# Prophylactic Antibiotics for the prevention of COPD acute exacerbation- CON

한양대학교 의과대학 호흡기내과
김 태 형

HANYANG UNIVERSITY

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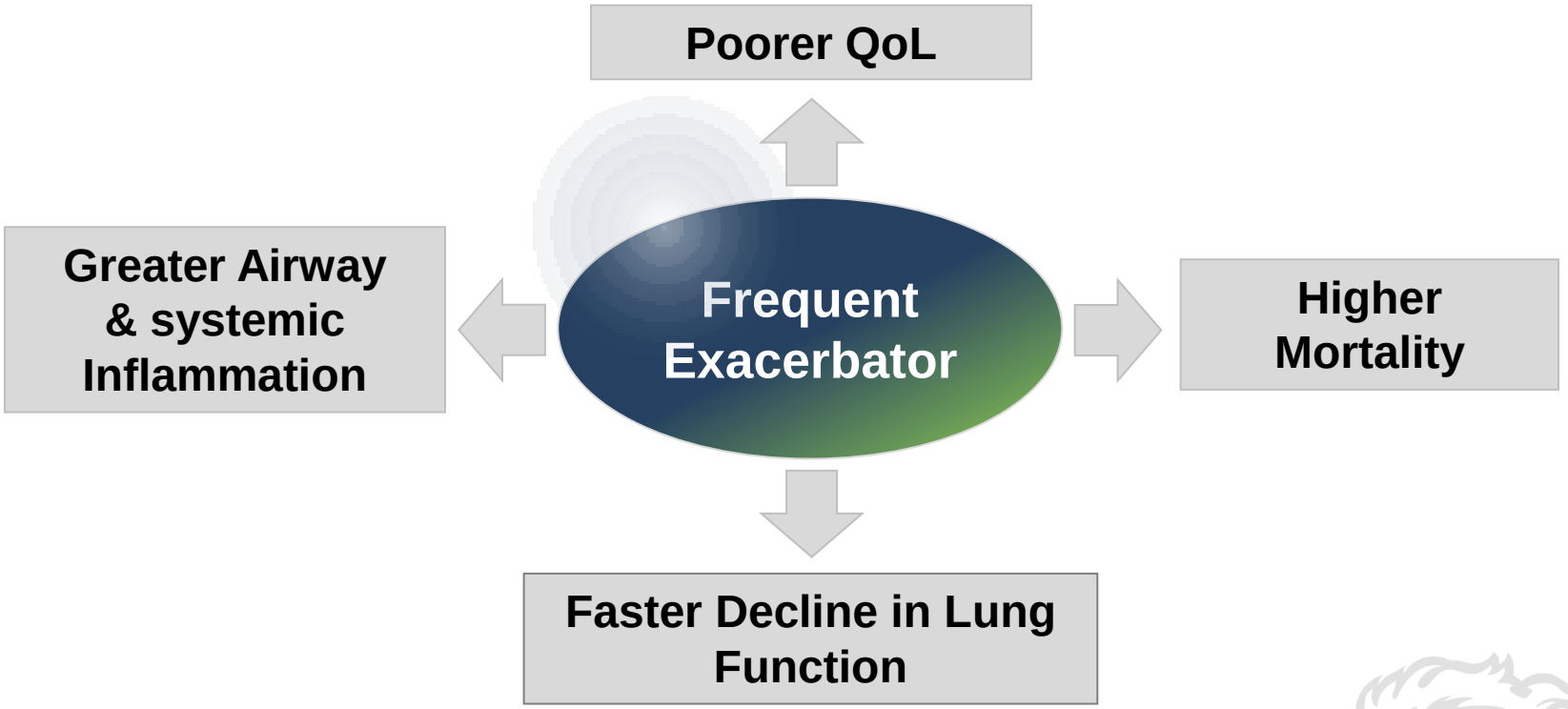
# COPD 의 급성 악화




- Major health economic burden
- Social isolation and Depression

# COPD 의 급성 악화에서 예방적 항균제 치료의 배경

- Respiratory bacterial infection in COPD : 40-50% of exacerbations

- The leading bacterial pathogen ; nontypeable *H. influenzae*
- The other major bacterial pathogens
  *Moraxella catarrhalis*, *S.pneumoniae* and *Pseudomonas aeruginosa*

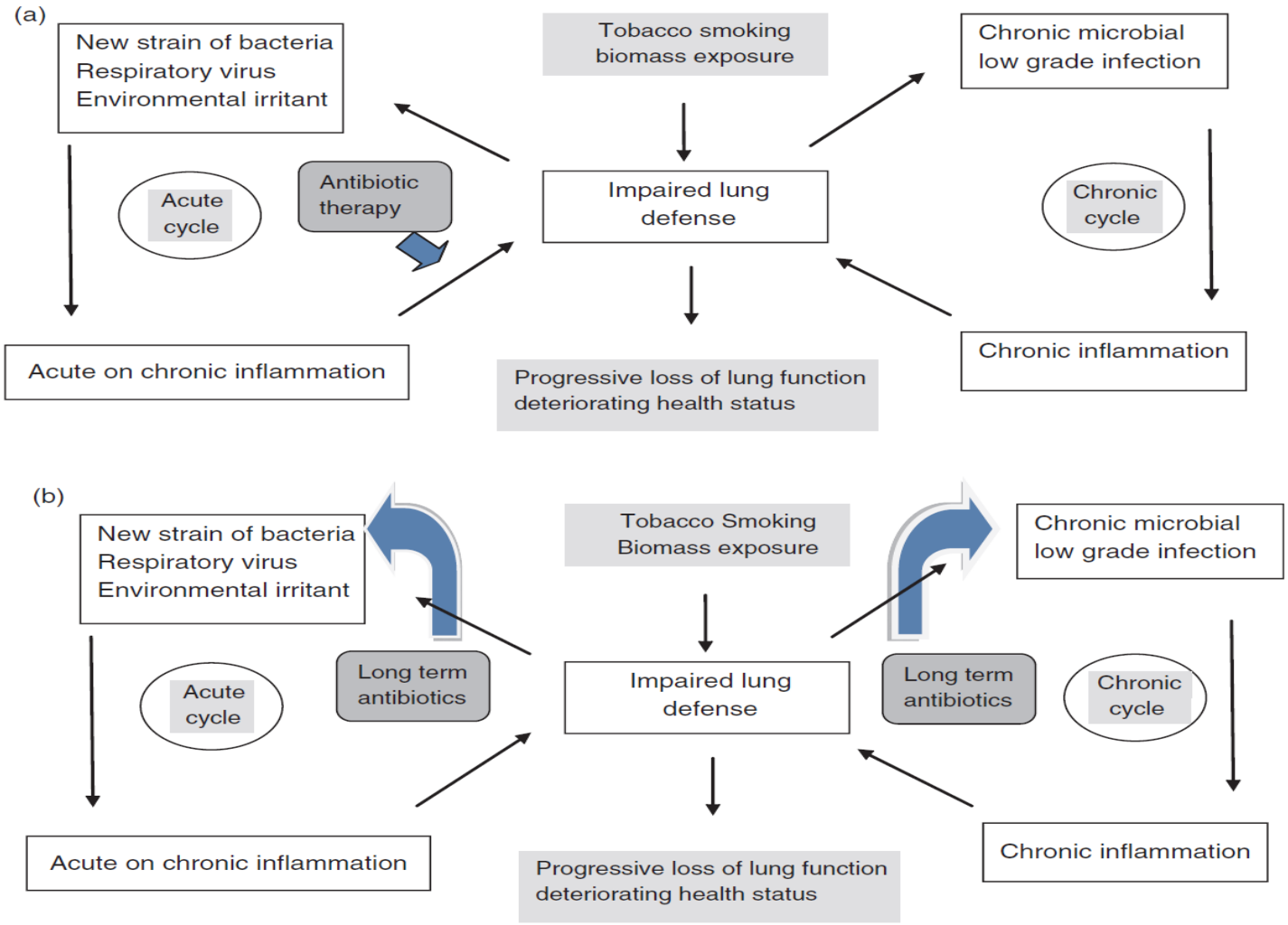
- The choice of the antibiotic should be **based on the local bacterial resistance pattern**.

- Usually initial empirical treatment is an aminopenicillin with or without clavulanic acid, macrolide, or tetracycline.

**Reduction of airway bacterial load and/or prevention of new strain acquisition may reduce the frequency and severity of exacerbations.**

**Anti-inflammatory or immune modulatory effect of specific antibiotics : macrolide ?**

# COPD 의 급성 악화에서 예방적 항균제 치료의 배경




Sethi S et al. Ther Adv Respir Dis 2011;5:207-216.

