Consensus of diagnosis and treatment of COPD and CHF in Taiwan

Shih-Lung Cheng MD, PhD

Division for Pulmonary Medicine ,

Department of Internal Medicine

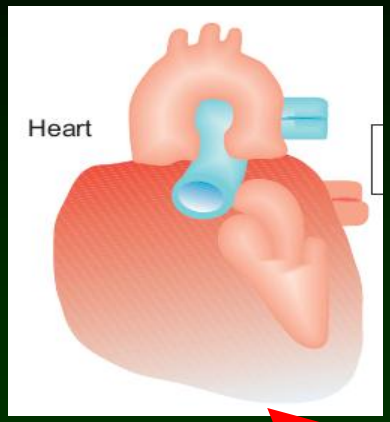
Far Eastern Memorial Hospital

Disclosure

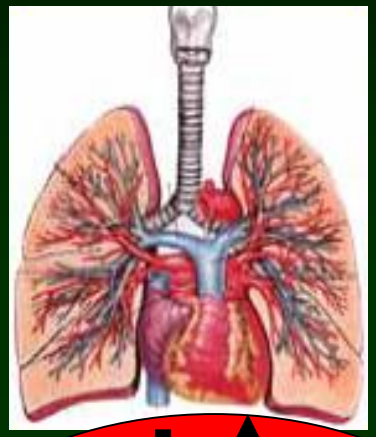
- I ,Shih-Lung Cheng, hereby disclose that my relationship with Taiwan Society of Pulmonary and Critical Care Medicine includes: speaker

Systemic Effects of COPD: Comorbidities

Angina
Acute coronary syndromes

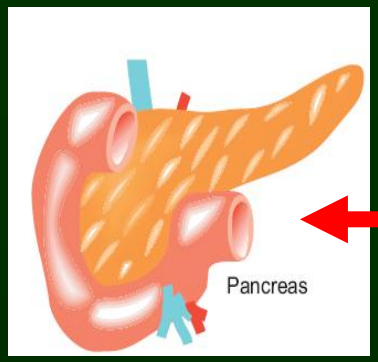


Lung Infections
Lung Cancer



Weight loss
Muscle weakness

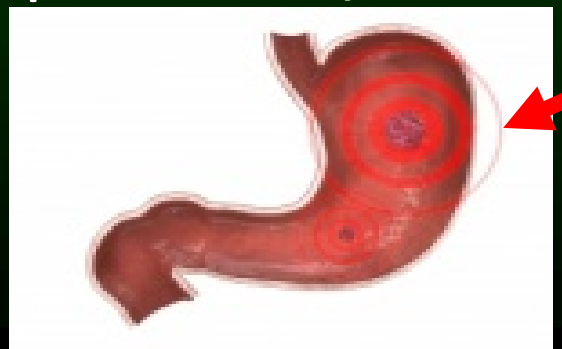
Diabetes
Metabolic syndrome



Systemic Inflammation Oxidatitive Stress

Osteoporosis

Peptic ulceration/reflux



Depression

From W MacNee

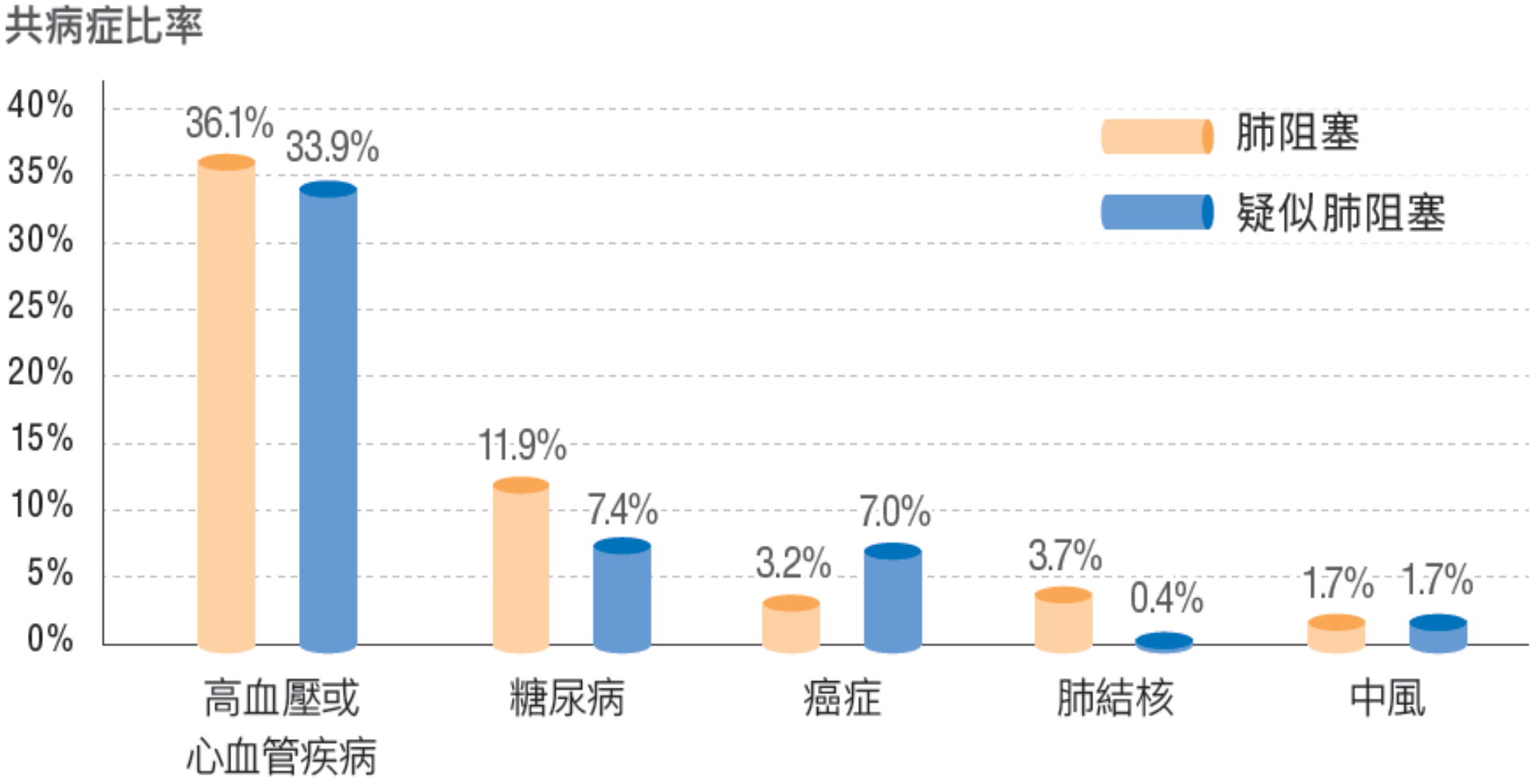
胸腔內科專家代表（依姓名筆劃排列）

姓名	服務單位	職稱
林孟志	台灣胸腔暨重症加護醫學會 高雄長庚紀念醫院	理事長 教授
王鶴健	台灣胸腔暨重症加護醫學會 臺大醫院	呼吸道委員會主委 內科部副主任／胸腔內科主任
林慶雄	彰化基督教醫院	副院長
林鴻銓	林口長庚紀念醫院	胸腔內科主治醫師
柯信國	臺北榮民總醫院	胸腔部呼吸治療科主治醫師
陳家弘	中國醫藥大學附設醫院	內科部胸腔暨重症系主治醫師
詹明澄	臺中榮民總醫院	呼吸治療科主任
楊聰明	嘉義長庚紀念醫院	胸腔內科系呼吸道及睡眠醫學科主治醫師
鄭世隆	亞東紀念醫院	臨床試驗中心主任／實證醫學中心主任
魏裕峰	義大醫療財團法人義大醫院	呼吸胸腔內科主任

心臟內科專家代表（依姓名筆劃排列）

姓名	服務單位	職稱
黃瑞仁	中華民國心臟學會 臺大醫院雲林分院	理事長 院長
王俊傑	林口長庚紀念醫院	心臟血管內科主治醫師 健康促進中心主任
宋思賢	臺北榮民總醫院	內科部心臟科主治醫師
吳彥雯	亞東紀念醫院	心臟血管醫學中心主任
張坤正	中國醫藥大學附設醫院	內科系副院長 內科部主任兼心臟血管系主任
張鴻猷	振興醫療財團法人振興醫院	心臟醫學中心心臟血管內科主治醫師
黃金隆	臺中榮民總醫院	心臟血管中心心臟衰竭科主任
曾炳憲	亞東紀念醫院	心衰竭中心主任
黃偉春	高雄榮民總醫院	重症醫學部主任
趙庭興	成功大學醫學院附設醫院	心臟血管科主任
廖家德	奇美醫療財團法人奇美醫院	心臟血管內科主治醫師
顏學偉	高雄醫學大學附設中和紀念醫院	心臟血管內科主治醫師

台灣肺阻塞流行病學調查



Cheng SL, etc. International Journal of COPD 2015:10 2459–2467

COPD mortality: CV diseases

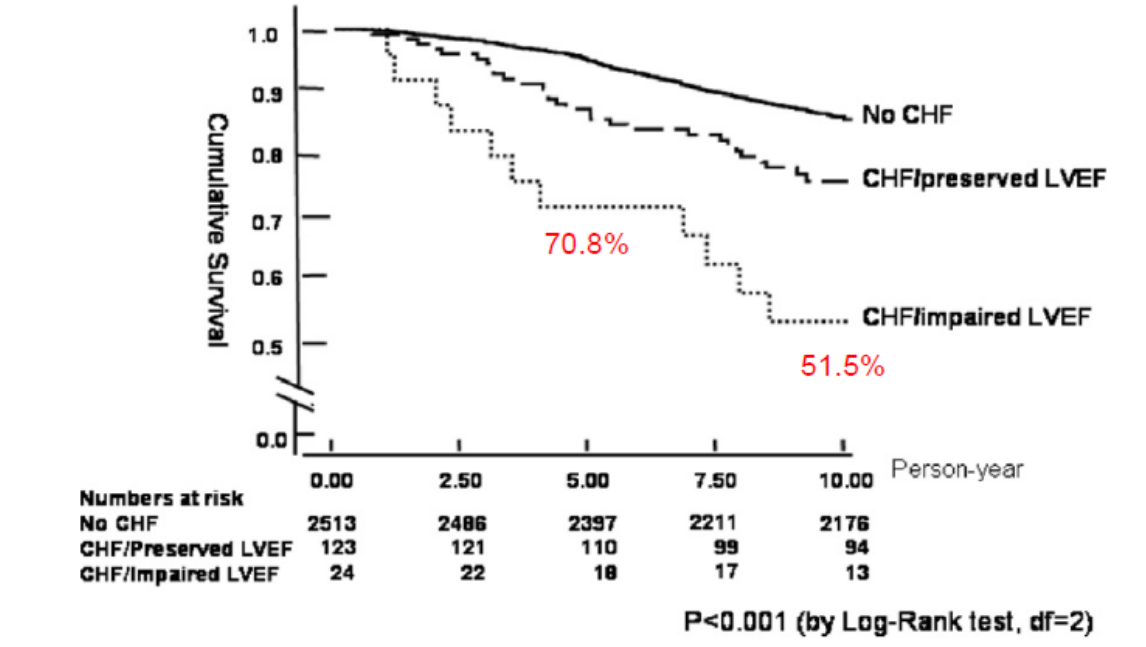
【表 1】輕中度肺阻塞病人死因（心血管疾病及呼吸道疾病）比較[10]

平均用力呼氣一秒量[a]（% 預測值）[b]	疾病佔死亡原因的比例		研究樣本數	死亡人數
	心血管疾病	呼吸道疾病		
GOLD[c] A (FEV_1 ≧ 50%)	26%	6%	3601	174
GOLD[c] B (FEV_1 ≧ 50%)	34%	12%	2883	189

Am J Respir Crit Care Med. 2014;189:A1123.

Heart failure in Taiwan: Prevalence

- Chin-Shan community cardiovascular cohort, 2660 subjects (1991-1992)
- The prevalence of HF was 5.5%: 4.6% for HFpEF; 0.9% for HFrEF (LVEF<55%)



Huang et al. EJHF 2007;9:587-593

中華民國心臟學會
Taiwan Society of Cardiology

HF and COPD: Epidemiology

- 在 北美洲及歐洲的群體分析中發現心臟衰竭病人的肺阻塞盛行率介於 9~52%
- 在 Cardiovascular Health Study 中亦顯示心臟衰竭病人的肺阻塞盛行率較一般族群為高（ 20 vs. 13 p =0.001 ）。

Curr Opin Pulm Med. 2010 Mar;16(2):106-11.
Eur J Heart Fail. 2009 Feb;11(2):130-9.
Am J Cardiol. 2001 Feb 15;87(4):413-9.

