

Risk for Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease

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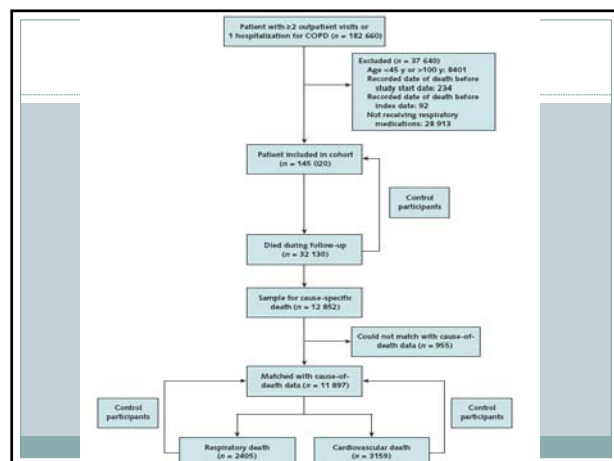
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背景

- 根據研究，使用ipratropium的病人有兩倍的心血管死亡率。
(Anthonisen NR, Connett JE, Enright PL, Manfreda J. Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med. 2002; 166: 333-9)
- FDA研究指出，使用tiotropium的COPD病人，stroke risk會增加。
(Center for Drug Evaluation and Research. Early communication about ongoing safety review of tiotropium. Silver Spring, MD: U.S. Food and Drug Administration; 18 July 2008)

研究設計

- Nested case-control study
- 由美國退伍軍人醫療資料庫，找出在1999/10/1 ~ 2003/9/30 之間新診斷出COPD的案例，進行資料追蹤至死亡，或是至2004/9/30。
- 藥物使用定義：在追蹤結束日期的前180天內有使用的藥物。

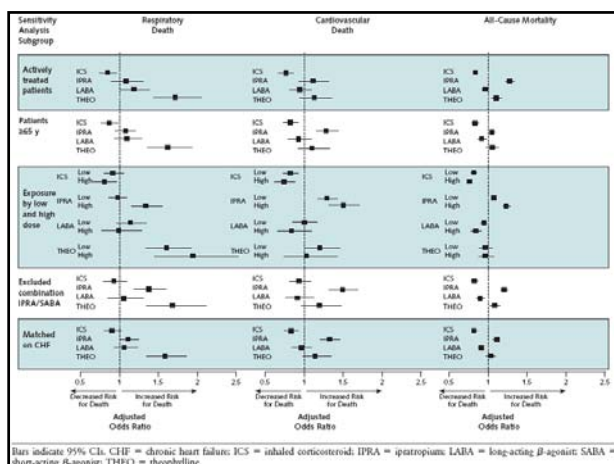


定義

- respiratory death: respiratory system disease (ICD-10 codes J00 to J99)
- cardiovascular death: ischemic heart disease (ICD-10 codes I20 to I25), cardiomyopathy, cardiac arrest, or arrhythmias (ICD-10 codes I42 to I51)
- COPD medications: inhaled corticosteroids, ipratropium, long-acting B-agonists, and theophylline in the 6 months preceding death.

Table 3. Adjusted Odds of Mortality

Regimen	Adjusted Odds Ratio (95% CI)			
	All-Cause Mortality*	Respiratory Death†	Cardiovascular Death‡	Respiratory or Cardiovascular Death§
Medication				
None or short-acting β -agonists only	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Inhaled corticosteroids	0.80 (0.78-0.82)	0.88 (0.79-1.00)	0.80 (0.72-0.88)	0.86 (0.80-0.93)
Ipratropium	1.11 (1.08-1.15)	1.07 (0.96-1.20)	1.24 (1.22-1.27)	1.27 (1.19-1.36)
Long-acting β -agonists	0.92 (0.88-0.96)	1.12 (0.97-1.30)	0.97 (0.84-1.11)	0.98 (0.89-1.09)
Theophylline	1.05 (0.99-1.10)	1.71 (1.46-2.00)	1.16 (0.99-1.37)	1.40 (1.25-1.57)
Medication regimen				
None or short-acting β -agonists only	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Inhaled corticosteroids	0.85 (0.79-0.91)	0.97 (0.74-1.26)	0.90 (0.72-1.13)	0.92 (0.74-1.16)
Ipratropium	1.12 (1.08-1.17)	1.06 (0.93-1.22)	1.42 (1.27-1.59)	1.42 (1.28-1.58)
Long-acting β -agonists	0.99 (0.84-1.04)	1.14 (0.74-1.75)	1.08 (0.73-1.60)	1.08 (0.73-1.59)
Theophylline	1.04 (0.94-1.15)	1.71 (1.23-2.39)	1.33 (0.98-1.81)	1.33 (0.98-1.82)
Inhaled corticosteroids plus ipratropium	0.88 (0.84-0.92)	1.01 (0.79-1.28)	1.04 (0.90-1.22)	1.03 (0.89-1.19)
Inhaled corticosteroids plus long-acting β -agonists plus ipratropium	0.82 (0.77-0.87)	1.38 (1.05-1.81)	1.16 (0.93-1.45)	1.12 (0.90-1.40)
Long-acting β -agonists plus ipratropium	1.03 (0.96-1.11)	1.04 (0.69-1.57)	1.14 (0.88-1.47)	1.11 (0.86-1.43)
Inhaled corticosteroids plus long-acting β -agonists	0.78 (0.71-0.87)	1.04 (0.69-1.57)	0.79 (0.54-1.17)	0.78 (0.53-1.15)
Ipratropium plus theophylline	1.17 (1.07-1.28)	1.84 (1.37-2.47)	1.47 (1.09-1.98)	1.50 (1.12-2.02)
Inhaled corticosteroids plus ipratropium plus theophylline	1.00 (0.89-1.11)	2.00 (1.37-2.97)	1.11 (0.76-1.60)	1.10 (0.76-1.59)
Other	0.86 (0.78-0.95)	1.48 (1.08-2.02)	1.22 (0.96-1.55)	1.30 (0.93-1.81)