# COPD 의 세균성 급성 악화에서 원인 균주의 분포

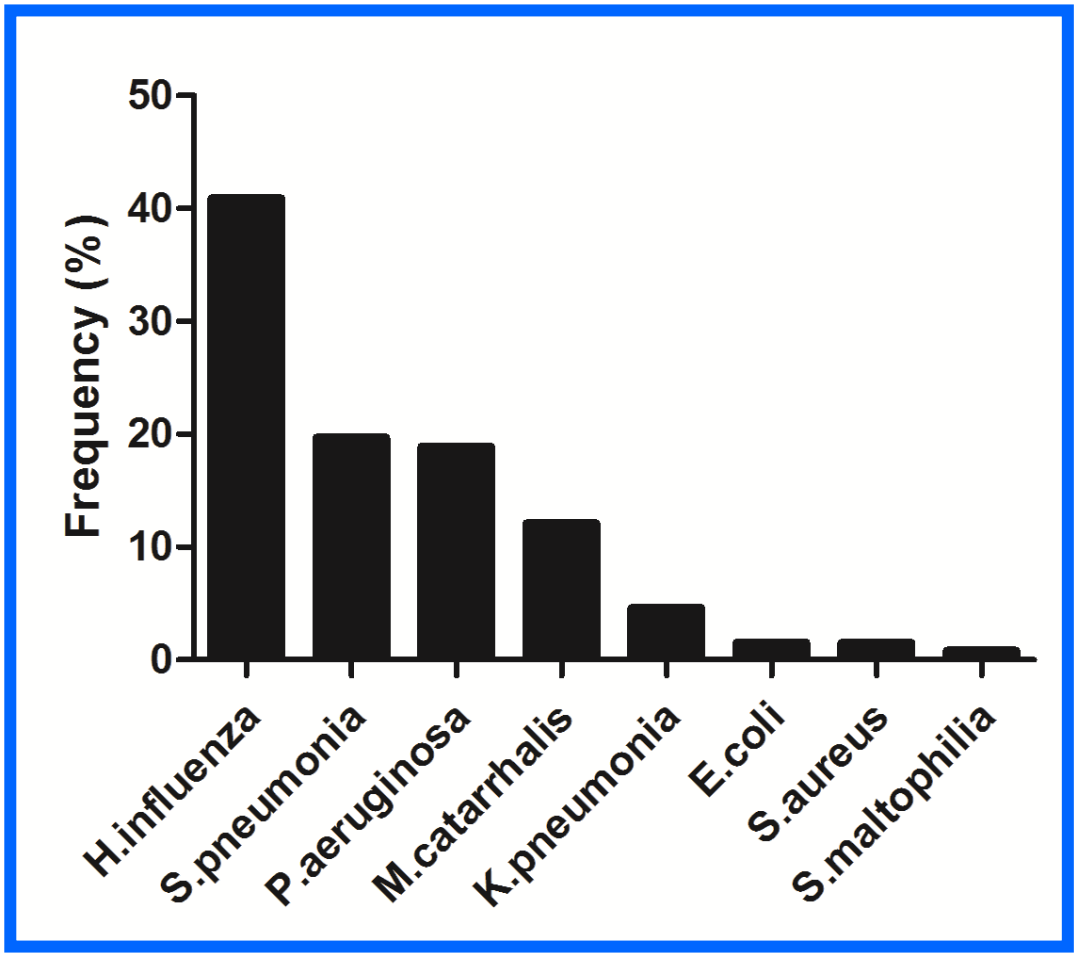



**Figure 1.** Distribution of typical bacteria isolated from COPD patients with moderate exacerbation in South Korea. Our study identified potential pathogens in 34.8% (119/342) of AECOPD outpatients, with 3.8% (13/342) of patients being caused by more than one pathogen. (unpublished data).

# 모든 COPD 환자들에게 효과적인가?

- ***Even Antibiotics for the treatment of AECOPD,***

- In summary, antibiotics should be given to patients with
  1) **exacerbations of COPD who have three cardinal symptoms** – increase in dyspnea, sputum volume, and sputum purulence (Evidence B)
  2) **have two of the cardinal symptoms, if increased purulence of sputum is one** of the two symptoms (Evidence C)
  3) **require mechanical ventilation** (invasive or noninvasive) (Evidence B).
- The recommended length of antibiotic therapy is usually 5-10 days (Evidence D).

GOLD 2015.

The frequent exacerbator with/without suspicious chronic bacterial colonization could be a candidates for prophylactic antibiotics treatments.

# Exacerbation

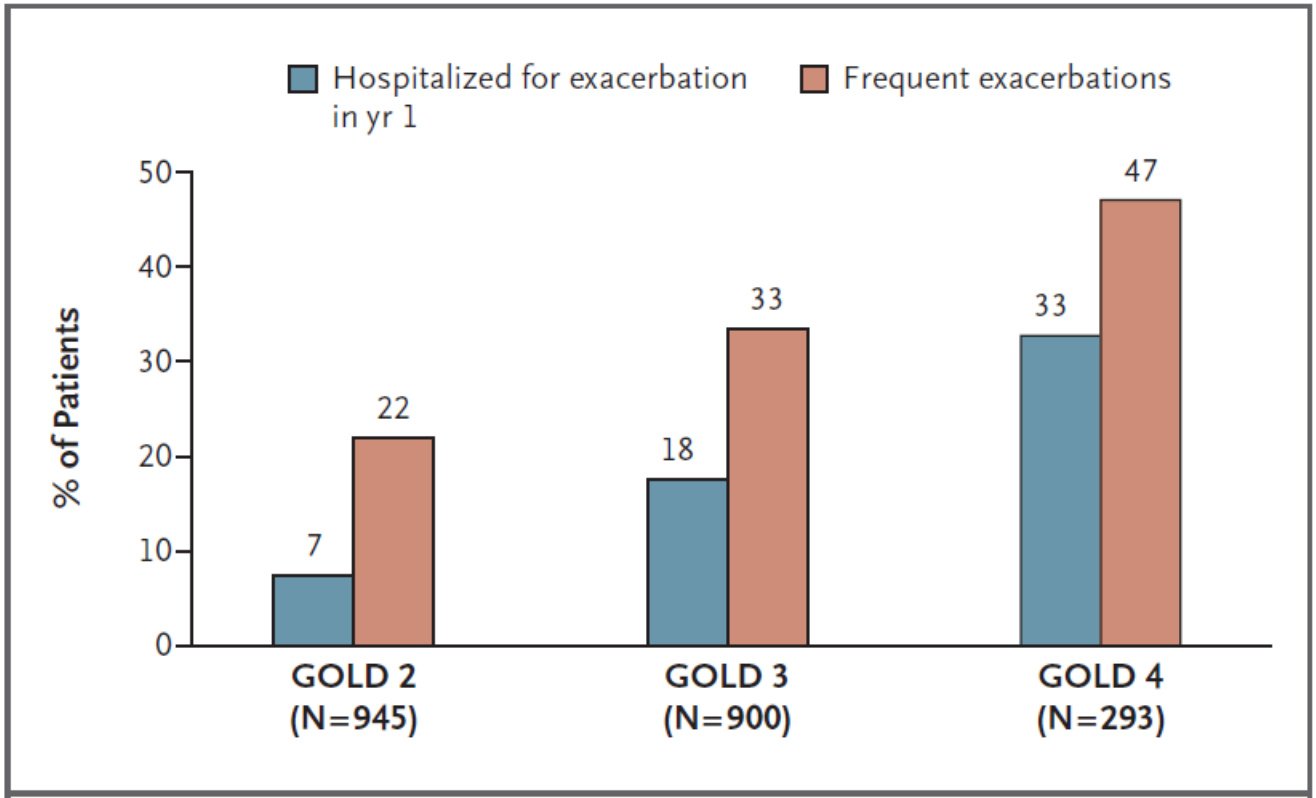



**Figure 1.** Association of Disease Severity with the Frequency and Severity of Exacerbations during the First Year of Follow-up in Patients with Chronic Obstructive Pulmonary Disease.