Heart failure and COPD in Taiwan: hospitalization

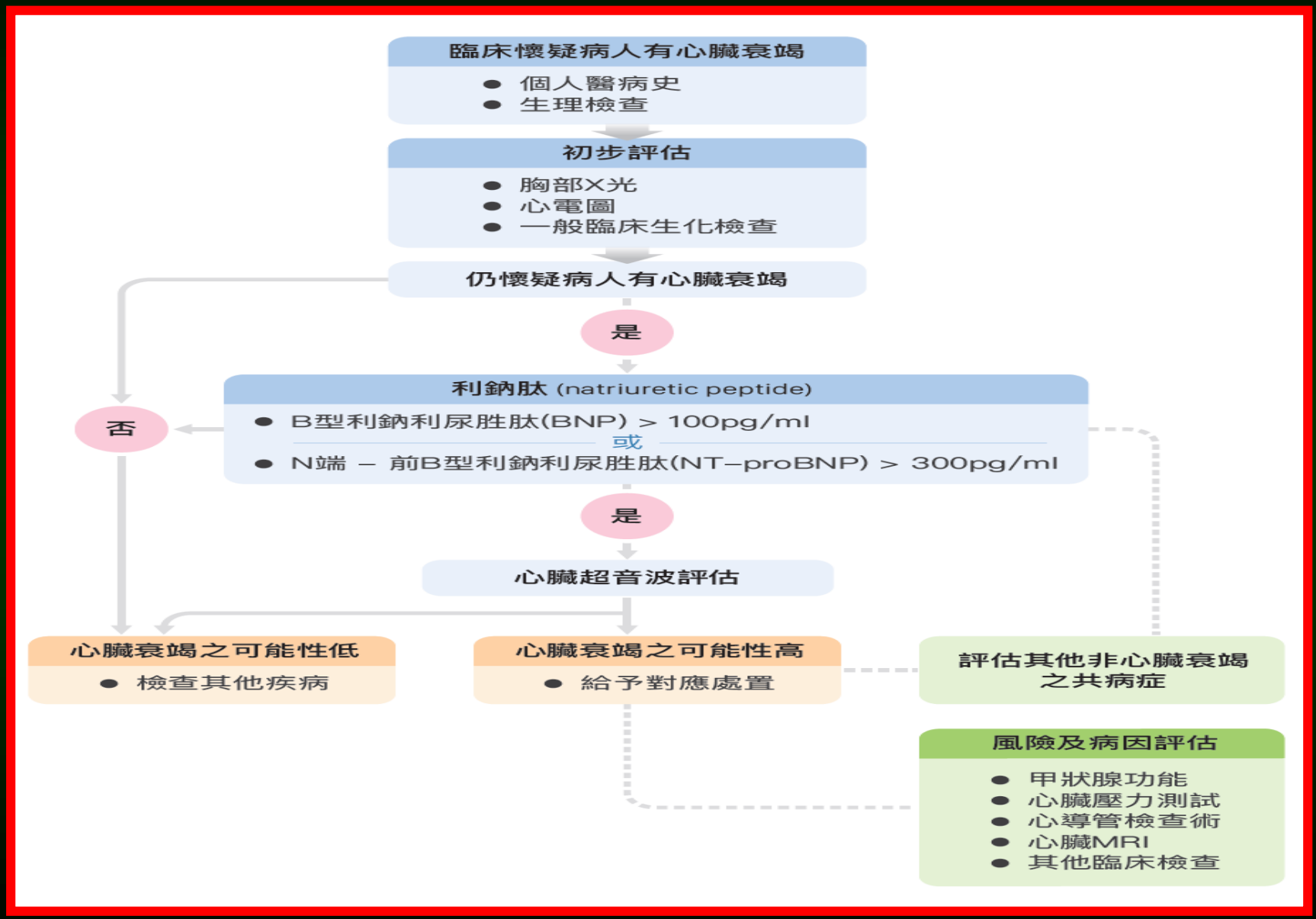
2014年國人每住院者平均住院日數前二十大疾病

排名	CCS	CCS疾病名	住院人數	平均日/人	標準差
1	659	思覺失調症及其他精神病疾患	31,530	190.86	143.16
2	131	成人呼吸衰竭	32,791	82.81	117.74
3	109	腦出血	52,640	17.98	22.69
4	19	肺癌	17,032	17.57	18.93
5	16	肝癌	21,046	15.36	17.46
6	45	接受化學或放射治療就醫	44,516	15.09	17.84
7	2	敗血症	66,400	14.61	16.10
8	127	慢性阻塞性肺疾病	22,457	14.29	23.19
9	122	肺炎	165,601	12.44	19.45
10	218	嬰兒活產	17,218	12.19	17.30
11	108	心臟衰竭	22,511	11.94	15.08

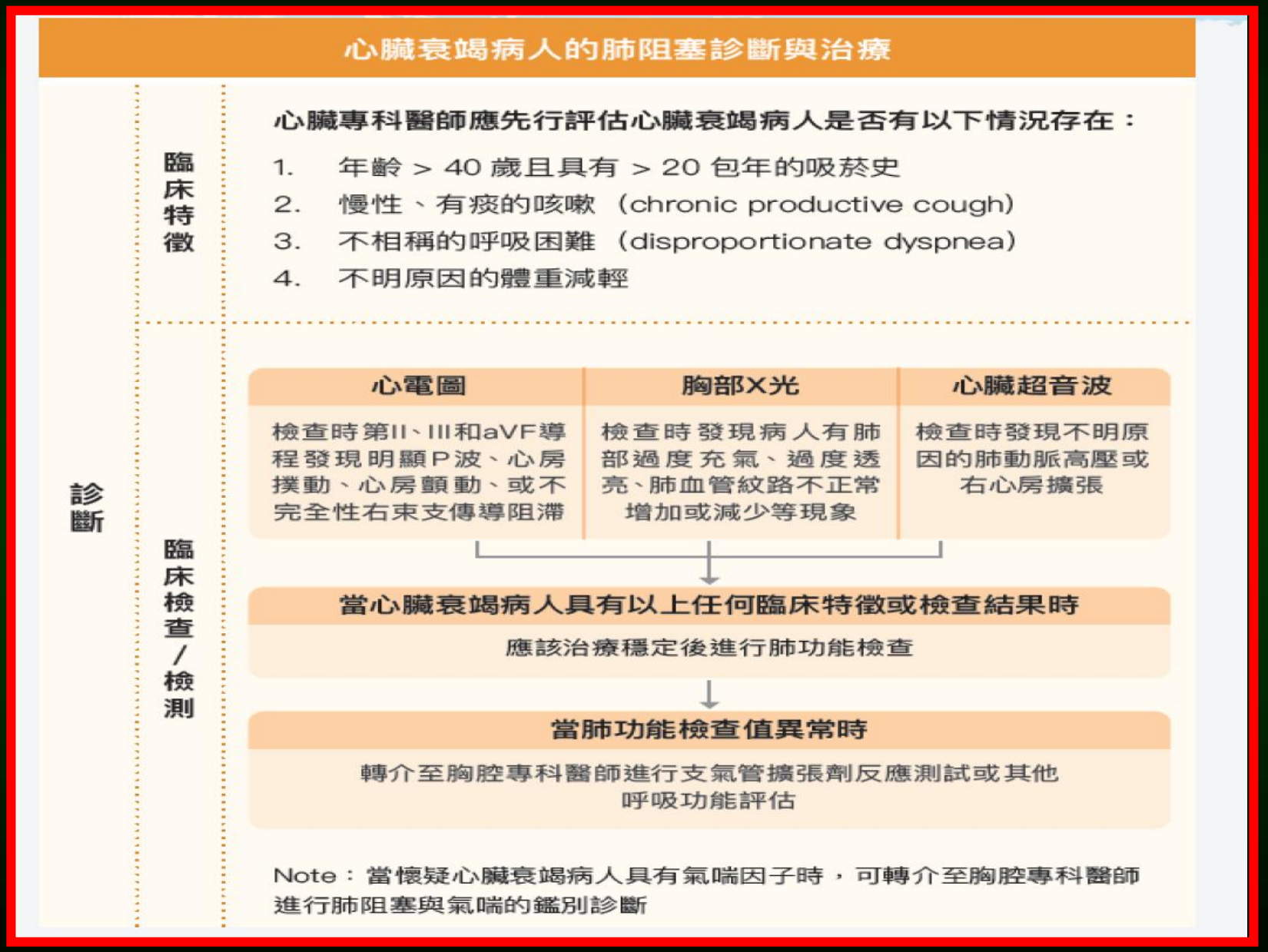
More than 22,000 patients admitted due to COPD in 2014

More than 22,000 patients admitted due to HF in 2014

肺阻塞病人的心臟衰竭診斷



心臟衰竭病人的肺阻塞診斷

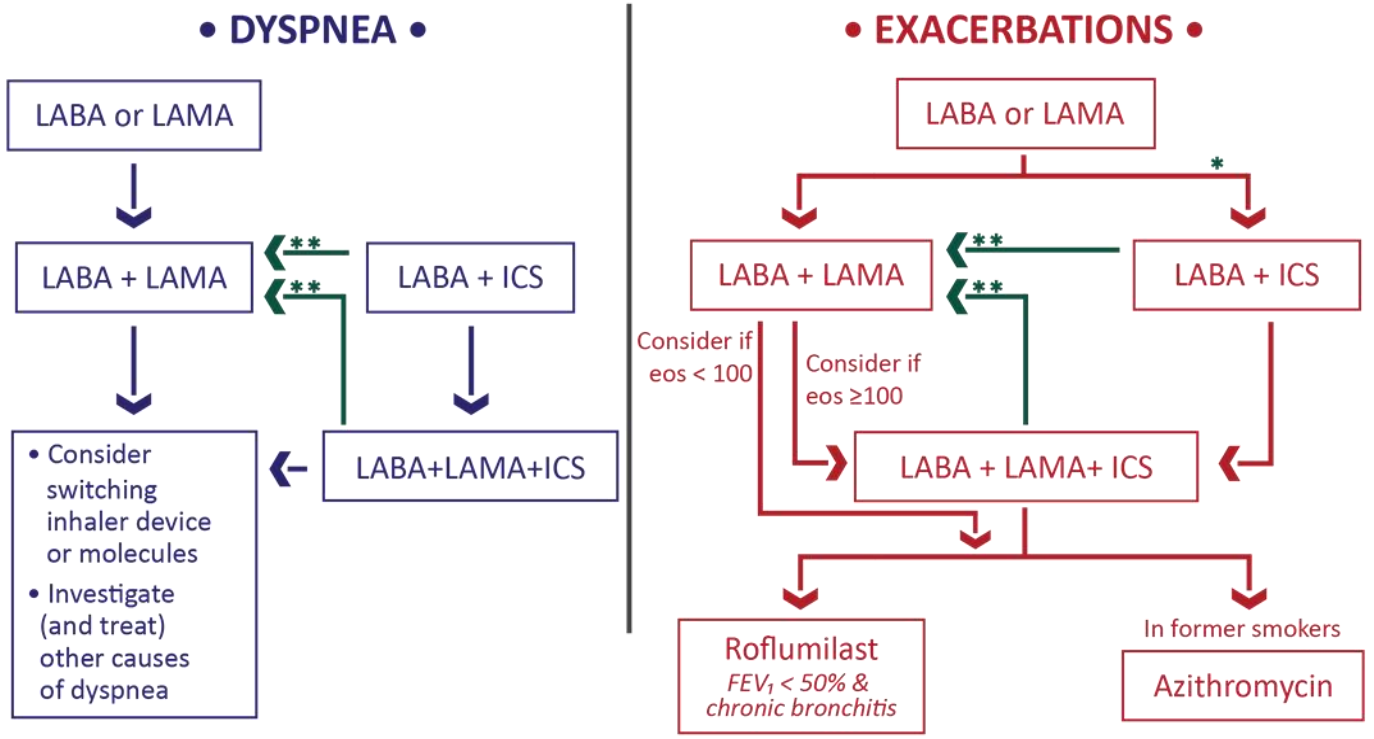


Diagnostic Hints/Pitfalls

- 慢性心臟衰竭可能由於心臟擴大、肺積水或胸腔積液而導致肺容積降低，其肺功能顯示為侷限型 。
- 急性 心臟衰竭可能因為氣管黏膜下及間質水腫，肺功能顯示為阻塞型，造成假性的肺阻塞診斷。
- 當心臟衰竭病人狀態達到穩定後 (例如：出院前或出院後一個月內回診時))，才進行肺量計檢查 。 另外 也 可 進行 六分鐘行走測試 (6 min walk test) test)，監測病人的經皮血氧飽和濃度狀態及有無出現呼吸困難的症狀，若病人行走測試時出現低血氧情形時，需進一步檢查其心、肺狀況。
- 長期患有肺阻塞會增加心臟右心室的負荷，進而導致右心衰竭。
- 肺阻塞病人因其有較低的橫膈及右心擴大，或不完全性右束支傳導阻滯
- (ICRBBB)，可能導致心電圖中 leads II 、 III 、 aVF 導程有比較明顯的 P 波。臨床上，心臟衰竭或肺阻塞病人都可能在心電圖上呈現心房撲動（ atrial flutter ）或心房顫動（ atrial fibrillation ）的心律不整異常。

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCD assessment at diagnosis



eos = blood eosinophil count (cells/µL)
** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*
*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

FIGURE 4.4

心臟衰竭病人的肺阻塞治療

心臟衰竭病人的肺阻塞診斷與治療

治療

- 經評估心臟衰竭病人個體狀況後，建議起始使用的肺阻塞治療用藥順位如下：
  - ✓ 在症狀較不嚴重且急性惡化風險較低的病人，可以優先使用單一劑型的長效型乙二型交感神經刺激劑（LABA）或長效型抗膽鹼藥物（LAMA）作為起始治療藥物
  - ✓ 若以單一支氣管擴張劑治療後仍症狀控制不佳，可以改用複方支氣管擴張劑（LABA+LAMA）。一開始症狀即較嚴重之病人，則可優先使用複方支氣管擴張劑
  - ✓ 吸入型類固醇（ICS）適用於合併氣喘急病、經常發生急性惡化或是血液中嗜酸性球較高的肺阻塞病人
- 可考慮低劑量茶鹼類藥物（theophylline）的合併使用，每日劑量須限制為 100–200 毫克
- 目前肺阻塞病人並不建議單獨使用吸入型類固醇（ICS），且應避免長期使用高劑量吸入型類固醇（ICS）
- 當心臟衰竭病人的肺阻塞程度嚴重時，則建議轉介至胸腔專科醫師進行進一步呼吸功能的評估與治療
- 個案管理師可協助教育病人藥物吸入器（inhaler）的正確使用，以確認病人確實吸入藥物

