10.1001/jamainternmed.2017.7720

PMID: 29297057

Association of Cardiovascular Risk With Inhaled Long-Acting Bronchodilators in Patients With Chronic Obstructive Pulmonary Disease

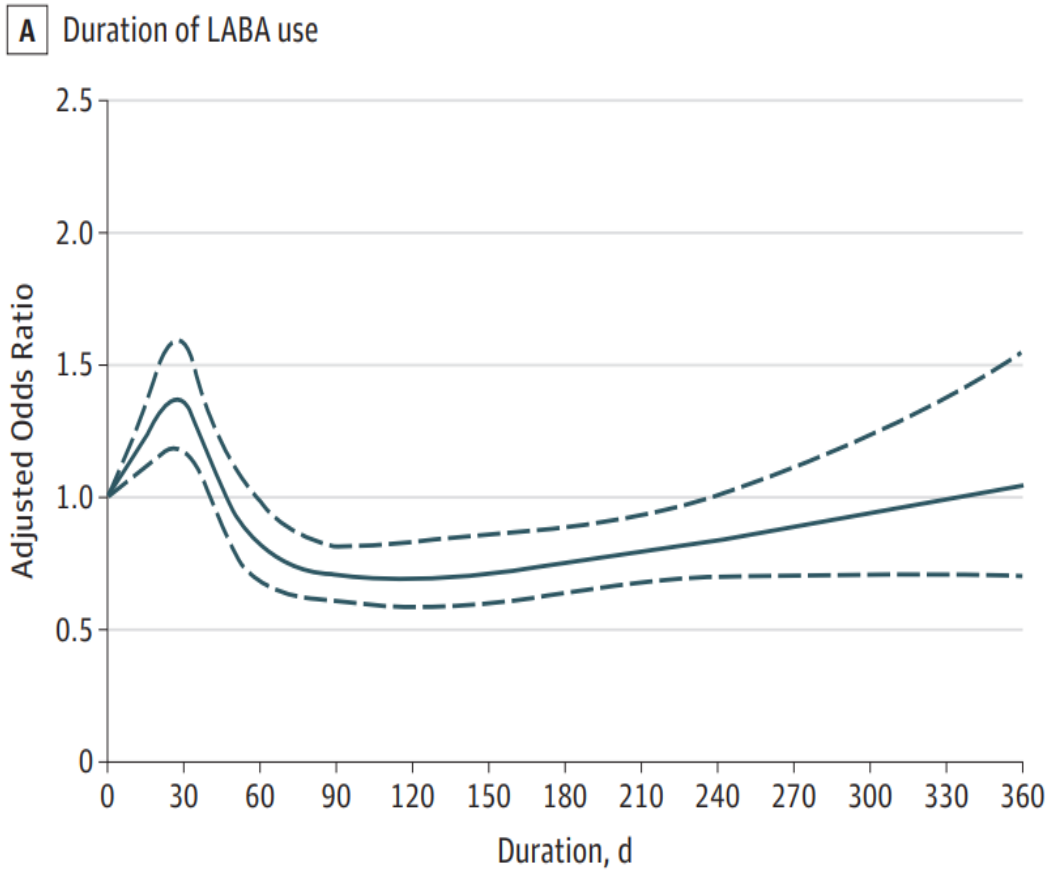
Key Points

Question

Does the duration since initial use and new use of inhaled long-acting β_2-agonists (LABAs) or antimuscarinic antagonists (LAMAs) for the treatment of chronic obstructive pulmonary disease (COPD) act as important determinants of the risk of cardiovascular disease?

Findings

In this nested case-control study of more than 280 000 patients with COPD, new use of LABAs or LAMAs is associated with an approximate 1.5-fold increased cardiovascular risk within 30 days of initiation therapy.



MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

ĐỐI TƯỢNG NGUY CƠ CAO CVE

	Patients with Asthma		
	Cases (n = 142)	Controls (n = 244)	Odds Ratio (95% Confidence Interval)*
Use of inhaled β-agonists in past 3 months	Number		
No use in past 2 years	41	108	1.0
Number of metered-dose canister in past 3 months			
0	26	61	0.8 (0.4–1.6)
1	10	16	1.1 (0.4–3.3)
2 (without inhaled steroids)	33	22	2.5 (1.1–5.4)
2 (with inhaled steroids)	13	37	0.6 (0.2–1.6)
Use of nebulizers in past 3 months	19	7	3.8 (1.1–12.3)

Lemaitre et al. Am J Med. 2002;113:711–716

ĐỐI TƯỢNG NGUY CƠ CAO CVE/COPD

Table 4. Multivariable analysis[a] of odds of cardiovascular event within 90 days of initiation of long-acting bronchodilators.