Hurst JR et al. NEJM. 2011

# Chronic bronchitis phenotype

- N=1,061, GOLD II-IV, COPDgene study

| Variable | CB+ (N=290) | CB− (N=771) | *P* Value |
|---|---|---|---|
| Symptoms and quality of life | | | |
| MMRC dyspnea score[a] | 3 (2-4) | 2 (1-3) | <.0001[b] |
| SGRQ, total | 49.9 ± 19.7 | 36.6 ± 20.0 | <.0001[b] |
| SGRQ, respiratory | 62.5 ± 19.0 | 38.0 ± 22.4 | <.0001[b] |
| Nasal symptoms, % | 69.3 | 53.4 | <.0001[b] |
| Ocular symptoms, % | 52.8 | 40.2 | <.0001[b] |
| Wheezing, % | 86.5 | 67.6 | <.0001[b] |
| Awakened by cough, % | 45.9 | 19.1 | <.0001[b] |
| Awakened by dyspnea, % | 39.3 | 24.4 | <.0001[b] |
| Exacerbations in the previous year | | | |
| Total exacerbations, No./pt | 1.21 ± 1.62 | 0.63 ± 1.12 | .027[b] |
| History of severe exacerbations, % | 26.6 | 20.0 | .024[b] |
| Radiology | | | |
| % Emphysema[c] | 14.2 ± 13.0 | 16.0 ± 13.4 | .212 |
| % Gas trapping | 42.0 ± 20.0 | 42.8 ± 20.3 | .593 |
| Total lung capacity,[d] L | 6.30 ± 1.50 | 5.88 ± 1.40 | .0004[b] |
| Functional residual capacity,[d] L | 4.22 ± 1.19 | 3.92 ± 1.28 | .002[b] |
| Mean segmental WA%[e] | 63.2 ± 2.9 | 62.6 ± 3.1 | .013[b] |
| Mean segmental AWT,[e] mm | 1.60 ± 0.21 | 1.60 ± 0.22 | .700 |
| Pi10,[d] mm | 3.800 ± 0.129 | 3.798 ± 0.126 | .816 |

Kim V et al. Chest 2011

# 대규모 연구의 입적 기준 (1)

**Eligible participants**

- >= 40 years of age
- clinical diagnosis of COPD
  - smoking history of at least 10 pack-year
  - post-BD FEV1/FVC <70%, and post-BD FEV1 <80%
- **Either on continuous supplemental oxygen OR Received systemic glucocorticoids within the previous year**
- **ER visit or hospitalized due to AECOPD**

**Exclusion criteria**

- Asthma
- Resting heart rate >100 bpm
- QTc > 450 msec
- Medications that prolong the QTc or associated with torsades de pointes (with the exception of amiodarone)
- Hearing impairment by audiometric testing.

Albert RK et al. NEJM 2013.

# Drugs increase QTc interval

- Antiarrhythmics class IA

  quinidine, hydroquinidine, disopyramide

- Antiarrhythmics class III

  amiodarone, sotalol, dofetilide, ibutilide

- Neuroleptics

  phenothiazines, pimozide, sertindole, haloperidol, sultopride

- Tricyclic antidepressive agents

- **Certain antimicrobials**

  sparfloxacin, IV erythromycin, pentamidine

- Antimalarials : halofantrine

- **Antihistamines** :terfenadine, astemizole, mizolastine

- **others** : cisapride, vincamine IV, bepridil, diphemanil

# 대규모 연구의 입적 기준 (2)

**Inclusion criteria**

Male or female out-patients, aged ≥ 45 years

**Chronic bronchitis**

Pre-BD $FEV_1 \leq 80\%$ , $FEV_1/FVC \leq 70\%$ predicted

**Sputum production, on most days, even when exacerbation-free**

**At least 2 (requiring antibiotics and/or systemic steroid administr ation) acute exacerbation episodes during the last 12 mo.**

Smoking history >= 20 pack-years

Ability to complete questionnaires and diary as required

Sethi et al. Respir Res 2010.

# 대규모 연구의 입적 기준

**Exclusion criteria**

Known hypersensitivity to moxifloxacin or other quinolones
History of tendon disease/disorder
Known congenital or documented-acquired QT prolongation
; uncorrected hypokalemia, clinically relevant bradycardia
; clinically relevant heart failure with reduced EF
; previous history of symptomatic arrhythmias
; concomitant use of any drugs reported to increase the QT interval
Female with postmenopausal < 1 year, or not on acceptable birth control
Any known disease or condition with a life-expectancy < 1 year
Severe hepatic impairment and/or a transaminase level > 5 times normal
Known bronchial carcinoma, pulmonary tuberculosis, asthma, bronchiectasis
Active participation in intensive pulmonary rehabilitation programs
Known history of chronic colonization of pathogen resistant to moxifloxacin
Systemic or inhaled antibiotic therapy during the 6 weeks prior to screening

Sethi et al. Respir Res 2010.

# 모든 항균제가 유사한 효과를 보이는가?

- The choice of the antibiotic should be **based on the local bacterial resistance pattern**.

- Usually initial empirical treatment is an aminopenicillin with or without clavulanic acid, macrolide, or tetracycline.

- The development of new antibiotics and drug resistance
  → Changes in the commonly used antibiotics
  → Use of new generation macrolide or respiratory fluoroquinolone

# Acute exacerbation of chronic bronchitis

| Study or subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight % | IV, fixed SMD (95%CI) | Year |
|---|---|---|---|---|---|---|---|---|---|
| **Tetracyclines** | | | | | | | | | |
| Moyes and Kershaw[29] | 1.93 | 0.0 | 27 | 2.19 | 0.0 | 31 | | Not estimable | 1957 |
| Buchanan et al.[28] | 0.33 | 0.48 | 21 | 1.13 | 1.19 | 15 | 3.0 | −0.92 (−1.62–−0.22) | 1958 |
| Francis and Spicer,[25] arm 1 | 1.07 | 0.51 | 79 | 1.04 | 0.7 | 37 | 9.7 | 0.05 (−0.34–0.44) | 1960 |
| Pridie et al.,[26] arm 1 | 1.12 | 1.26 | 25 | 0.91 | 0.93 | 16 | 3.7 | 0.18 (−0.45–0.81) | 1960 |
| Djajadiningrat et al.,[23] arm 1 | 0.86 | 1.13 | 29 | 1.15 | 1.07 | 13 | 3.4 | −0.26 (−0.91–0.40) | 1964 |
| Fletcher and Oldham[22] | 3.04 | 3.09 | 181 | 3.45 | 3.08 | 192 | 35.8 | −0.13 (−0.34–0.07) | 1966 |
| Johnston et al.[24] | 2.1 | 2.17 | 21 | 5.1 | 6.14 | 17 | 3.4 | −0.67 (−1.33–−0.01) | 1969 |
| **Subtotal (95%CI)** | | | **383** | | | **321** | **59.1** | **−0.16 (−0.32–−0.00)** | |
| Heterogeneity: $\chi^2 = 9.24$, df = 5 ($P = 0.10$); $I^2 = 46\%$ | | | | | | | | | |
| Test for overall effect: $Z = 1.99$ ($P = 0.05$) | | | | | | | | | |
| **Penicillins** | | | | | | | | | |
| Francis and Spicer,[25] arm 2 | 0.92 | 0.84 | 73 | 1.04 | 0.7 | 37 | 9.4 | −0.15 (−0.55–0.25) | 1960 |
| Pridie et al.,[26] arm 2 | 0.96 | 1.14 | 25 | 0.91 | 0.93 | 16 | 3.8 | 0.05 (−0.58–0.67) | 1960 |
| Johnston et al.[20] | 0.5 | 0.62 | 18 | 0.61 | 0.7 | 18 | 3.5 | −0.16 (−0.82–0.49) | 1961 |
| Djajadiningrat et al.,[23] arm 2 | 1.1 | 1.11 | 31 | 1.4 | 1.06 | 15 | 3.9 | −0.27 (−0.89–0.35) | 1964 |
| **Subtotal (95%CI)** | | | **147** | | | **86** | **20.5** | **−0.14 (−0.41–0.13)** | |
| Heterogeneity: $\chi^2 = 0.51$, df = 3 ($P = 0.92$); $I^2 = 0\%$ | | | | | | | | | |
| Test for overall effect: $Z = 1.01$ ($P = 0.31$) | | | | | | | | | |
| **Others** | | | | | | | | | |
| Darke et al.[18] | 2.5 | 0.0 | 18 | 3.55 | 0.0 | 20 | | Not estimable | 1972 |
| Davies and Darke[17] | 0.83 | 0.97 | 110 | 1.43 | 1.36 | 108 | 20.3 | −0.51 (−0.78–−0.24) | 1978 |
| Liippo et al.[16] | 0.6 | 0.0 | 13 | 0.6 | 0.0 | 11 | | Not estimable | 1987 |
| **Subtotal (95%CI)** | | | **141** | | | **139** | **20.3** | **−0.51 (−0.78–−0.24)** | |
| Heterogeneity: Not applicable | | | | | | | | | |
| Test for overall effect: $Z = 3.68$ ($P = 0.0002$) | | | | | | | | | |
| **Total (95%CI)** | | | **671** | | | **546** | **100.0** | **−0.23 (−0.35–−0.11)** | |
| Heterogeneity: $\chi^2 = 14.98$, df = 10 ($P = 0.13$); $I^2 = 33\%$ | | | | | | | | | |
| Test for overall effect: $Z = 3.65$ ($P = 0.0003$) | | | | | | | | | |
| Test for subgroup differences: $\chi^2 = 5.22$, df = 2 ($P = 0.07$), $I^2 = 61.7\%$ | | | | | | | | | |