肺阻塞病人的心臟衰竭治療

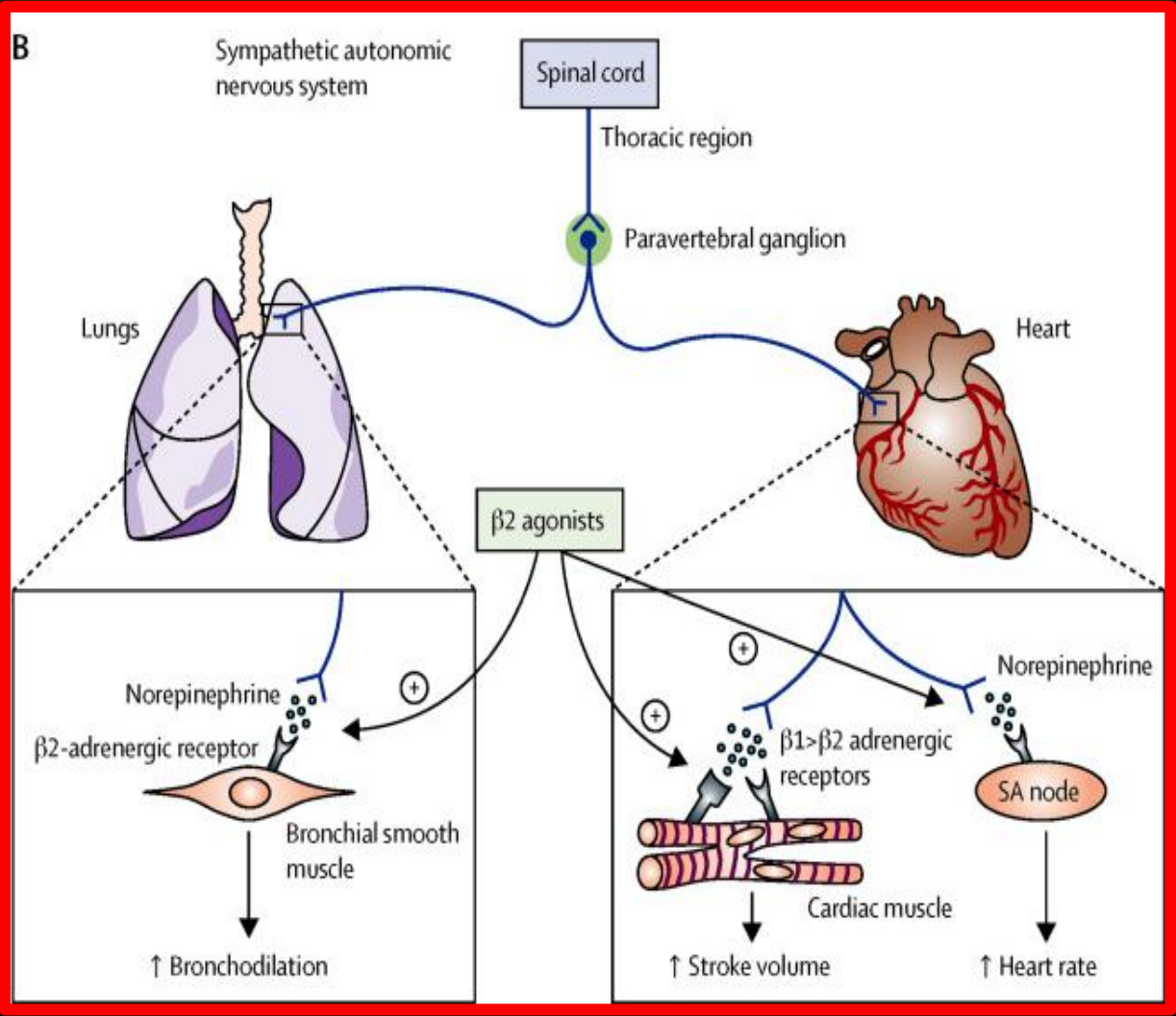
肺阻塞病人的心臟衰竭診斷與治療

治療

- 經評估肺阻塞病人個體狀況後，建議使用的心臟衰竭治療用藥如下：
  - ✓ 血管收縮素轉化酶抑制劑（ACEi）
  - ✓ 血管收縮素受體阻斷劑（ARB）
  - ✓ 血管收縮素受體－腦啡肽酶抑制劑（ARNI）
  - ✓ 心臟選擇性乙型交感神經阻斷劑（cardioselective β–blocker，如 bisoprolol、metorprolol、nebivolol）
  - ✓ 鹽皮質激素受體拮抗劑（MRA）
  - ✓ 竇性心律且心搏偏快可考慮使用 Ivabradine
- 鈣離子阻斷劑 (calcium channel blocker；CCB) 中的 non–DHP 類藥物，如 verapamil 和 diltiazem 不建議用於收縮性心臟衰竭病人
- 為增加病人服藥順從性，可考慮使用複方單錠藥物
- 當肺阻塞病人的心臟衰竭程度嚴重時，則建議轉介至心臟專科醫師進行進一步心臟功能的評估與治療
- 個案管理師可協助提供病人關於疾病及用藥的相關衛教

Inhaled bronchodilator therapy in patients with COPD & HF

LABA

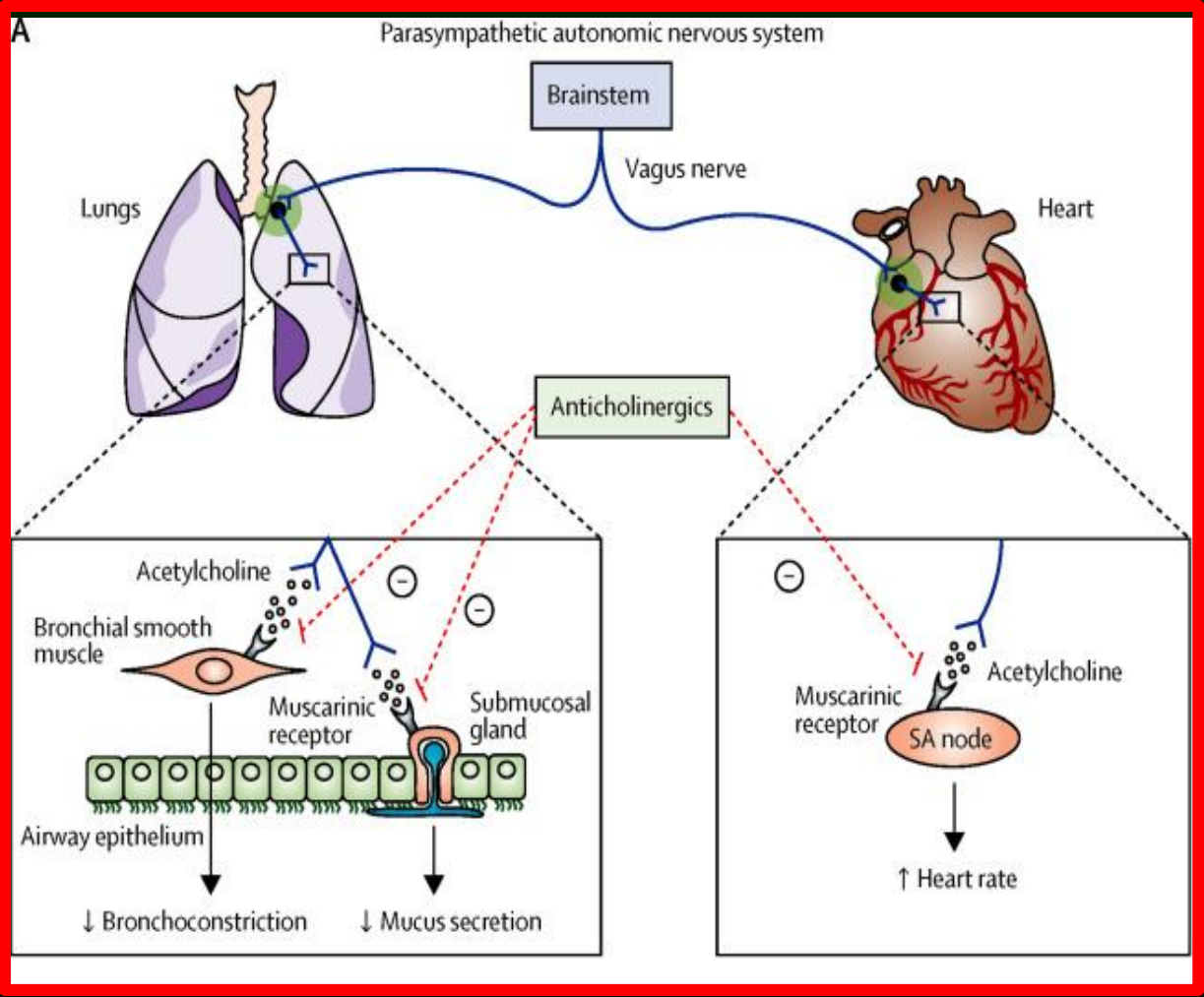


β2-adrenalreceptors (β2ARs)

- Facilitate to release norepinephrine.
- The positive inotropic and chronotropic responses resulting in an increased heart rate and myocardial oxygen demand, and direct myocardial injury.
- Reflex tachycardia caused by peripheral vasodilatation.
- Lower plasma K^+ levels by simulating the Na^+, K^+-ATPase coupled to β2-ARs in skeletal muscles, which pumps extracellular potassium ions into the cell, thereby causing hypokalemia that has been associated with ventricular tachycardia and fibrillation

Lancet Respir Med 2016 Feb;4(2):149-64.

LAMA



Muscarinic receptors

- Increase tachycardia from suppressing the vagal effect of M2-receptors of the sinoatrial nodal pacemaker
- Stimulation of M3 receptors protects the heart from ischemic injuries by activating antiapoptotic signaling substances, enhancing endogenous antioxidant levels,
- Decreasing intracellular $Ca2^{+}$ overload, delayed rectifying K^{+} current, which exerts negative chronotropic responses and exhibits antidysrhythmic activity

Lancet Respir Med 2016 Feb;4(2):149-64.

diseases

MDPI

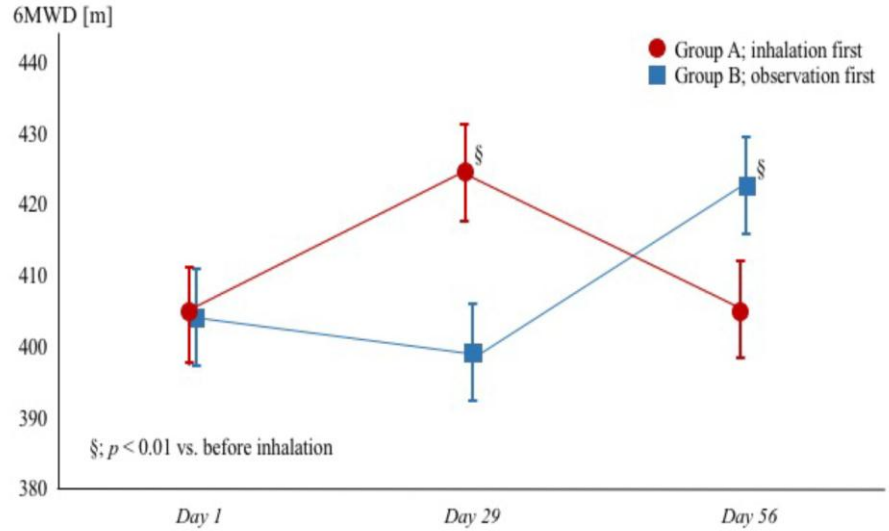
Article

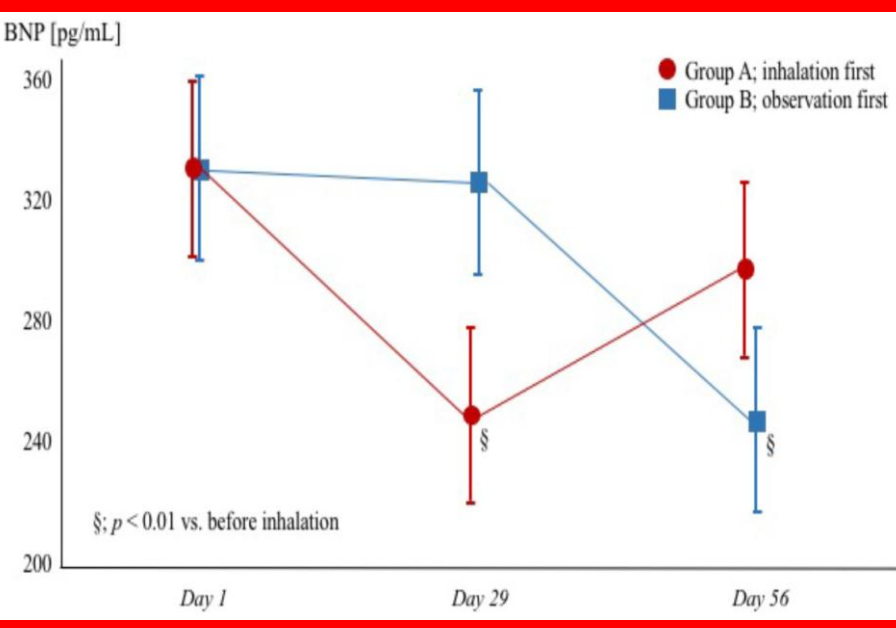
The Impact of Bronchodilator Therapy on Systolic Heart Failure with Concomitant Mild to Moderate COPD

Mahoto Kato [1,*], Kazuo Komamura [2], Masafumi Kitakaze [3] and Atsushi Hirayama [1]

Table 2. Group A: tiotropium + observation.