Patient characteristics	Odds ratio (95% confidence interval)
Treatment group	
Group 1 (CVD and CVD treatment)	3.50 (2.89, 4.24)
Group 2 (CVD with no CVD treatment)	2.15 (1.71, 2.70)
Group 3 (no CVD but CVD treatment)	1.36 (1.01, 1.82)
Group 4 (no CVD and no CVD treatment)	1.00
Age	
40–49	1.00
50–59	1.45 (1.16, 1.80)
60–69	1.90 (1.54, 2.35)
Above 70	3.29 (2.66, 4.07)
Gender	
Female	1.00
Male	1.36 (1.25, 1.48)
First long-acting bronchodilator	
LAMA	1.00
LABA	1.33 (1.13, 1.57)
LABA-ICS	1.13 (1.03, 1.25)
SABA	0.91 (0.83, 1.00)
SABA-SAMA	0.90 (0.80, 1.00)
SAMA	1.14 (0.97, 1.33)
Theophylline	0.87 (0.70, 1.09)
COPD specifics, yes versus no	
Spirometry	0.92 (0.85, 1.00)
Oxygen therapy	1.37 (1.23, 1.52)
Influenza vaccination	0.94 (0.85, 1.04)
Pneumococcal vaccination	0.81 (0.68, 0.98)
Comorbidities	
0	1.00
1	1.14 (1.01, 1.27)
2	1.65 (1.46, 1.86)
3+	2.53 (2.23, 2.87)
Short-acting COPD medication, yes versus no	
Inhaled steroids	0.78 (0.67, 0.90)
Oral steroids	1.04 (0.95, 1.15)

Aljaafareh et al (2016). Risk of cardiovascular events after initiation of long-acting bronchodilators in patients with chronic et al ()obstructive lung disease: A population-based study

MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

ĐỐI TƯỢNG NGUY CƠ CAO CVE

Tương tác dược lực học

+ IND: Erythromycin,

Ketoconazole, Ritonavir, Verapamil

+ OLO: Ketoconazole

+ SAL: Erythromycin, Ketoconazole

+ VIL: Ketoconazole, Verapamil

Tương tác dược động học

+ Lợi tiểu

+ Corticoid

+ Thuốc làm dài QT

+ Giảm oxy máu

S. P. Bhatt (ed.), Cardiac Considerations in Chronic Lung Diseas

HEN DỊ ỨNG TP. HCM
MIỄN DỊCH LÂM SÀNG
HCMC Society of Asthma, Allergy and Clinical Immunology
Hội nghị thường niên 2023

Sử dụng đồng vận beta-2 ở BN đồng mắc tim mạch & Hen/COPD

- Bệnh sử và Khám LS nhận diện nhóm nguy cơ cao CVE (tuổi cao, giới nam, dùng nhiều SABA, tương tác thuốc, CVD nền…)
- Chú ý tương tác với các thuốc điều trị bệnh đồng mắc
- Theo dõi sát 30 ngày đầu (tần số tim, suy tim, ECG), nhất là ở BN nguy cơ cao
- Olodaterol, Formoterol

KẾT LUẬN

- CVD: bệnh đồng mắc quan trọng ở Hen/COPD
- Beta-blockers:

+ 1 trong bốn tứ trụ ảnh hưởng tiên lượng lâu dài của HFrEF

+ thường không được kê toa ở BN Hen/COPD có CVD đồng mắc

+ bằng chứng: đúng chỉ định an toàn

KẾT LUẬN

- Đồng vận Beta-2:

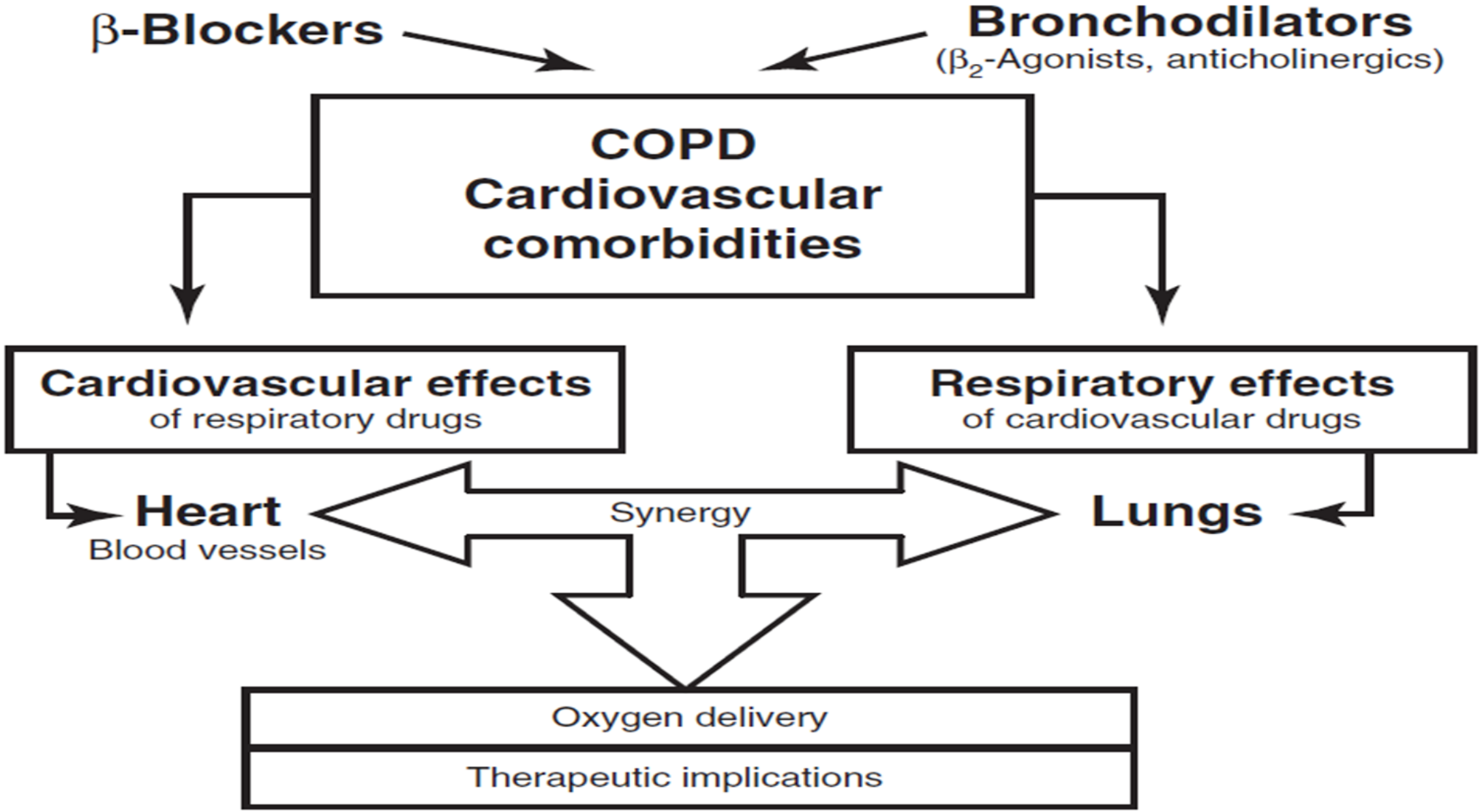
+ Nền tảng trong điều trị Hen/COPD

+ RCT: không ↑ nguy cơ tim mạch ??? NC quan sát: ↑ nguy cơ tim mạch

+ Nguy cơ thấp và Lợi ích >>> Nguy cơ

- Đúng liều, đúng chỉ định, loại chọn lọc, theo dõi sát: nguy cơ của đồng vận beta-2 thấp và beta-blocker an toàn

- Cần thêm RCT, tiêu chuẩn chọn giống nghiên cứu đời thực (nguy cơ cao CVD, COPD nặng…)



Drug Discovery Today

TRÂN TRỌNG CẢM ƠN

QUÝ THẦY CÔ & QUÝ ĐỒNG NGHIỆP.