A

IV, fixed SMD 95%CI

Tetracyclin
Oxatetracycline

Penicillin V
Penethicillin

Sulramethopyrazine
Trimethoprime

−2 −1 0 1 2

Favours antibiotics Favours placebo

# Cochrane review 2013.

**Antibiotics versus placebo for COPD (data from pulsed and continuous courses of antibiotics presented in the same table)**

**Patient or population:** Adults (aged 40 or over) with COPD presenting with 1 or more exacerbations in the previous year. The 2 larger studies (Albert 2011; Sethi 2010) recruited patients who required systemic steroids or antibiotics for exacerbations or patients on supplemental oxygen
**Settings:** Outpatients presenting to hospital clinics
**Intervention:** Administration of an oral prophylactic antibiotic continuously or intermittently
**Comparison:** Administration of a placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control | Antibiotics versus placebo | | | | |
| **Number of people with one or more exacerbations** | **60 per 100** | **49 per 100** (41 to 58) | **OR 0.64** (0.45 to 0.9) | 2411 (4 studies) | ⊕⊕⊕◯ **moderate**[1] | The four studies looked at a different antibiotics (azithromycin and moxifloxacin) and the trial by Albert 2011 is on continuous antibiotics while Sethi 2010 trial is on pulsed antibiotics. Therefore there is clinical heterogeneity in the combined results and we downgraded by one point for inconsistency |
| **Number of people with one or more exacerbations - Continuous antibiotics** Follow-up: 6 to 12 months | **69 per 100** | **55 per 100** (46 to 63) | **OR 0.55** (0.39 to 0.77) | 1262 (3 studies) | ⊕⊕⊕⊕ **high** | |
| **Number of people with one or more exacerbations - Pulsed antibiotics** Follow-up: 18 months | **51 per 100** | **47 per 100** (42 to 53) | **OR 0.87** (0.69 to 1.09) | 1149 (1 study) | ⊕⊕⊕◯ **moderate**[2] | |

# 부작용의 발생은 경미한가?



- 청력 이상 : macrolides

- 부정맥 및 심혈관계 위험성 : macrolides, fluoroquinolones

  고령, 여성, 심질환 (심부전, 좌심실비대)

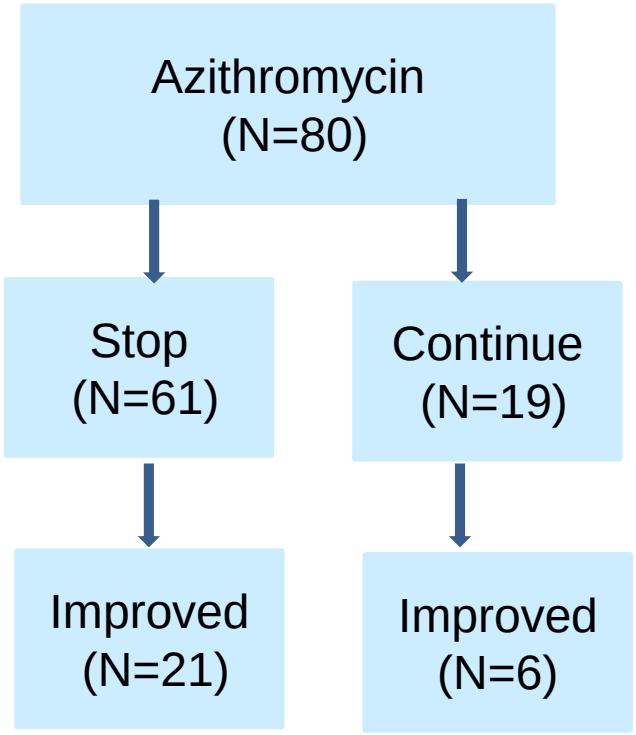
  전해질 불균형( $K^{+}$, $Mg^{2+}$)

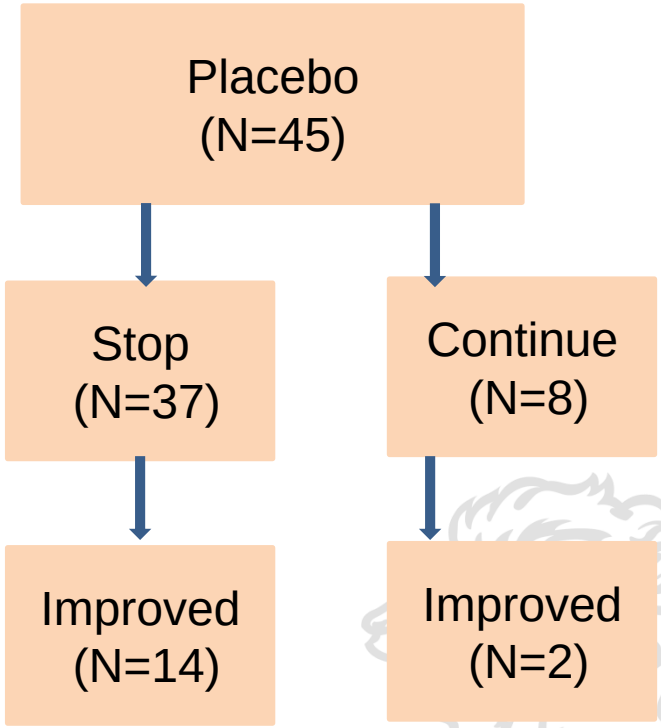
  복합 약물 처방 (QTc 간격 증가 가능성)

  과거 부정맥 발생

# 청력 이상

- Audiogram confirmed hearing decrement
  : 140 (25%) of azithromycin group vs 100 (20%) of placebo group (p=0.04).




Albert RK et al. NEJM 2011.

# Fluoroquinolone and macrolide induced arrhythmia cases

**Table 3** Summary of case reports of fluoroquinolone and macrolide-induced arrhythmia

| | Fluoroquinolones (34) | Macrolides (42) | *P* value |
|---|---|---|---|
| Drugs (Number of cases) | Ciprofloxacin (12)<br>Gatifloxacin (6)<br>Levofloxacin (9)<br>Sparfloxacin (2)<br>Moxifloxacin (5) | Erythromycin (21)<br>Azithromycin (9)<br>Clarithromycin (9)<br>Roxithromycin (3) | |
| Patient characteristics | | | |
| Age (median) Years | 68 | 63 | 0.36 |
| Gender (F) | 64.7% | 64.2% | 0.84 |
| Heart disease | 70.6% | 69% | 0.90 |
| Renal impairment | 24% | 26.2% | 0.79 |
| Electrolyte imbalance | 20.6% | 19% | 0.86 |
| Baseline QTc (median) ms | 444 | 440 | 0.82 |
| Bradycardia | 26.5% | 23.8% | 0.79 |
| Drug interaction | 50% | 47.6% | 0.84 |
| Antiarrhythmic | 29.4% | 26.1% | 0.75 |
| Antipsychotic | 14.7% | 5% | 0.23 |
| Intravenous | 32.4% | 42.6% | 0.34 |
| Outcome | | | |
| Max QTc (median) ms | 590 | 603 | 0.42 |
| TdP | 79% | 71.4% | 0.42 |
| Death | 9% | 9.5% | 0.68 |
| Time to diagnosis (median) days | 2 | 3 | 0.53 |

# Azithromycin use and cardiovascular death

**Table 1.** Demographic and Clinical Characteristics of Patients at the Time That the Prescriptions for the Study Antibiotics Were Filled and at the Beginning of the Control Period for Persons Who Received No Antibiotic Treatment.*

| Characteristic | No Antibiotic | Amoxicillin† | Ciprofloxacin | Levofloxacin | Azithromycin |
|---|---|---|---|---|---|
| Prescriptions (no.) | 1,391,180 | 1,348,672 | 264,626 | 193,906 | 347,795 |
| Mean age (yr) | 48.6 | 47.7 | 50.5 | 51.5 | 48.6 |
| Female sex (%) | 77.5 | 73.3 | 75.5 | 73.5 | 77.5 |
| Coexisting conditions (%) | | | | | |
| Heart failure | 4.3 | 3.9 | 5.3 | 6.8 | 4.3 |
| Chronic obstructive pulmonary disease | 5.5 | 4.6 | 5.1 | 6.8 | 5.4 |