	Day 1	Day 29	Day 56	ANOVA
Systolic BP, mmHg	120 ± 6	115 ± 5 §	118 ± 4 ¶	<0.01
Diastolic BP, mmHg	79 ± 10	75 ± 9 ¶	74 ± 9 §	<0.01
Heart rate, bpm	73 ± 6	66 ± 5 ¶	68 ± 4 ¶	<0.05
BW, kg	59.5 ± 13.7	59.0 ± 13.6	59.3 ± 13.5	NS
SpO_2, %	96.2 ± 1.7	97.0 ± 1.3 ¶	96.3 ± 1.8	<0.01
Respiratory function				
FEV1.0, L	1.56 ± 0.11	1.74 ± 0.16 §	1.51 ± 0.15	<0.001
FEV1.0(%predict), %	78.1 ± 5.7	87.2 ± 7.9 §	75.7 ± 7.4	<0.001
FVC, L	2.64 ± 0.14	2.75 ± 0.13 §	2.55 ± 0.13	<0.001
FEV/FVC, %	59.3 ± 5.3	63.6 ± 6.4 §	59.5 ± 6.0	<0.001
Echocardiography				
LVDd, mm	57.3 ± 3.7	59.3 ± 3.6 ¶	56.2 ± 3.2	<0.05
LVDs, mm	49.5 ± 66.9	48.3 ± 4.2	48.0 ± 3.6	NS
LVEF, %	36.3 ± 2.4	41.8 ± 5.9 §	37.8 ± 7.8	<0.01
PG(RA-RV), mmHg	18.9 ± 4.8	16.7 ± 4.3 §	16.5 ± 5.1 §	<0.05
IVC, mm	9.7 ± 1.8	9.6 ± 1.7	9.5 ± 1.6	NS
Laboratory testing				
BNP, pg/mL	374 ± 94	263 ± 92 §	293 ± 78	<0.001
Norepinephrine, pg/mL	821 ± 251	468 ± 203 §	501 ± 191 ¶	<0.001



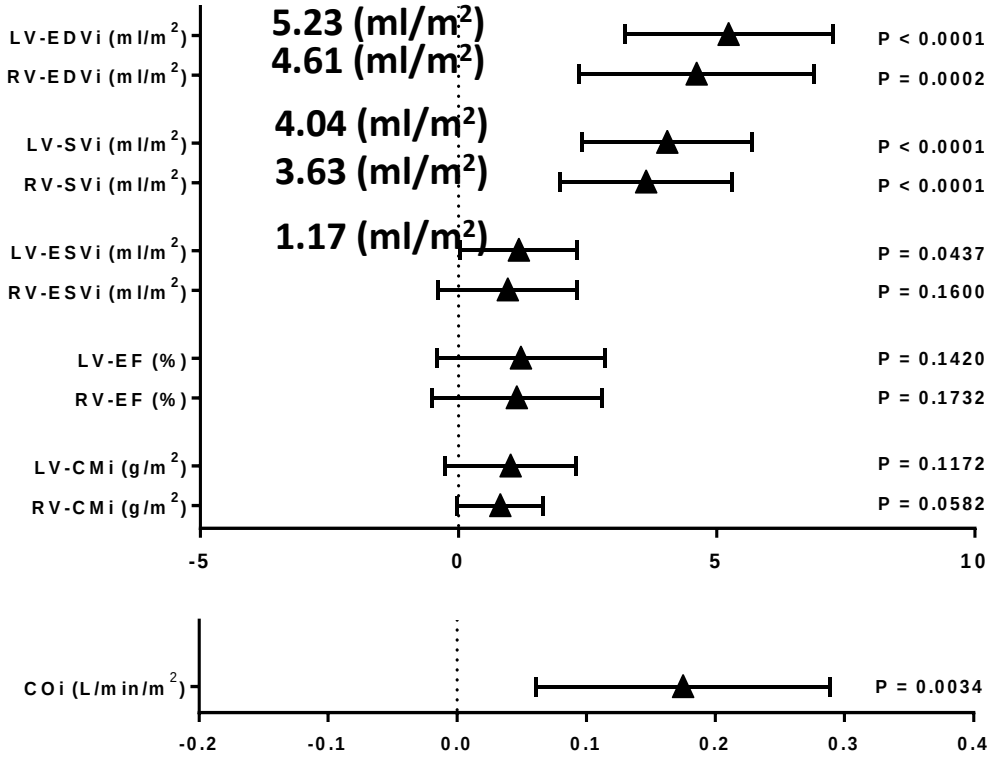


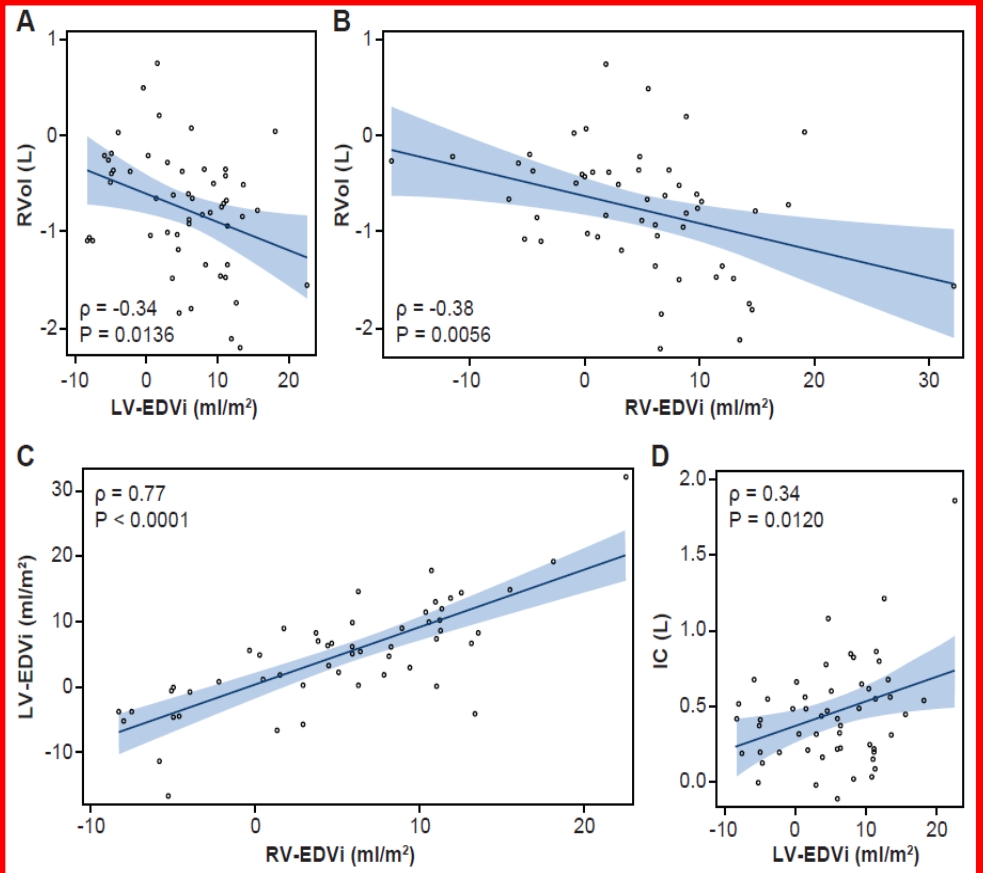
Diseases 2018, 6, 4; doi:10.3390

Effect of lung deflation with indacaterol plus glycopyrronium on ventricular filling in patients with hyperinflation and COPD (CLAIM): a double-blind, randomised, crossover, placebo-controlled, single-centre trial

Jens M Hohlfeld*, Jens Vogel-Claussen*, Heike Biller, Dominik Berliner, Korbinian Berschneider, Hanns-Christian Tillmann, Simone Hiltl, Johann Bauersachs, Tobias Welte

Overview of the effect of 14-day dual bronchodilation on cardiac endpoints



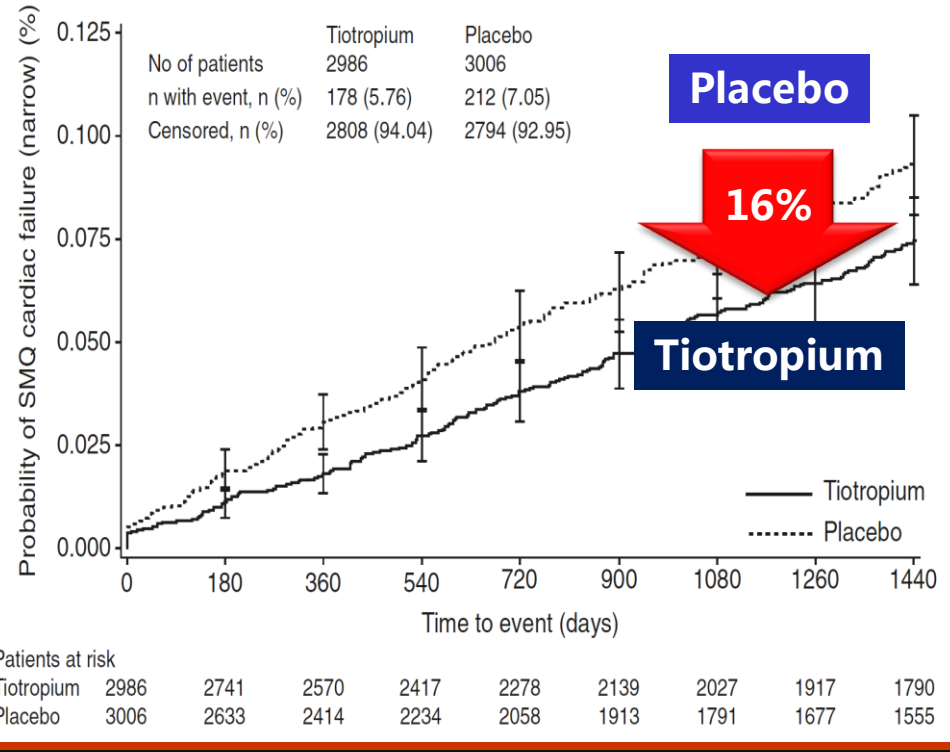


LV: left ventricular; RV: right ventricular; EDV: end-diastolic volume; SV: stroke volume; ESV: end-systolic volume; EF: ejection fraction; CM: cardiac mass; CO: cardiac output; i: indexed to body surface area; CI: confidence interval

Hohlfeld JM et al. Lancet Respir Med. 2018; *in press*

Cardiac safety of tiotropium in patients with cardiac events: a retrospective analysis of the UPLIFT® trial

Donald P Tashkin[1*], Inge Leimer[2], Norbert Metzdorf[2] and Marc Decramer[3]

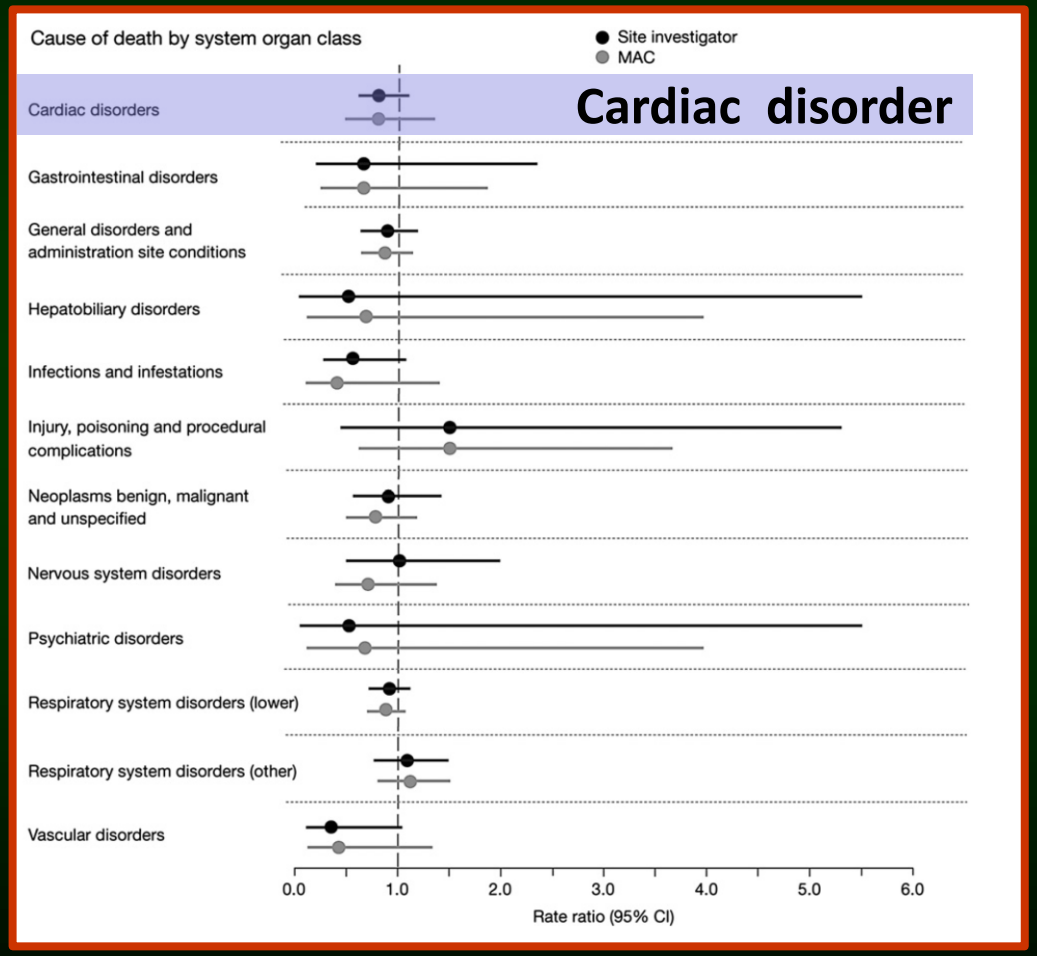


Respiratory Research (2015) 16:65

Respiratory Medicine (2012) 106, 515e521

Cause-specific mortality adjudication in the UPLIFT® COPD trial: Findings and recommendations

Lorcan P. McGarvey [a,*], Sheldon Magder [b], Deborah Burkhart [c], Steven Kesten [c], Dacheng Liu [c], Raymond C. Manuel [c], Denis E. Niewoehner [d]