Regimen	Respiratory Death, %		Cardiovascular Death, %		Respiratory or Cardiovascular Death, %		All-Cause Mortality, %	
	Case Patients (n = 2405)	Control Participants (n = 23 907)	Case Patients (n = 3159)	Control Participants (n = 31 534)	Case Patients (n = 5564)	Control Participants (n = 55 441)	Case Patients (n = 32 130)	Control Participants (n = 320 501)
Medication use within 6 mo of index date								
Short-acting β-agonists	71.2	61.9	70.0	62.3	70.5	61.8	65.9	61.2
Inhaled corticosteroids	31.0	24.8	24.7	24.9	27.4	24.8	24.2	24.7
Ipratropium	65.8	52.4	65.3	52.4	65.5	52.1	60.8	52.5
Long-acting β-agonists	16.0	10.7	11.0	10.2	13.1	10.5	12.9	12.2
Theophylline	12.8	6.4	7.3	6.3	9.7	6.3	7.0	6.0
Medication regimen use within 6 mo of index date								
None or short-acting β-agonists only	24.5	37.2	26.4	37.0	25.6	37.3	31.1	37.2
Inhaled corticosteroids	3.7	4.9	3.6	5.0	3.6	5.0	3.3	4.5
Ipratropium	31.6	30.1	40.0	30.4	36.4	30.1	35.6	30.0
Long-acting β-agonists	1.3	1.4	1.1	1.4	1.2	1.4	1.3	1.6
Theophylline	2.4	1.8	1.9	1.9	2.1	1.9	1.6	1.6
Inhaled corticosteroids plus ipratropium	14.3	12.0	13.2	12.1	13.7	11.8	11.7	11.4
Inhaled corticosteroids plus long-acting β-agonists plus ipratropium	6.0	3.8	4.2	3.6	5.0	3.9	5.1	4.6
Long-acting β-agonists plus ipratropium	4.3	2.6	3.2	2.5	3.7	2.6	3.6	2.9
Inhaled corticosteroids plus ipratropium plus theophylline	1.4	1.7	1.1	1.6	1.2	1.6	1.4	1.9
Inhaled corticosteroids plus ipratropium plus theophylline	4.0	1.7	2.3	1.6	3.0	1.6	2.2	1.5
Inhaled corticosteroids plus ipratropium plus theophylline	3.2	1.4	1.4	1.4	2.2	1.4	1.5	1.2
Other	3.3	1.6	1.7	1.5	2.4	1.5	1.8	1.6

結果

- Ipratropium 的使用與增加CV death有明顯相關 (OR, 1.34 [CI, 1.22 to 1.47])
- Ipratropium合併Inhaled corticosteroids，與 CV death就沒有明顯相關。OR, 1.04 (CI, 0.90–1.22)
- Inhaled corticosteroids能降低CV death與所有死亡的風險 (但在別的研究中，會增加PN risk) OR, 0.80 (0.72–0.88); OR, 0.80 (0.78–0.83)
- 關於Theophylline對resp. death 的影響，經過進一步分析使用Theophylline的病人，多數是病況較嚴重的病患，將疾病嚴重度列為變項重新迴歸後，Theophylline的使用對resp. death無明顯差異。

結論

- 本研究受到一些不可控制的變因限制，例如個別病患的抽菸狀況，肺功能差異，COPD嚴重程度，以及死因誤判等。
- 關於ipratropium可能會增加COPD病患的死亡風險，需要更進一步的研究。