**Table 2.** Cumulative Incidence of Death among Patients during a 5-Day Course of Azithromycin, as Compared with Persons Who Received No Antibiotic Treatment and Patients Who Took Amoxicillin, According to Cause of Death.

| Deaths | No Antibiotic | Amoxicillin | Azithromycin |
|---|---|---|---|
| **Total cardiovascular** | | | |
| No. | 41 | 42 | 29 |
| Cumulative incidence (no./1 million courses) | 29.8 | 31.5 | 85.2 |
| Hazard ratio (95% CI) | 1 | 0.95 (0.55–1.63) | 2.88 (1.79–4.63) |
| P value | | 0.85 | <0.001 |
| **Sudden cardiac** | | | |
| No. | 33 | 29 | 22 |
| Cumulative incidence (no./1 million courses) | 24.0 | 21.8 | 64.6 |
| Hazard ratio (95% CI) | 1 | 0.85 (0.45–1.60) | 2.71 (1.58–4.64) |
| P value | | 0.62 | <0.001 |
| **Other cardiovascular** | | | |
| No. | 8 | 13 | 7 |
| Cumulative incidence (no./1 million courses) | 5.8 | 9.7 | 20.6 |
| Hazard ratio (95% CI) | 1 | 1.30 (0.44–3.84) | 3.54 (1.28–9.76) |
| P value | | 0.64 | 0.01 |

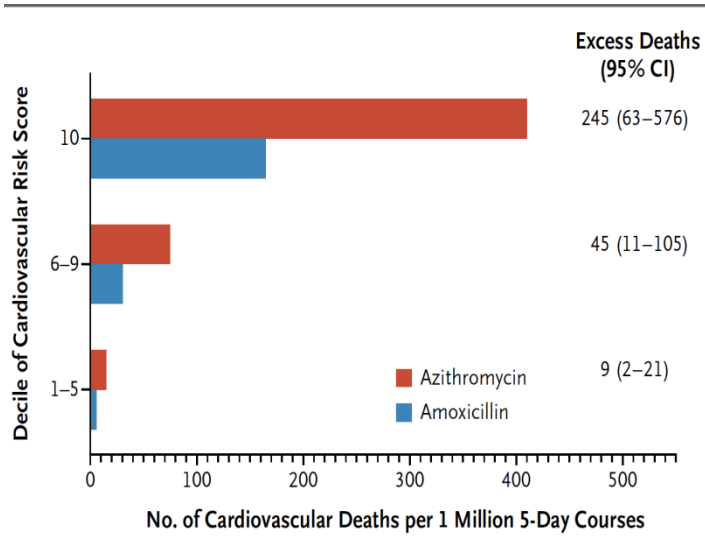



**Figure 3.** Excess Risk of Cardiovascular Death with Azithromycin as Compared with Amoxicillin, According to Decile of Cardiovascular Risk Score.

- Azithromycin vs amoxicillin 5 days

Ray WA. NEJM 2012

**Table 2. Risk of Death from Cardiovascular Causes with Azithromycin Use as Compared with No Antibiotic Use or Use of Penicillin V.**

| Antibiotic Use* | Propensity-Score–Matched Analysis | | | Propensity-Score–Adjusted Analysis | | |
|---|---|---|---|---|---|---|
| | Azithromycin (N = 1,102,050) | No Antibiotic (N = 1,102,050) | Rate Ratio (95% CI) | Azithromycin (N = 1,102,419) | Penicillin V (N = 7,364,292) | Rate Ratio (95% CI) |
| Current use | | | | | | |
| No. of events | 17 | 6 | | 17 | 146 | |
| No./1000 patient-yr | 1.1 | 0.4 | 2.85 (1.13–7.24) | 1.1 | 1.5 | 0.93 (0.56–1.55) |
| Recent use | | | | | | |
| No. of events | 7 | 5 | | 7 | 74 | |
| No./1000 patient-yr | 0.5 | 0.3 | 1.44 (0.46–4.54) | 0.5 | 0.8 | 0.75 (0.34–1.62) |

**Table 1. Baseline Characteristics of Persons with Azithromycin Use Included in Analyses, as Compared with Persons with No Antibiotic Use and Persons with Penicillin V Use.**

| Characteristic | Propensity-Score–Matched Cohort | | | Unmatched Cohort | | |
|---|---|---|---|---|---|---|
| | Azithromycin (N = 1,102,050) | No Antibiotic (N = 1,102,050) | P Value | Azithromycin (N = 1,102,419) | Penicillin V (N = 7,364,292) | P Value |
| Age — yr | 39.7±13.9 | 39.5±13.8 | <0.001 | 39.7±13.9 | 42.0±12.8 | <0.001 |
| Male sex — no. (%) | 383,973 (35) | 390,485 (35) | <0.001 | 384,279 (35) | 2,822,420 (38) | <0.001 |
| Acute coronary syndrome — no. (%) | 13,850 (1) | 13,686 (1) | 0.32 | 13,860 (1) | 114,441 (2) | <0.001 |
| Other ischemic heart disease — no. (%) | 29,316 (3) | 29,052 (3) | 0.27 | 29,358 (3) | 226,568 (3) | <0.001 |
| Heart failure or cardiomyopathy — no. (%) | 7,384 (1) | 7,301 (1) | 0.49 | 7,388 (1) | 56,850 (1) | <0.001 |
| Cerebrovascular disease — no. (%) | 14,098 (1) | 13,837 (1) | 0.12 | 14,098 (1) | 116,359 (2) | <0.001 |
| Renal disease — no. (%) | 6,852 (1) | 6,835 (1) | 0.88 | 6,854 (1) | 52,035 (1) | <0.001 |
| Chronic lung disease — no. (%) | 90,675 (8) | 88,131 (8) | <0.001 | 90,980 (8) | 464,349 (6) | <0.001 |
| Cancer — no. (%) | 31,836 (3) | 31,566 (3) | 0.28 | 31,859 (3) | 224,943 (3) | <0.001 |

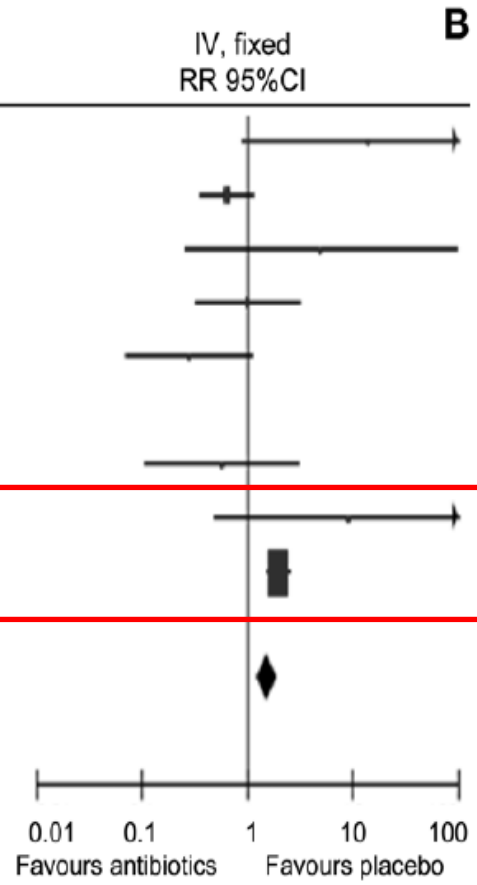
# 항균제 내성의 발생은 무시할 만 한가?



| Study or subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight % | IV, fixed RR (95%CI) | Year |
|---|---|---|---|---|---|---|---|
| Murdoch et al.,[27] arm 1 | 6 | 11 | 0 | 12 | 5.4 | 14.08 (0.88–224.16) | 1959 |
| Murdoch et al.,[27] arm 2 | 13 | 35 | 11 | 19 | 21.5 | 0.64 (0.36–1.14) | 1959 |
| Johnston et al.[20] | 2 | 18 | 0 | 18 | 4.9 | 5.00 (0.26–97.37) | 1961 |
| Johnston et al.[24] | 5 | 21 | 4 | 17 | 15.4 | 1.01 (0.32–3.19) | 1969 |
| Liippo et al.[16] | 2 | 13 | 6 | 11 | 13.1 | 0.28 (0.07–1.13) | 1987 |
| Banerjee et al.[15] | 0 | 31 | 0 | 36 | | Not estimable | 2005 |
| Seemungal et al.[14] | 2 | 23 | 3 | 20 | 10.7 | 0.58 (0.11–3.13) | 2008 |
| Sethi et al.[13] | 4 | 569 | 0 | 580 | 5.0 | 9.17 (0.50–170.00) | 2010 |
| Albert et al.[11] | 38 | 47 | 44 | 108 | 24.0 | 1.98 (1.52–2.59) | 2011 |
| **Total (95%CI)** | **72** | **768** | **68** | **821** | **100.0** | **1.54 (1.23–1.94)** | |

Heterogeneity: $\chi^2 = 24.50$, df = 7 ($P = 0.0010$); $I^2 = 71\%$

Test for overall effect: $Z = 3.70$ ($P = 0.0002$)




Lee JS. IJTLD 2013.