LAMA, LABA vs cardiac effects

LAMA

- Tiotropium : 6
- Glycopyrronium : 3
- Umeclidinium : 3

No conclusive increased cardiovascular adverse event

LABA

- Formoterol : 8
- Salmeterol : 4
- Indacaterol : 11
- Vilanterol : 1
- Olodaterol : 2

No conclusive increased cardiovascular adverse event

Lancet Respir Med 2016, S2213-2600(15)00518-4

ICS/LABA, LABA/LAMA vs cardiac effects

ICS + LABA

- Fluticasone + Vilanterol : 2
- Budesonide + Formoterol : 3
- Fluticasone + Salmeterol : 7
- Beclomethasone + Formoterol : 1

No conclusive increased cardiovascular adverse event

LABA + LAMA

- Indacaterol + Glycopyrronium : 4
- Umeclidinium + Vilanterol : 3
- Tiotropium + Olodaterol : 3

No conclusive increased cardiovascular adverse event

Lancet Respir Med 2016, S2213-2600(15)00518-4

The heart and other organs

Heart failure and chronic obstructive pulmonary disease: the challenges facing physicians and health services

Nathaniel M. Hawkins[1]*, Sean Virani[2], and Claudio Ceconi[3]

Table 4 Association between beta-agonists and incident heart failure, hospitalization, and mortality

References	Population	*n*	Study design	Bronchodilator and route	Follow-up	Outcome	Risk associated with bronchodilator use [95% CI]	Adjustment includes beta- blockade
Martin *et al.*[153]	Asthma	8098	Cohort	Bambuterol oral	Median 288 days	Incident HF	RR 3.41 [1.99–5.86], $P < 0.0001$	No
		15 407	Cohort	Salmeterol inhaled	Median 511 days	Incident HF	RR 1.10 [0.63–1.91], $P = 0.7$	No
Coughlin *et al.*[154]	General population	387	Case–control	β-Agonist oral	20 months	Incident DCM	OR 3.4 [1.1–11.0]	No
		387	Case–control	β-Agonist inhaled/nebule	20 months	Incident DCM	OR 3.2 [1.4–7.1]	No
Sengstock *et al.*[155]	Cardiology clinic	190	Case–control	β-Agonist inhaled	—	Incident DCM	OR 1.0	No
M								Yes
Au								Yes
								Yes
Au								Yes
Singer *et al.*[159]	Acute HF without COPD	7299	Cohort	Any bronchodilator inhaled	Inpatient	Death IV vasodilator ventilation	OR 1.02 (0.67–1.56) OR 1.40 (1.18–1.67) OR 1.69 (1.21–2.37)	Yes
Bermingham *et al.*[121]	HF	1294	Cohort	β-Agonist inhaled	Mean 2.9 years	Mortality	HR 1.04 (0.77–1.41)	Yes

Induced heart failure **LABA > LAMA**

CI, confidence interval; COPD, chronic obstructive pulmonary disease; DCM, idiopathic dilated cardiomyopathy; HF, heart failure; HR, hazard ratio; IV, intravenous; LVSD, left ventricular systolic dysfunction; OR, odds ratio; RR, relative risk.

European Heart Journal (2013) 34, 2795–2803

The Risk of Myocardial Infarction Associated with Inhaled β-Adrenoceptor Agonists

DAVID H. AU, ROZENN N. LEMAITRE, J. RANDALL CURTIS, NICHOLAS L. SMITH, and BRUCE M. PSATY

Division of Pulmonary and Critical Care Medicine, Department of Medicine; Cardiovascular Health Research Unit, Department of Medicine; and Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, Health Services, University of Washington, Seattle, Washington

RISK OF MYOCARDIAL INFARCTION ASSOCIATED WITH MDI β-AGONIST AMONG SUBJECTS WITH CARDIOVASCULAR DISEASE ACCORDING TO FREQUENCY AND RECENCY OF USE

Category of Use	Controls (*n* = 1,140)	Cases (*n* = 678)	OR, Adjusted for Matching Factors	OR, Adjusted for Matching Factors and Other Factors†
Never users*				1.0 (REF)
One-time users*				
No prescription in past 3 m				1 (0.76–1.93)
One canister prescription in past 3 mo (new users)	4	17	7.67 (2.54–23.2)	7.32 (2.34–22.8)
Greater than one-time users*				
No prescription in past 3 mo	39	29	1.39 (0.84–2.29)	1.14 (0.67–1.93)
One canister prescribed in past 3 mo	10	12	1.99 (0.84–4.68)	1.78 (0.73–4.33)
Several canisters prescribed in past 3 mo	38	25	1.23 (0.73–2.07)	1.28 (0.74–2.23)

SABAs : increase risk of CVD

AM J RESPIR CRIT CARE MED 2000;161:827–830.

Beta-blocker therapy in patients with HF & COPD

SUMMIT Study

FEV1 at 3 months, according to treatment allocation and use of β-blocker therapy at baseline

	Placebo (*n* = 4,111)	Fluticasone Furoate (*n* = 4,135)	Vilanterol (*n* = 4,118)	Fluticasone Furoate/Vilanterol (*n* = 4,121)
No β-blockers at baseline				
No β-blocker therapy, *n*	2,831	2,805	2,872	2,818
Adjusted change in FEV_1 from baseline at 3 mo, ml (SE)	−7 (5)	29 (5)	44 (5)	61 (5)
Treatment difference from placebo (baseline to 3 mo), ml (95% CI)		36 (23–50)	51 (38–65)	68 (54–82)
β-blockers at baseline				
β-blocker therapy, *n*	1,280	1,330	1,246	1,303
Adjusted change in FEV_1 from baseline at 3 mo, ml (SE)	1 (7)	31 (7)	59 (7)	85 (7)
Treatment difference from placebo (baseline to 3 mo, ml (95% CI)		30 (10–50)	58 (38–78)	85 (65–105)
Treatment × β-blocker interaction *P* value	0.27			

Definition of abbreviations: CI = confidence interval; FEV_1 = forced expiratory volume in one second; SE = standard error.
Data are presented as mean (SE).

There is no evidence to suggest that baseline β-blocker therapy reduces the respiratory benefits

Ann Am Thorac Soc. 2018;15(5):608-614

SUMMIT Study

Time to first outcome event, according to treatment allocation and use of β-blocker therapy at baseline

	Placebo (*n* = 4,111)	Fluticasone Furoate (*n* = 4,135)	Vilanterol (*n* = 4,118)	Fluticasone Furoate/Vilanterol (*n* = 4,121)
Time to first exacerbation of chronic obstructive pulmonary disease				
No β-blockers at baseline				
Hazard ratio vs. placebo (95% CI)		0.95 (0.86–1.04)	0.94 (0.85–1.03)	0.83 (0.75–0.91)
β-Blockers at baseline				
Hazard ratio vs. placebo (95% CI)		1.00 (0.87–1.15)	0.86 (0.75–1.00)	0.73 (0.63–0.85)
Treatment × β-blocker interaction *P* value	0.18			
Time to first cardiovascular event				
No β-blockers at baseline				
Hazard ratio vs. placebo (95% CI)		0.82 (0.62–1.07)	0.87 (0.66–1.13)	0.94 (0.72–1.22)
β-Blockers at baseline				
Hazard ratio vs. placebo (95% CI)		1.02 (0.72–1.45)	1.23 (0.88–1.72)	0.97 (0.68–1.37)
Treatment × β-blocker interaction *P* value	0.33			
Time to death				
No β-blockers at baseline				
Hazard ratio vs. placebo (95% CI)		0.86 (0.70–1.05)	0.90 (0.73–1.10)	0.80 (0.65–0.99)
β-Blockers at baseline				
Hazard ratio vs. placebo (95% CI)		1.01 (0.75–1.37)	1.11 (0.82–1.50)	1.09 (0.81–1.48)
Treatment × β-blocker interaction *P* value	0.41			

Definition of abbreviation: CI = confidence interval.

No evidence to suggest that baseline β-blocker therapy to increases the CV risk of inhaled LABA in patients COPD and heightened CV risk

Ann Am Thorac Soc. 2018;15(5):608-614

TONADO Research Program

TABLE 3] Adjusted Mean (SE) Trough FEV_1 and Trough FVC Responses (Change From Baseline) After 24 and 52 Weeks of Treatment by β-Blocker Use at Baseline (Full Analysis Set): Combined Data

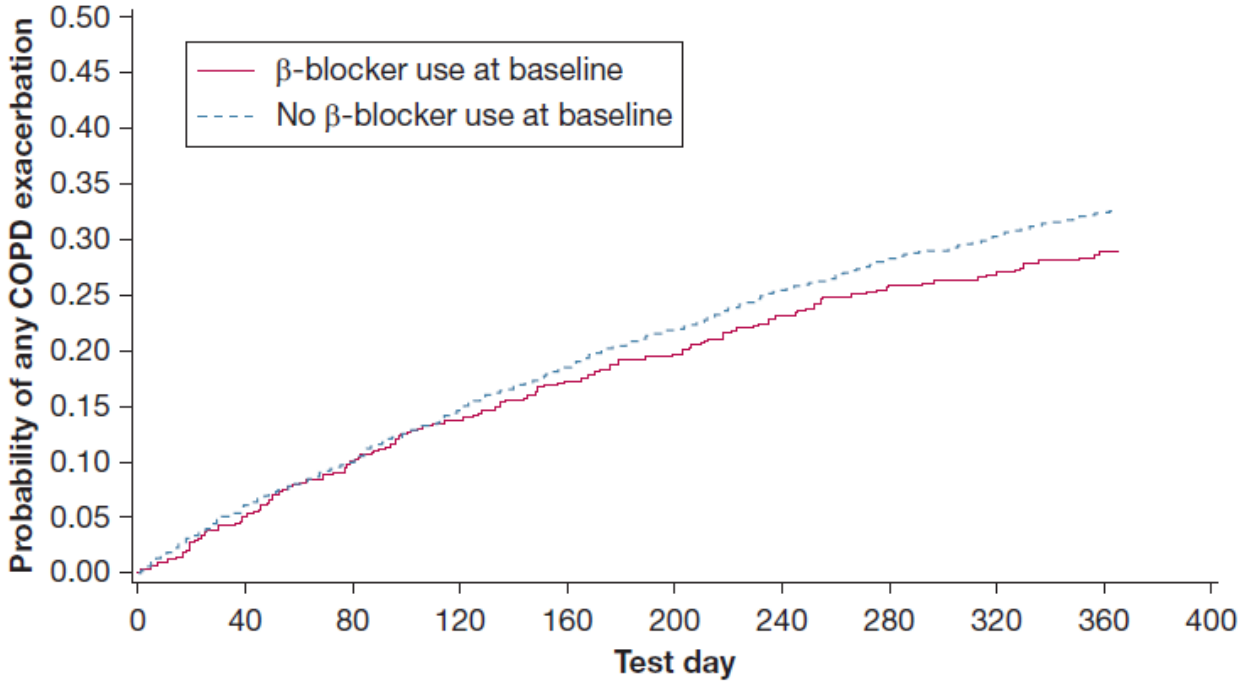
Response	β-Blocker (n = 557)	No β-Blocker (n = 4,605)	Treatment Difference (95% CI), L
24 wk			
Trough FEV_1 response, adjusted mean (SE), L	0.080 (0.009)	0.070 (0.003)	0.010 (−0.009 to 0.028)
Trough FVC response, adjusted mean (SE), L	0.140 (0.018)	0.150 (0.006)	−0.010 (−0.048 to 0.028)
52 wk			
Trough FEV_1 response, adjusted mean (SE), L	0.044 (0.009)	0.049 (0.003)	−0.005 (−0.024 to 0.014)
Trough FVC response, adjusted mean (SE), L	0.111 (0.018)	0.119 (0.006)	−0.008 (−0.047 to 0.030)

Data obtained from fitting a mixed-effects model for repeated measures, including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors; and Kenward-Roger approximation of denominator degrees of freedom.

- 5,162 patients
- Moderate to very severe COPD
- 557 of 5,162 patients (11%) received β-blockers at baseline

Chest. 2018;153(6):1315-1325

TONADO Research Program



No. at risk										
β-blocker use at baseline	557	514	480	450	425	405	385	369	357	340
No β-blocker use at baseline	4,605	4,251	3,980	3,722	3,499	3,304	3,115	2,970	2,857	2,710

	Hazard ratio	95% CI	*P* value
β-blocker use at baseline vs no β-blocker use at baseline	0.878	0.732-1.053	.1604

Lung function, overall respiratory status, and safety of tiotropium/olodaterol (LAMA/LABA) were not influenced by baseline β-blocker treatment in patients with moderate to very severe COPD.

Chest. 2018;153(6):1315-1325

β-blockers may reduce mortality in Pts with COPD

Table 2. Crude and Adjusted Hazard Ratios (HRs) for Mortality According to β-Blocker Use in 2230 Patients With a Diagnosis of Chronic Obstructive Pulmonary Disease[a]

Variable	HR (95% Confidence Interval)		
	Any β-Blocker	Cardioselective β-Blocker	Nonselective β-Blocker
Unadjusted (crude)	0.70 (0.59-0.84)	0.69 (0.57-0.83)	0.80 (0.61-1.06)
Covariates included in the Cox model to calculate adjusted HRs +			
Age	0.66 (0.56-0.79)	0.64 (0.54-0.78)	0.80 (0.61-1.05)
Sex	0.69 (0.58-0.82)	0.66 (0.55-0.80)	0.84 (0.63-1.11)
Current or former smoker	0.69 (0.58-0.81)	0.66 (0.55-0.79)	0.83 (0.63-1.10)
Diabetes, hypertension, cardiovascular diseases	0.65 (0.54-0.79)	0.64 (0.52-0.79)	0.77 (0.57-1.03)
Cardiovascular drugs other than β-blocker	0.67 (0.55-0.81)	0.64 (0.52-0.79)	0.82 (0.61-1.10)
Pulmonary drugs	0.67 (0.55-0.82)	0.65 (0.53-0.80)	0.82 (0.61-1.10)
Referral to a pulmonologist	0.68 (0.56-0.83)	0.67 (0.55-0.83)	0.82 (0.61-1.10)
Adjusted with propensity score[b]	0.64 (0.52-0.77)	0.63 (0.51-0.77)	0.80 (0.60-1.05)

Arch Intern Med. 2010;170(10):880-887

β-blockers may reduce risk of exacerbations in Pts with COPD

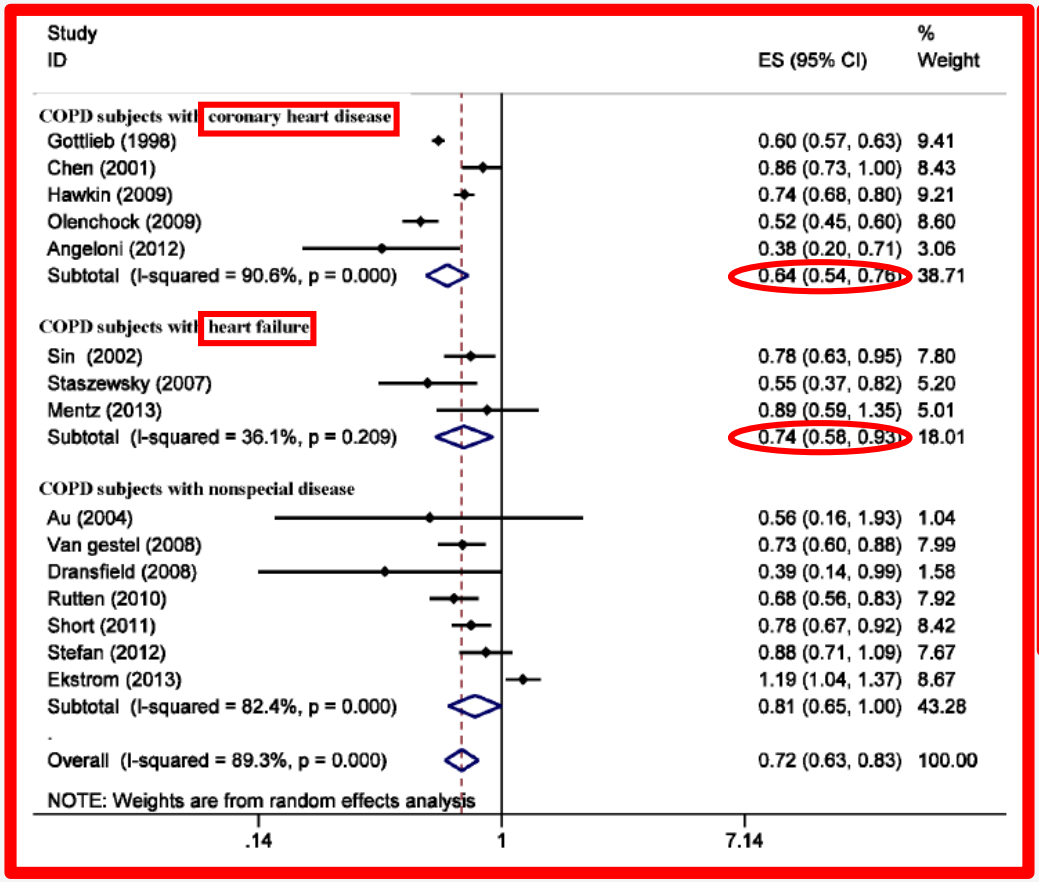
Table 4. Crude and Adjusted Hazard Ratios (HRs) for Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) According to β-Blocker Use in 2230 Patients With a Diagnosis of COPD[a]

Variable	HR (95% Confidence Interval)		
	Any β-Blocker	Cardioselective β-Blocker	Nonselective β-Blocker
Unadjusted (crude)	0.73 (0.63-0.83)	0.75 (0.65-0.87)	0.72 (0.57-0.90)
Covariates included in the Cox model to calculate adjusted HRs +			
Age	0.71 (0.62-0.82)	0.74 (0.64-0.86)	0.71 (0.56-0.89)
Sex	0.71 (0.62-0.81)	0.74 (0.64-0.85)	0.70 (0.56-0.89)
Current or former smoker	0.70 (0.61-0.80)	0.73 (0.63-0.84)	0.71 (0.56-0.89)
Diabetes, hypertension, cardiovascular diseases	0.63 (0.54-0.74)	0.68 (0.58-0.80)	0.66 (0.52-0.84)
Cardiovascular drugs other than β-blocker	0.58 (0.50-0.68)	0.64 (0.54-0.75)	0.66 (0.52-0.84)
Pulmonary drugs	0.67 (0.57-0.79)	0.72 (0.61-0.85)	0.72 (0.56-0.91)
Referral to a pulmonologist	0.71 (0.60-0.83)	0.78 (0.66-0.92)	0.74 (0.58-0.94)
Adjusted with propensity score[b]	0.64 (0.55-0.75)	0.68 (0.58-0.80)	0.70 (0.56-0.89)

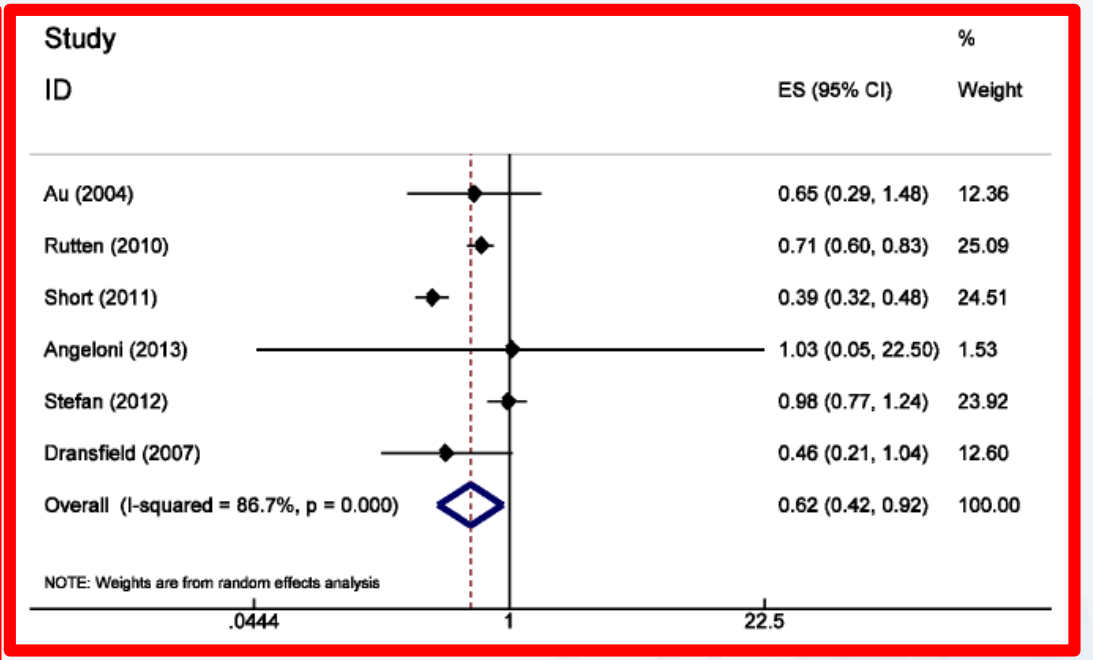
Arch Intern Med. 2010;170(10):880-887

β-Blockers Reduced the Risk of Mortality and Exacerbation in Pts with COPD: A Meta-Analysis of Observational Studies

Beta-blockers use and **mortality risk** in COPD Pts



Beta-blockers use and **exacerbation of COPD risk** in COPD Pts



*15 original observational cohort studies with a follow-up time from 1 to 7.2 years were included.

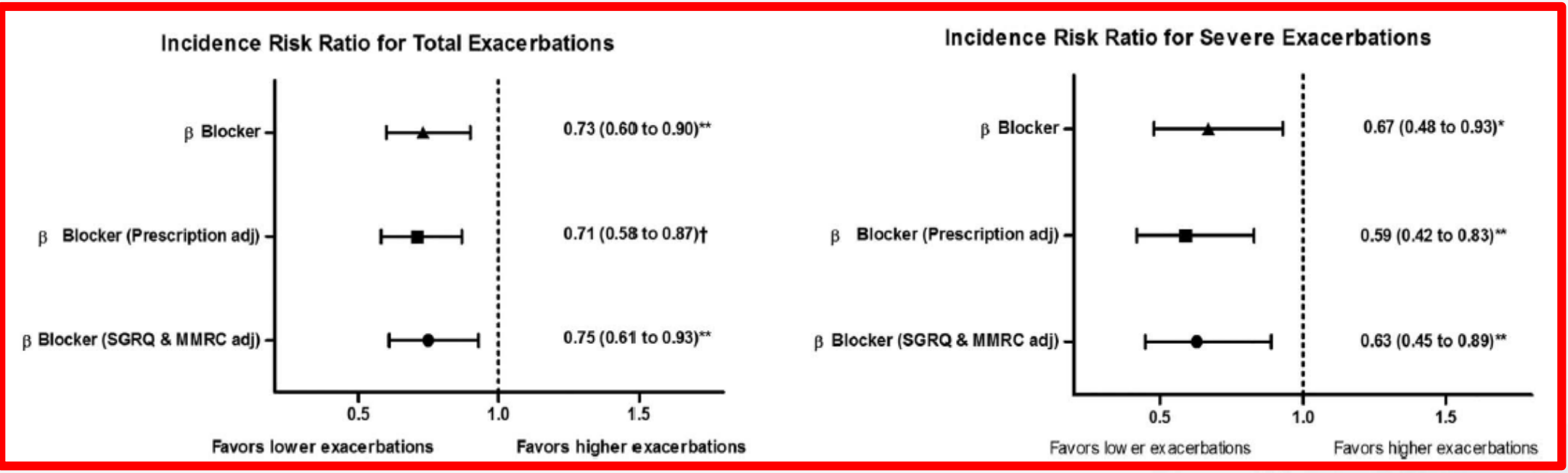
PLoS One. 2014;9(11):e113048

中華民國心臟學會
Taiwan Society of Cardiology

台灣胸腔暨重症加護醫學會
Taiwan Society of Pulmonary and Critical Care Medicine

β-Blockers are associated with a significant reduction in COPD exacerbations regardless of severity of airflow obstruction

Comparison of adjusted incidence risk ratios (IRRs) for total and severe exacerbations occurring during long-term follow-up in patients with COPD who are on or not on β-blocker therapy



SGRQ, St. George's Respiratory Questionnaire; MMRC, Modified Medical Research Council dyspnoea scale; Prescription adj, adjusted for propensity to prescribe β-blockers based on demographics, coronary artery disease, congestive heart failure and severity of airflow obstruction; SGRQ and MMRC adj, adjusted for propensity to prescribe β-blockers based on demographics, coronary artery disease, congestive heart failure and severity of airflow obstruction, as well as respiratory quality of life using SGRQ and dyspnoea per MMRC score.

Thorax. 2016;71(1):8-14

中華民國心臟學會
Taiwan Society of Cardiology

台灣胸腔暨重症加護醫學會
Taiwan Society of Pulmonary and Critical Care Medicine

Cardioselective β1-blockers produced no changes in lung function and did not impair treatment response to β2-agonists, even in long-term therapy

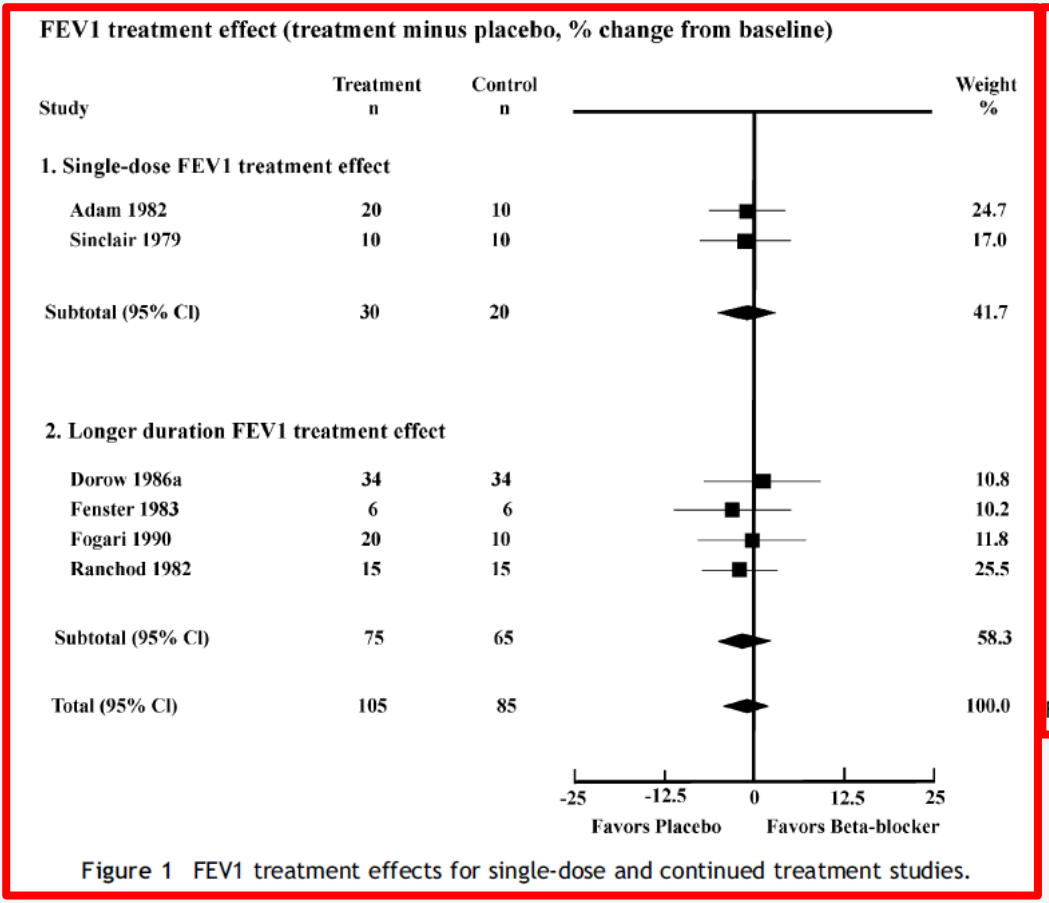


Figure 1 FEV1 treatment effects for single-dose and continued treatment studies.