# Macrolide-resistant M. pneumoniae



Table 1. MICs of macrolide antimicrobial drugs for 123 *Mycoplasma pneumoniae* strains in a study of macrolide resistance, South Korea, 2000–2011*

| | Strains with 23S rRNA mutation, n = 69 | | | Strains without 23S rRNA mutation, n = 54 | | |
|---|---|---|---|---|---|---|
| Macrolides | Range | $MIC_{50}$ | $MIC_{90}$ | Range | $MIC_{50}$ | $MIC_{90}$ |
| Erythromycin | 2 to >128 | 16 | 128 | 0.001 to 0.004 | 0.001 | 0.002 |
| Clarithromycin | 8 to >128 | 64 | 128 | 0.001 to 0.002 | 0.001 | 0.002 |
| Roxithromycin | 0.008 to 128 | 8 | 32 | 0.001 to 0.008 | 0.001 | 0.004 |
| Azithromycin | 1 to 64 | 8 | 16 | 0.001 to 0.001 | 0.001 | 0.001 |
| Josamycin | 1 to 8 | 4 | 8 | 0.001 to 0.016 | 0.001 | 0.008 |

Table 2. MICs of tetracyclines and fluoroquinolones for *Mycoplasma pneumoniae* strains in a study of macrolide resistance, South Korea, 2000–2011*

| | Strains with 23S rRNA mutation, n = 69 | | | Strains without 23S rRNA mutation, n = 54 | | |
|---|---|---|---|---|---|---|
| Antimicrobial drug | Range | $MIC_{50}$ | $MIC_{90}$ | Range | $MIC_{50}$ | $MIC_{90}$ |
| Tetracyclines | | | | | | |
| Tetracycline | 0.016 to 0.5 | 0.06 | 0.25 | 0.016 to 0.5 | 0.06 | 0.25 |
| Doxycycline | 0.002 to 0.125 | 0.06 | 0.06 | 0.004 to 0.125 | 0.03 | 0.06 |
| Fluoroquinolones | | | | | | |
| Levofloxacin | 0.016 to 0.5 | 0.25 | 0.25 | 0.016 to 0.5 | 0.25 | 0.5 |
| Ciprofloxacin | 0.125 to 1.0 | 0.5 | 1.0 | 0.06 to 1.0 | 0.5 | 1.0 |
| Moxifloxacin | 0.008 to 0.06 | 0.016 | 0.06 | 0.004 to 0.06 | 0.016 | 0.06 |

*$MIC_{50}$ and $MIC_{90}$ are minimum inhibitory concentrations at which 50% and 90% of the isolates, respectively, were inhibited by the drug.

Hong KB. Emer Inf Dis. 2013.

# Prevalence of macrolide-resistant M. pneumoniae



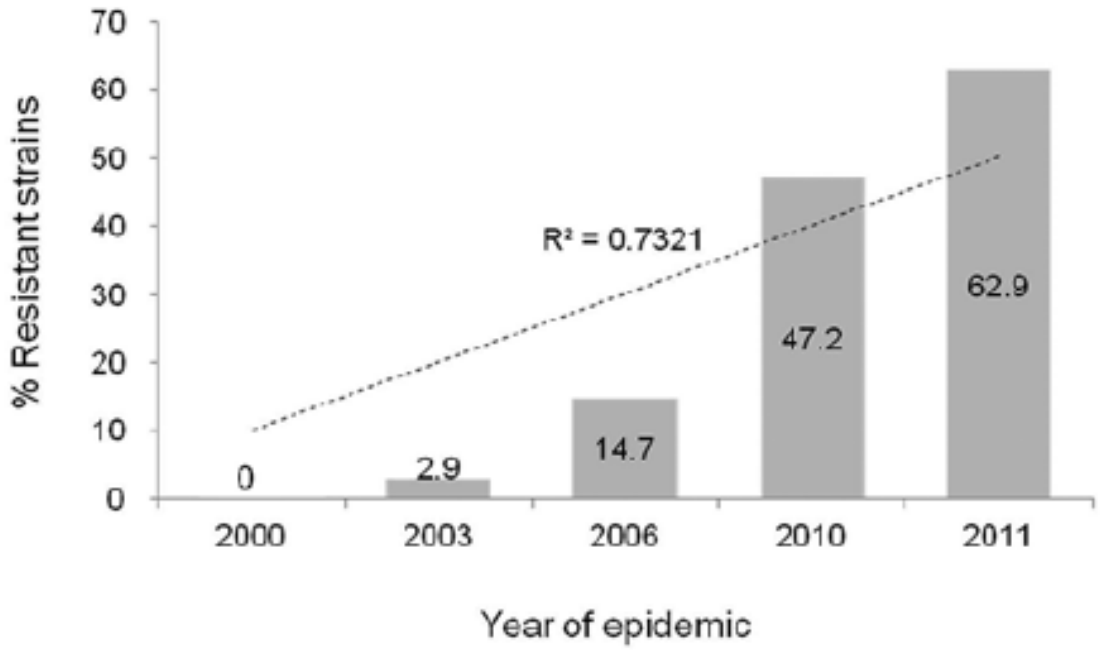



Figure. Increased prevalence of macrolide resistance of *Mycoplasma pneumoniae* strains isolated from children during epidemics of lower respiratory tract infections, South Korea, 2000–2011. During the 2000 epidemic, 0 of 30 strains were resistant, but during the epidemics of 2003 and 2006, 1 of 34 and 10 of 68 strains, respectively, showed resistance. During the 2010–2011 outbreak, 25 of 53 (2010) and 44 of 70 (2011) strains were resistant. Numbers on the bars are the percentages of resistant strains for each year.

Hong KB.
Emer Inf Dis. 2013.

# Non-tuberculous mycobacterium

- Macrolide : Essential treatment regimen in the MAC infection
- Macrolide resistance in MAC infection → treatment failure

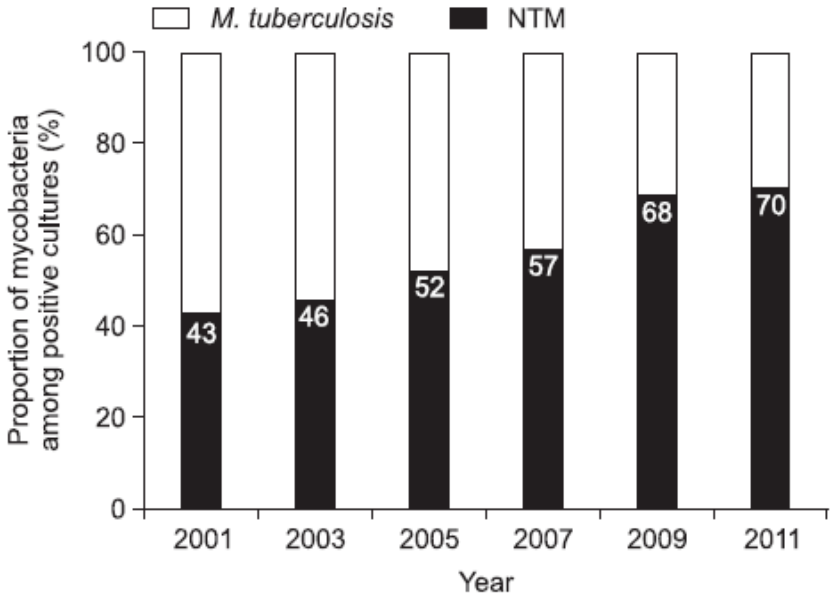



Figure 2. Changes in the proportions of *Mycobacterium tuberculosis* and nontuberculous mycobacteria (NTM) of all positive mycobacterial cultures during the study period. The proportion of NTM increased significantly.