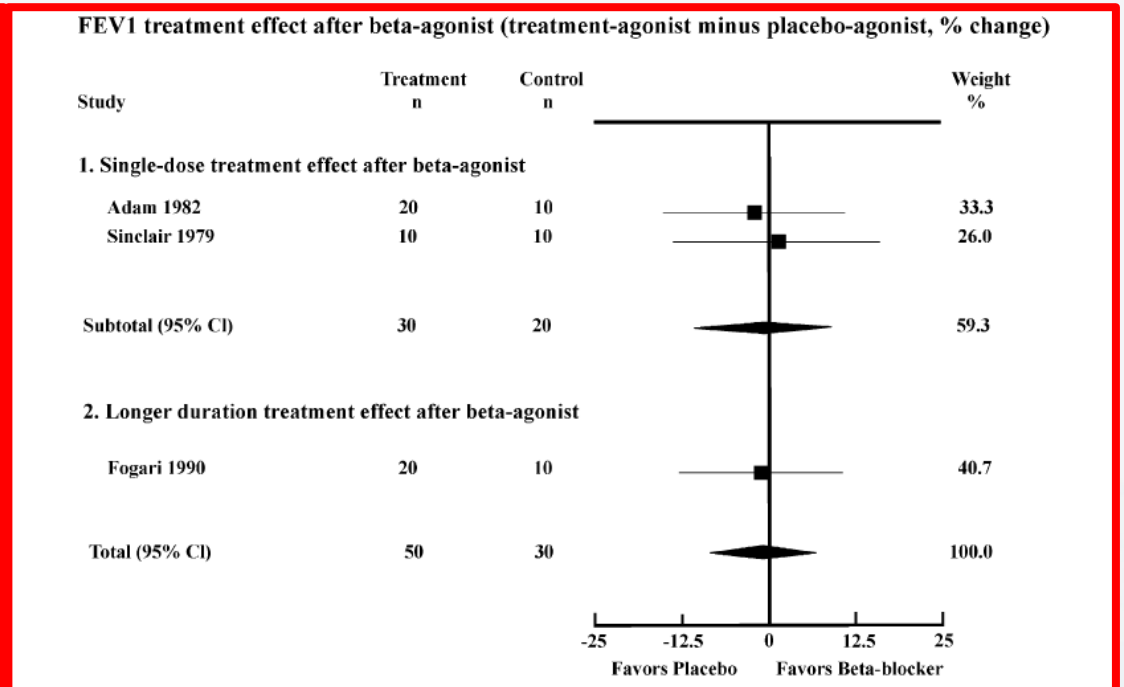


Figure 2 FEV1 treatment effects after beta2-agonists for single-dose and continued treatment studies.

Respir Med. 2003;97(10):1094-1101.

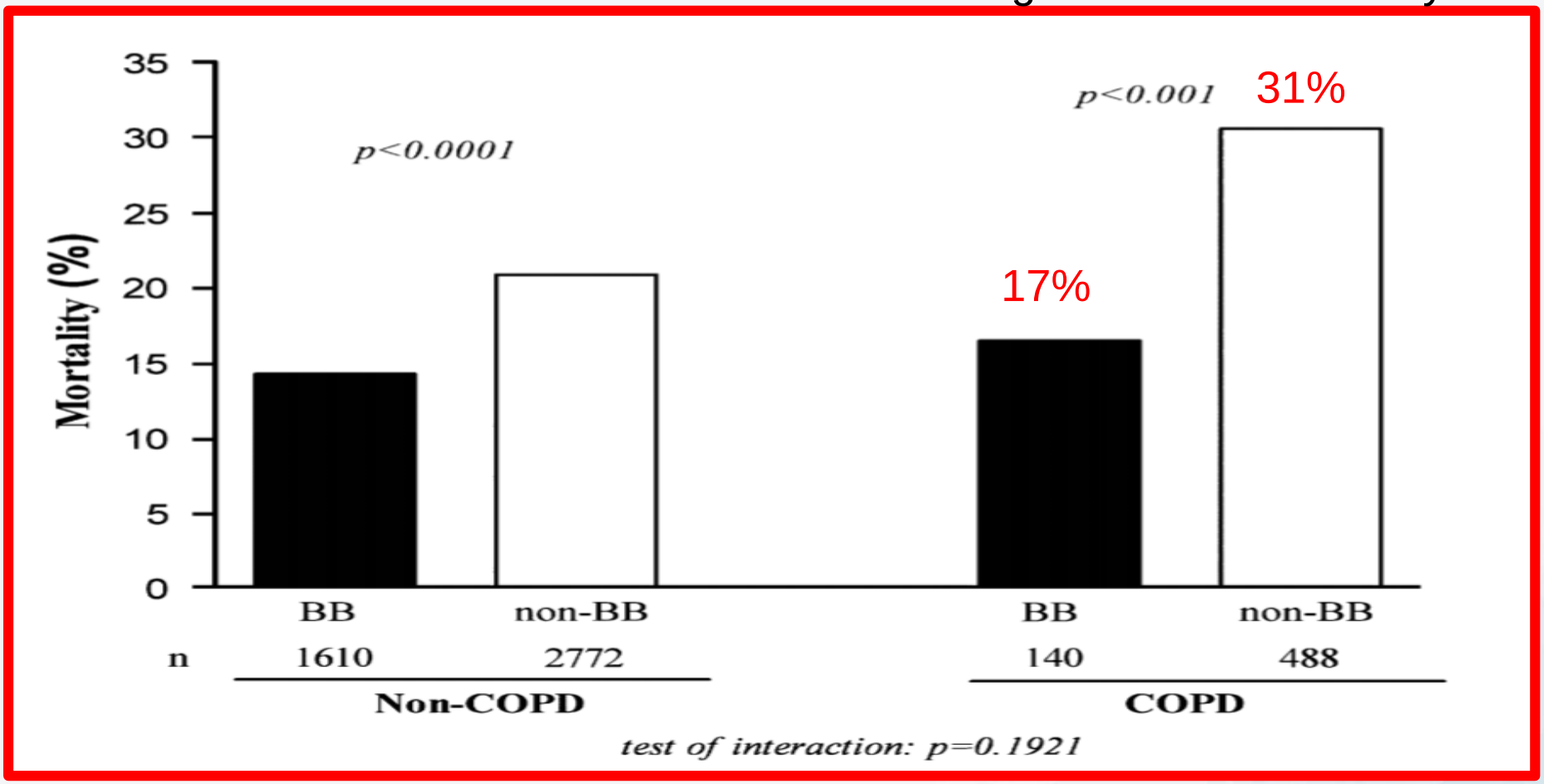
中華民國心臟學會
Taiwan Society of Cardiology

台灣胸腔暨重症加護醫學會
Taiwan Society of Pulmonary and Critical Care Medicine

Val-HeFT trial

Patients with coexisting HF and COPD

Average 23-month mortality rate



J Card Fail. 2007;13(10):797-804

中華民國心臟學會
Taiwan Society of Cardiology

台灣胸腔暨重症加護醫學會
Taiwan Society of Pulmonary and Critical Care Medicine

Survival Effects of β-Blockers in Pts with coexisting HF and COPD in Taiwan

Bisoprolol:
Low dose: ≥1.25 and <10 mg/day
High dose: ≥10 mg/day

TABLE 2. Adjusted Survival Effects of Carvedilol, Bisoprolol, and Metoprolol*

Characteristics	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age ≥ 65	2.29 (2.03–2.58)	<0.001	1.89 (1.68–2.14)	<0.001
Male sex	1.35 (1.24–1.47)	<0.001	1.18 (1.08–1.30)	<0.001
Comorbidities				
Diabetes mellitus	1.54 (1.41–1.69)	<0.001	1.42 (1.29–1.55)	<0.001
Dysrhythmia	1.29 (1.18–1.41)	<0.001	1.18 (1.08–1.29)	<0.001
Ischemic stroke	1.94 (1.76–2.14)	<0.001	1.59 (1.44–1.76)	<0.001
Intracranial hemorrhage	1.88 (1.52–2.31)	<0.001	1.31 (1.06–1.62)	0.014
Hypertension	1.33 (1.16–1.52)	<0.001	1.15 (1.00–1.32)	0.046
Ischemia heart disease	1.24 (1.13–1.36)	<0.001		
Chronic kidney disease	1.81 (1.64–2.00)	<0.001	1.55 (1.40–1.72)	<0.001
Cirrhosis	1.70 (1.34–2.16)	<0.001	1.68 (1.32–2.14)	<0.001
COPD severity				
Mild	Referent		Referent	
Moderate	1.43 (1.28–1.58)	<0.001	1.13 (1.02–1.27)	0.026
Severe	4.80 (4.23–5.45)	<0.001	2.56 (2.22–2.95)	<0.001
HF severity				
Mild	Referent		Referent	
Moderate	1.60 (1.45–1.77)	<0.001	1.35 (1.22–1.49)	<0.001
Severe	6.37 (5.64–7.20)	<0.001	4.11 (3.60–4.70)	<0.001
Beta-blockers use				
Nonuse	Referent		Referent	
Carvedilol, low dose	1.18 (0.98–1.42)	0.090	1.00 (0.83–1.21)	0.971
~~Carvedilol, high dose~~	~~0.83 (0.57–1.21)~~	~~0.333~~	~~0.81 (0.56–1.18)~~	~~0.277~~
Bisoprolol, low dose	0.72 (0.56–0.92)	0.009	0.76 (0.59–0.97)	0.030
Bisoprolol, high dose	0.35 (0.23–0.54)	<0.001	0.40 (0.26–0.63)	<0.001
~~Metoprolol, low dose~~	~~0.53 (0.25–1.12)~~	~~0.096~~	~~0.60 (0.29–1.26)~~	~~0.178~~
Metoprolol, high dose	0.32 (0.08–1.27)	0.106	0.36 (0.09–1.43)	0.146

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HF = heart failure, HR = hazard ratio, NS = nonsignificant.
* Multivariable analysis is conducted by time-dependent Cox proportional hazards model. All factors with $P < 0.1$ in univariate analyses were selected for Cox multivariable stepwise selection analysis.

Medicine (Baltimore). 2016;95(5):e2427

中華民國心臟學會 Taiwan Society of Cardiology
台灣胸腔暨重症加護醫學會 Taiwan Society of Pulmonary and Critical Care Medicine

Effects of β-blockers in Pts with coexisting HF and COPD in Taiwan

Table 2 Primary and secondary end points for β-blocker users and β-blocker nonusers among heart failure patients with COPD

Outcome	Events	Person-years	cHR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
Death from any cause						
Nonuser (reference)	220	3,676.19	–	–	–	–
User	40	1,266.41	0.52 (0.37–0.73)	<0.001*	0.67 (0.47–0.96)	0.028*
Hospitalization due to HF exacerbation						
Nonuser (reference)	121	3,354.41	–	–	–	–
User	23	1,154.71	0.53 (0.34–0.83)	0.006*	0.62 (0.39–0.98)	0.042*
Hospitalization due to COPD exacerbation						
Nonuser (reference)	84	3,411.12	–	–	–	–
User	26	1,228.93	0.82 (0.53–1.28)	0.381	1.15 (0.73–1.83)	0.549

Note: *Statistically significant ($P<0.05$).

Abbreviations: aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval; HF, heart failure.

Bisoprolol (≥1.25 mg/day) was found to reduce mortality and HF exacerbation compared to carvedilol and metoprolol.

Int J Chron Obstruct Pulmon Dis. 2017;12:2573-2581

中華民國心臟學會 Taiwan Society of Cardiology

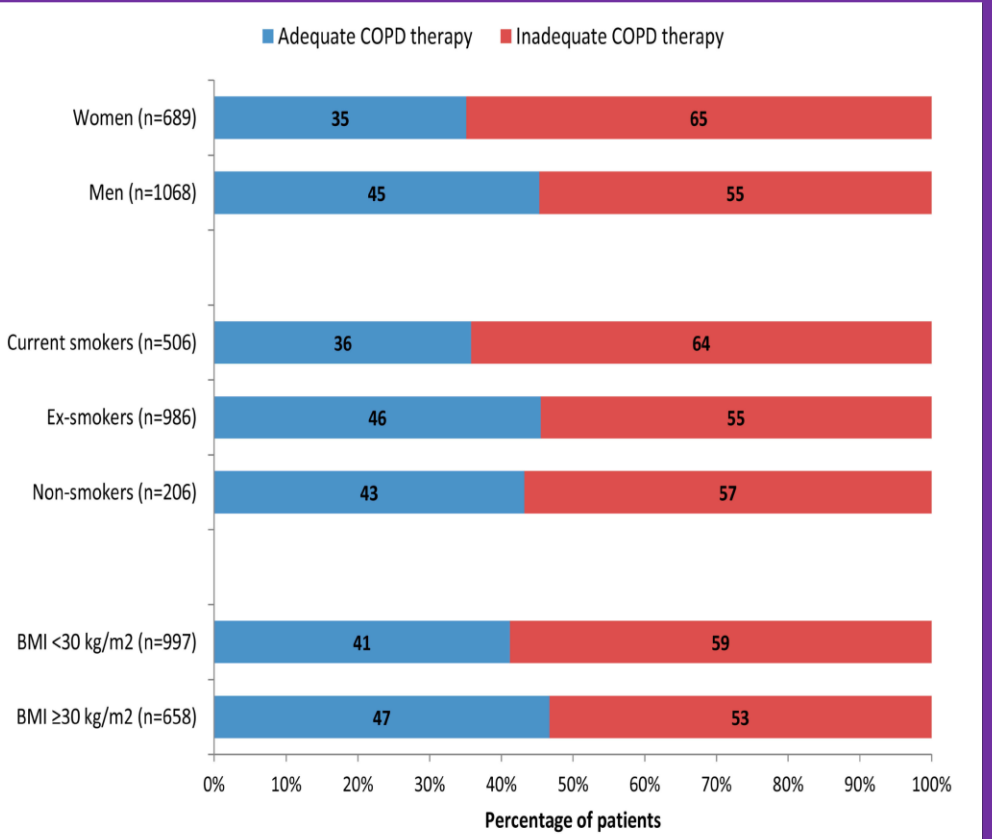
台灣胸腔暨重症加護醫學會 Taiwan Society of Pulmonary and Critical Care Medicine

Open Access Full Text Article

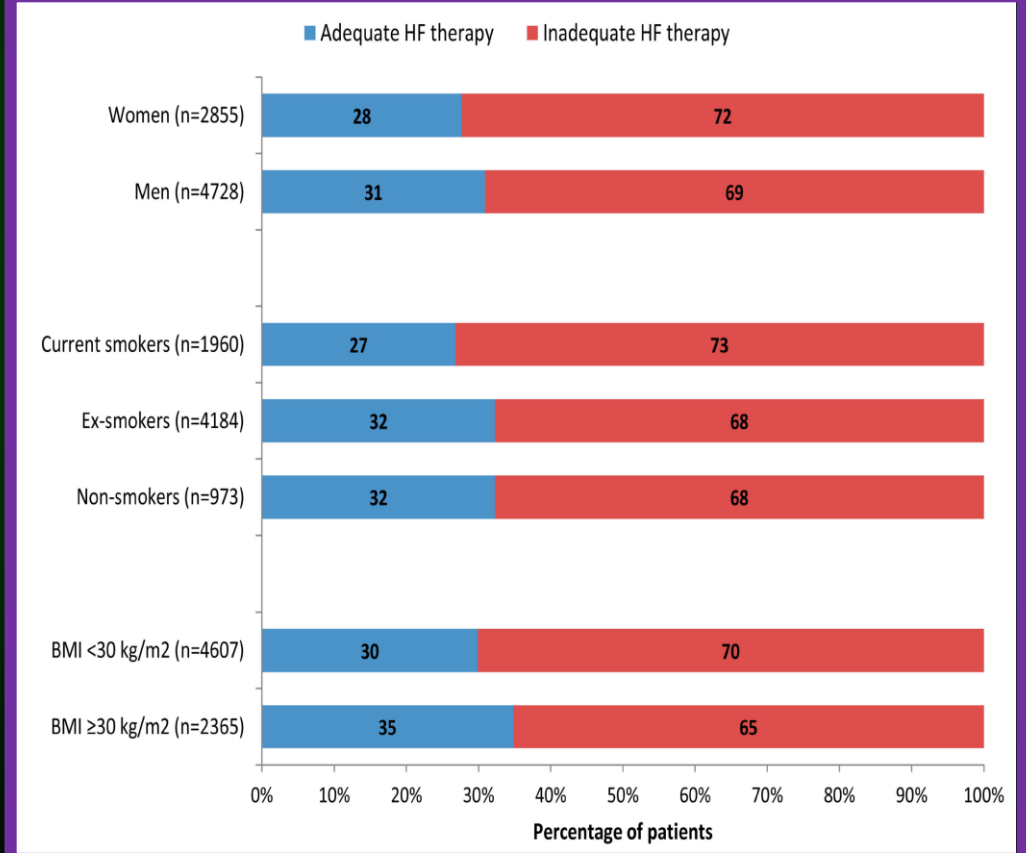
ORIGINAL RESEARCH

Adequacy of Therapy for People with Both COPD and Heart Failure in the UK: Historical Cohort Study

Heart failure with COPD



COPD with Heart failure



Pragmatic and Observational Research 2020:11 55–66

Oxygen therapy

Recommendations

1. Oxygen therapy is not routinely recommended for patients with acute HF without hypoxemia.
2. Keep SpO2 within 94-98% (88-92% in patients at risk of hypercapnic respiratory failure).
3. Supply oxygen if SpO2 < 94% (88% in patients at risk of hypercapnic respiratory failure).
4. Taper the oxygen concentration if SpO2 > 98% (> 92% in patients at risk of hypercapnic respiratory failure).
5. NIV (BiPAP or CPAP) should not routinely be used (only for patients with acute pulmonary edema with a high respiratory rate (> 25 breaths per minute) and persistent systemic hypoxemia (< 90%) despite high-flow oxygen supplementation.

Recommendations for the management of patients with acute heart failure: oxygen therapy and ventilatory support

Recommendations	Class [a]	Level [b]	Ref [c]
Monitoring of transcutaneous arterial oxygen saturation (SpO_2) is recommended.	I	C	
Measurement of blood pH and carbon dioxide tension (possibly including lactate) should be considered, especially in patients with acute pulmonary oedema or previous history of COPD using venous blood. In patients with cardiogenic shock arterial blood is preferable.	IIa	C	
Oxygen therapy is recommended in patients with AHF and SpO_2 <90% or PaO_2 <60 mmHg (8.0 kPa) to correct hypoxaemia.	I	C	
Non-invasive positive pressure ventilation (CPAP, BiPAP) should be considered in patients with respiratory distress (respiratory r… …ress and reduce th… Non-invasive … patients. Blood pressure should be monitored regularly when this treatment is used.	IIa	B	541–545
Intubation is recommended, if respiratory failure, leading to hypoxaemia (PaO_2 <60 mmHg (8.0 kPa)), hypercapnia ($PaCO_2$ >50 mmHg (6.65 kPa)) and acidosis (pH <7.35), cannot be managed non-invasively.	I	C	

NIV Positive Pressure Ventilation (CPAP, BiPAP)

- **RR >25, SpO_2 <90%**

AHF = acute heart failure; BiPAP = bilevel positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood; PaO_2 = partial pressure of oxygen in arterial blood; SpO_2 = transcutaneous oxygen saturation.

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting recommendations.

European Heart Journal (2016) 37, 2129–2200

6MWT (Submaximal Exercise Test) & CPET (Maximal Exercise Test)

Studies providing a correlation between 6-minute walking distance and peak VO_2 in patients with heart failure.

Study	Peak VO_2
Guyatt and colleagues[2]	$r = 0.42$, $p < 0.001$
Cahalin and colleagues[12]	$r = 0.64$, $p < 0.001$
Roul and colleagues[41]	$r = 0.65$, $p = 0.011$*
Lucas and colleagues[42]	$r = 0.28$, $p =$ NS
Rostagno and colleagues[43]	$r = 0.56$, $p < 0.05$
Zugck and colleagues[9]	$r = 0.68$, $p < 0.01$
Opasich and colleagues[44]	$r = 0.59$, $p < 0.001$
Cheetham and colleagues[6]	$r = 0.81$, $p < 0.001$
Guazzi and colleagues[4]	$r = 0.68$, $p < 0.001$
Jehn and colleagues[45]	$r = 0.72$, $p < 0.001$
Carvalho and colleagues[46]	$r = 0.70$, $p = 0.0002$
Forman and colleagues[50]	$r = 0.54$, $p < 0.001$
Deboeck and colleagues[47]	$r = 0.52$, $p < 0.05$
Omar and colleagues[48]	$r = 0.40$, $p < 0.001$
Uszko-Lecer and colleagues[17]	$r = 0.58$, $p < 0.001$
Yoshimura and colleagues[49]	$r = 0.62$, $p < 0.001$

*Only in patients with low activity status.

	HF	COPD
Gold standard for the evaluation of exercise capacity	CPET	6MWT
Reliable information about daily activity	6MWT	6MWT
Low activity status	6MWT (Severely impaired patients with advanced HF)	6MWT
High activity status	CPET	CPET
Expensive, demands special equipment and trained personnel, limited availability	CPET	CPET
Simple, inexpensive test, well-tolerated	6MWT	6MWT

Ther Adv Cardiovasc Dis 2019, Vol. 13: 1–10

Question: Do the patients who have COPD need regular examinations for concomitant cardiovascular diseases? If yes, what and how often is the examination suggested?

- a. the presence of orthopnea or paroxysmal nocturnal dyspnea
- b. existing two or more risk factors, e.g., hypertension, dyslipidemia, diabetes mellitus, smoking
- c. the symptom of disproportionate dyspnea.
- Apart from history taking and physical examinations, electrocardiogram and chest X-ray can be arranged for the first line of examinations

Question : Is acute exacerbation of COPD a risk factor for ADHF?

- Approximately 16% of patients during AECOPD demonstrated a considerable increase in serum troponin-I and NT-proBNP .
- The hypoxemia and hypercapnia resulting from AECOPD can also be proarrhythmogenic, and this can lead to arrhythmias, in turn triggering ADHF
- Kwong et al. found that myocardial infarction (MI) risk was sixfold higher during the first week of respiratory tract infection than during the control period.
- The data in the General Practice Research Database in the United Kingdom demonstrate that MI risk is four times higher during the first 3 days

Question: What is the role of theophylline in the treatment of patients with coexisting COPD and HF? What is the optimal dose of theophylline in this scenario?

- All studies demonstrating the efficacy of theophylline in patients with COPD have been performed with sustained-release preparations.
- Oral theophylline treatment can be used for COPD treatment when inhaled long-acting bronchodilators or ICSs are unavailable. However, the lowest effective dose of theophylline (100 – 200 mg/day) is recommended to avoid adverse effects.

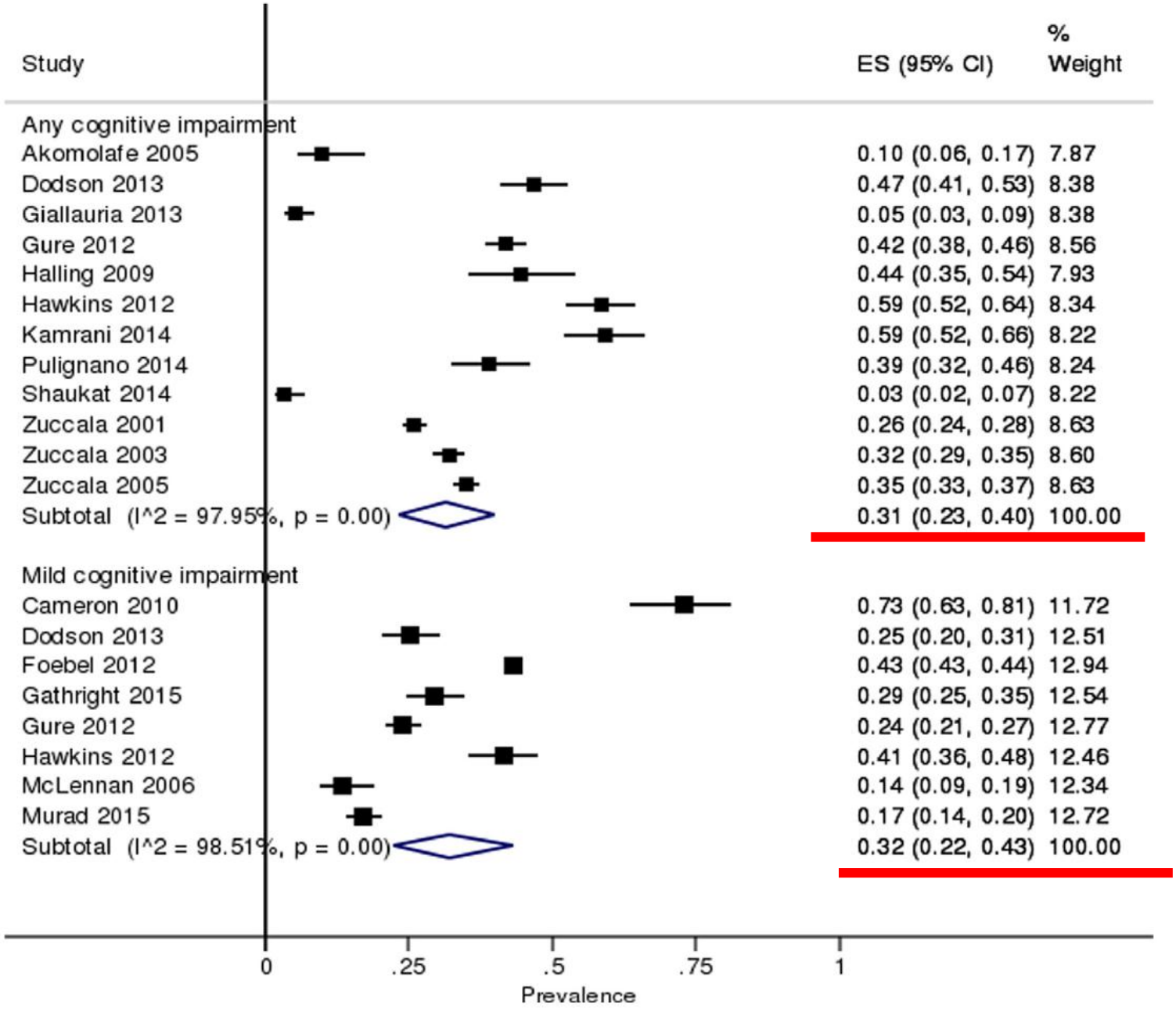


Fig. 4. Meta-analysis for studies with ACI and MCI in patients with CHF.

Thanks for Your Attention !