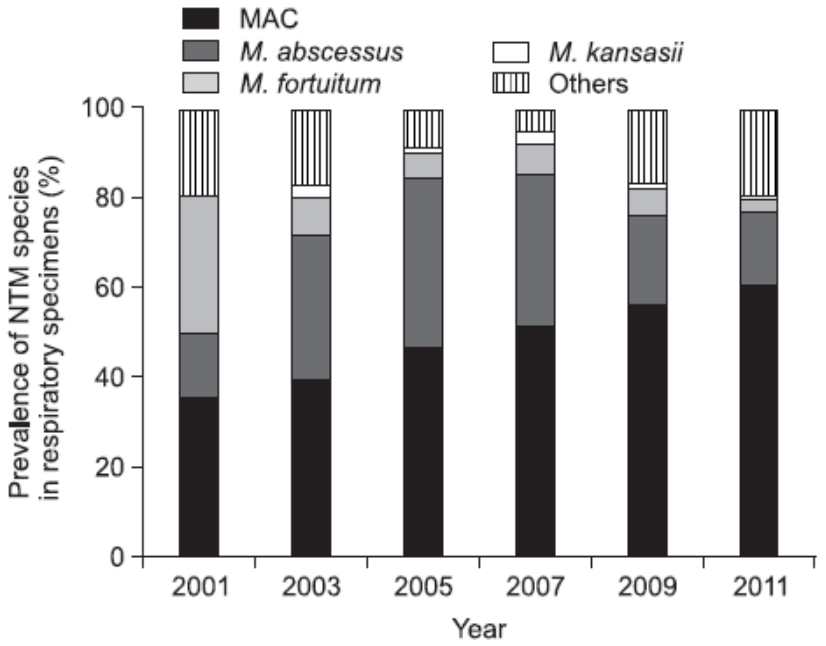
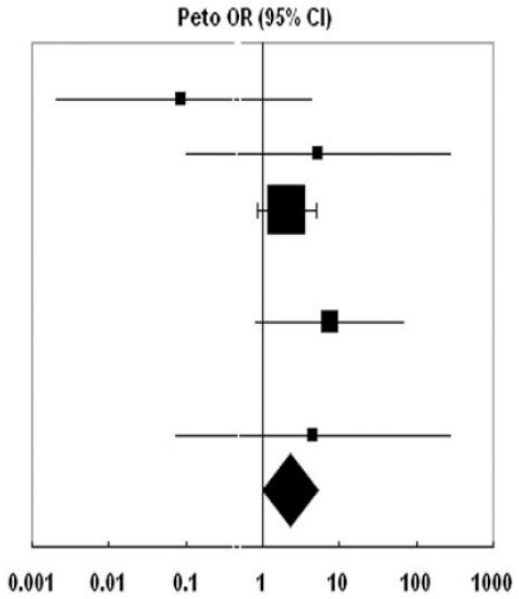



Figure 4. Prevalence of nontuberculous mycobacteria (NTM) species in respiratory specimens. *Mycobacterium avium-intracellulare* complex (MAC) and *Mycobacterium abscessus-massiliense* complex accounted for the majority of the isolated NTM species.

Koh WJ et al. TRD 2013.

# ICS and the risk of TB

| Author, Year[Ref.] [Study ID no][b] | ICS treatment Event/Total | Non-ICS treatment Event/Total | Peto OR (95% CI) | Weight, % |
|---|---|---|---|---|
| **LABA-ICS and ICS vs LABA and PL** | | | | |
| Doherty et al, 2012[20] [P04230AM4] | 0/717 | 1/479 | 0.08 (0.002-4.50) | 3.88 |
| Tashkin et al, 2012[21] [P04229AM4] | 1/634 | 0/421 | 5.28 (0.10-288.99) | 3.88 |
| Calverley et al, 2007[8] [SCO30003] | 13/3,098 | 8/3,086 | 2.09 (0.85-5.13) | 76.55 |
| **LABA-ICS vs TIO** | | | | |
| Wedzicha et al, 2008[9] [SCO40037] | 3/658 | 0/665 | 7.49 (0.78-72.14) | 12.10 |
| **LABA-ICS vs PL** | | | | |
| Zheng et al, 2007[29] [SCO100540] | 1/297 | 0/148 | 4.47 (0.07-286.68) | 3.59 |
| **Overall** | 18/5,404 | 7/4,799 | 2.29 (1.04-5.03) | 100.00 |
| Test for heterogeneity: $X^2$=4.02, df=4, P=0.404, $I^2$=0.4% | | | | |
| Test for overall effect: z= 2.06, P= 0.039 | | | | |




Risk of TB associated with ICS treatment (ICS alone and LABA-ICS) compared with non-ICS treatment (TIO, LABA, or PL) using the Peto approach. b Only trials reporting on at least one TB event were included in the meta-analysis

Chest 2014

# ICS, COPD and NTM infection

**Table 3** ORs for non-tuberculous mycobacterial pulmonary disease in northern Denmark according to the presence of chronic respiratory disease and inhaled corticosteroid use

| Exposure | Case patients (n=112) | Population controls (n=1120) | Unadjusted OR (95% CI) | Adjusted OR* (95% CI) | Adjusted OR (95% CI) for Denmark as a whole |
|---|---|---|---|---|---|
| COPD | | | | | 15.6 (11.4 to 21.5) |
| Absent | 58 (51.8) | 1053 (94.0) | 1.0 (ref.) | 1.0 (ref.) | |
| Present | 54 (48.2) | 67 (6.0) | 16.2 (9.8 to 26.6) | 13.1 (7.4 to 23.3) | |
| Present, first COPD diagnosis | | | | | |
| Within 2 years | 17/54 (31.5) | 16/67 (23.9) | 20.1 (9.0 to 44.8) | 14.7 (6.1 to 35.6) | 22.5 (13.1 to 38.5) |
| 2–5 years earlier | 15/54 (27.8) | 21/67 (31.3) | 7.9 (3.3 to 18.9) | 4.7 (1.8 to 12.4) | 16.2 (9.8 to 26.7) |
| >5 years earlier | 22/54 (40.7) | 30/67 (44.8) | 13.6 (7.2 to 25.7) | 11.6 (5.5 to 24.6) | 12.9 (8.58 to 19.4) |
| Present, with hospitalised COPD exacerbation | | | | | |
| 0 within last year | 29/54 (53.7) | 51/67 (76.1) | 11.1 (6.2 to 19.9) | 9.5 (5.0 to 18.1) | 6.3 (4.2 to 9.4) |
| 1 within last year | 7/54 (13.0) | 6/67 (8.9) | 25.8 (7.5 to 89.5) | 23.5 (6.9 to 80.0) | 44.0 (21.8 to 88.9) |
| 2 within last year | 5/54 (9.3) | 4/67 (6.0) | 21.8 (4.9 to 97.5) | 20.3 (4.1 to 101.4) | 17.5 (5.6 to 54.7) |
| ≥3 within last year | 13/54 (24.1) | 6/67 (8.9) | 53.6 (16.5 to 174.2) | 39.0 (9.1 to 167.5) | 64.5 (28.5 to 146.2) |
| Present with no history of ICS use | 13/54 (24.1) | 31/67 (46.3) | 7.9 (3.8 to 16.6) | 7.6 (3.4 to 16.8) | |
| Present with ever use of ICS | 41/54 (75.9) | 36/67 (53.7) | 24.6 (163.5 to 45.1) | 19.6 (9.7 to 39.6) | |
| Ever use of ICS | | | | | |
| Current ICS use (within 6 months) | 38/41 (92.7) | 26/36 (72.2) | 30.4 (15.9 to 58.0) | 29.1 (13.3 to 63.8) | |
| Former ICS use (>6 months ago) | 3/41 (7.3) | 10/36 (27.8) | 7.3 (1.9 to 28.6) | 3.8 (0.9 to 16.8) | |
| Current use, mean daily dose of ICS | | | | | |
| Low (0–799 μg/day over 365 days) | 15/38 (39.4) | 15/26 (57.7) | 21.9 (9.4 to 50.7) | 28.1 (10.7 to 73.4) | |
| High (800+ μg/day over 365 days) | 7/38 (18.4) | 3/26 (11.5) | 52.7 (12.1 to 230.0) | 47.5 (9.5 to 236.7) | |
| Missing dose | 16/38 (42.1) | 8/26 (30.8) | 37.5 (14.5 to 97.0) | 26.3 (8.7 to 79.0) | |
| Current use, type of ICS | | | | | |
| Beclometasone | 1/38 (2.6) | 0 | | | |
| Budenoside | 16/38 (42.1) | 15/26 (57.7) | 22.2 (9.5 to 51.8) | 19.8 (7.2 to 54.4) | |
| Fluticasone | 21/38 (55.3) | 10/26 (38.5) | 42.3 (16.6 to 107.9) | 40.8 (14.0 to 119.5) | |

Andrejak C et al. Thorax 2013.

# Co-morbidity

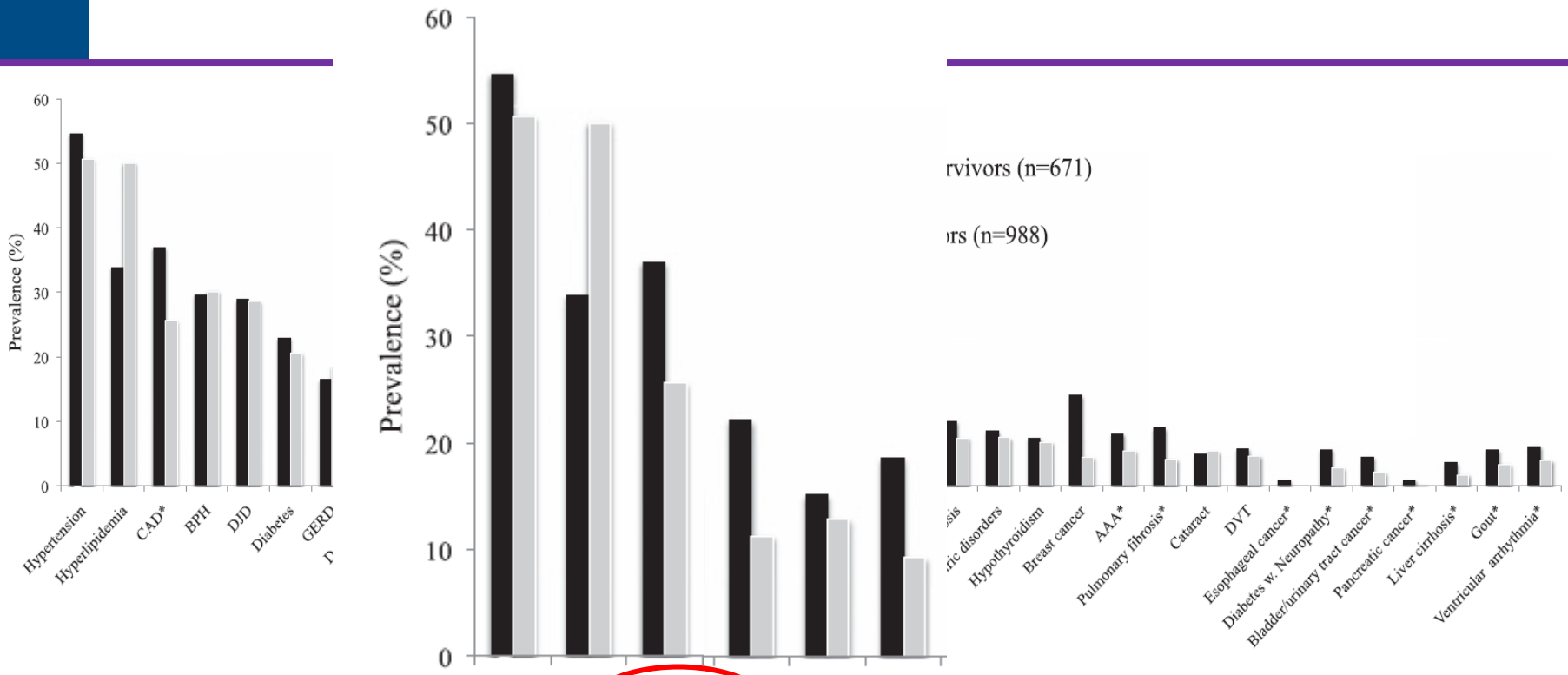



***Figure 1.*** Comorbidities with r
comorbidities with a significar
(*see* Figure E2 and Table E1 for
CHF = congestive heart failure;
thrombosis; GERD = gastroeso
heart failure.

rvivors (n=671)

ırs (n=988)

nonsurvivors (*red bars*). The figure also includes those
d with survivors regardless of their absolute prevalence
ın prostatic hypertrophy; CAD = coronary artery disease;
ınt; DJD = degenerative joint disease; DVT = deep venous
ılmonary HTN+RHF = pulmonary hypertension and right

Divo et al. AJRCCM 2012

# Multi-morbidity

Database of (n=1,751,841) in Scotland, U.K 2007

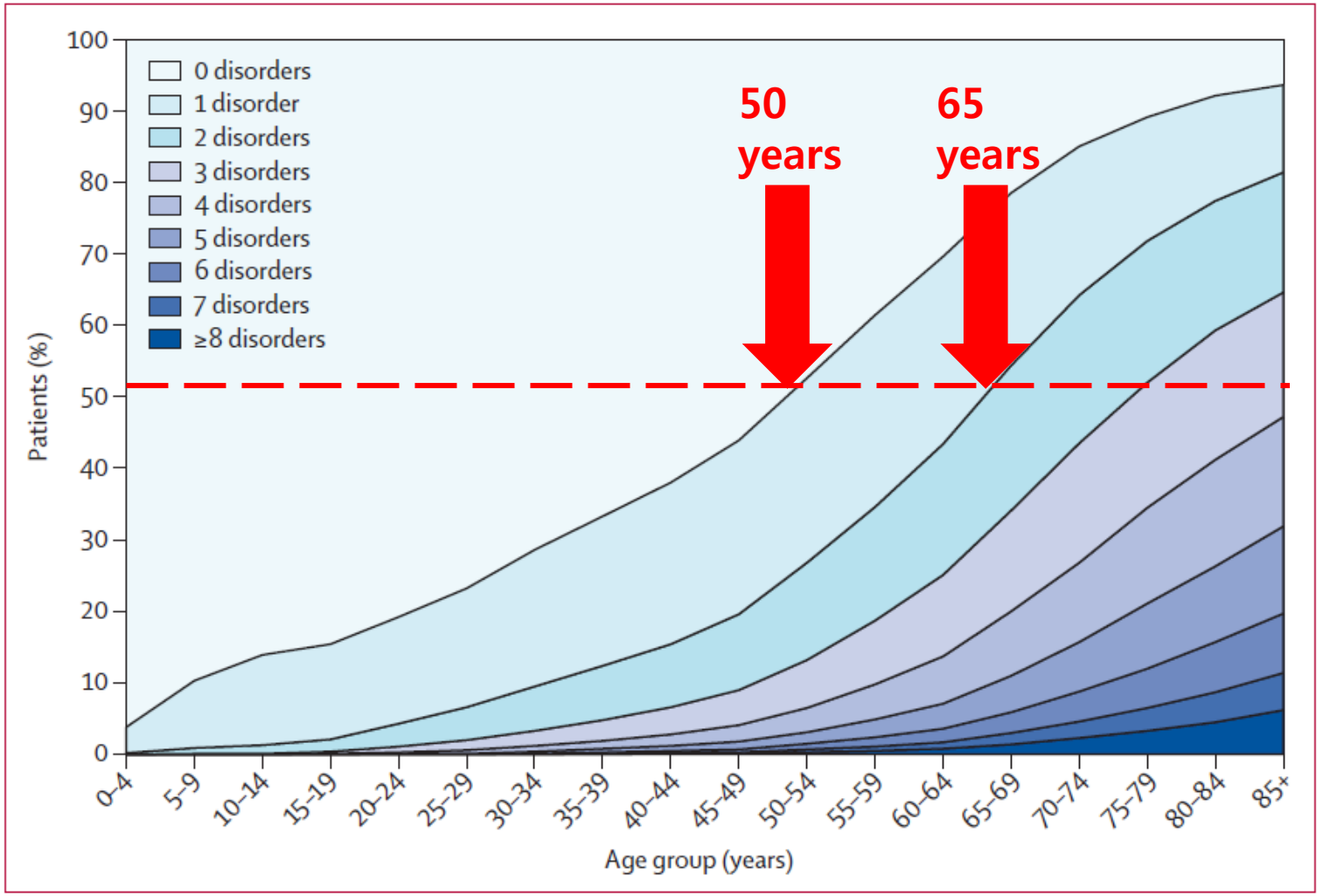



*Figure 1*: Number of chronic disorders by age-group

Barnett et al. Lancet 2012

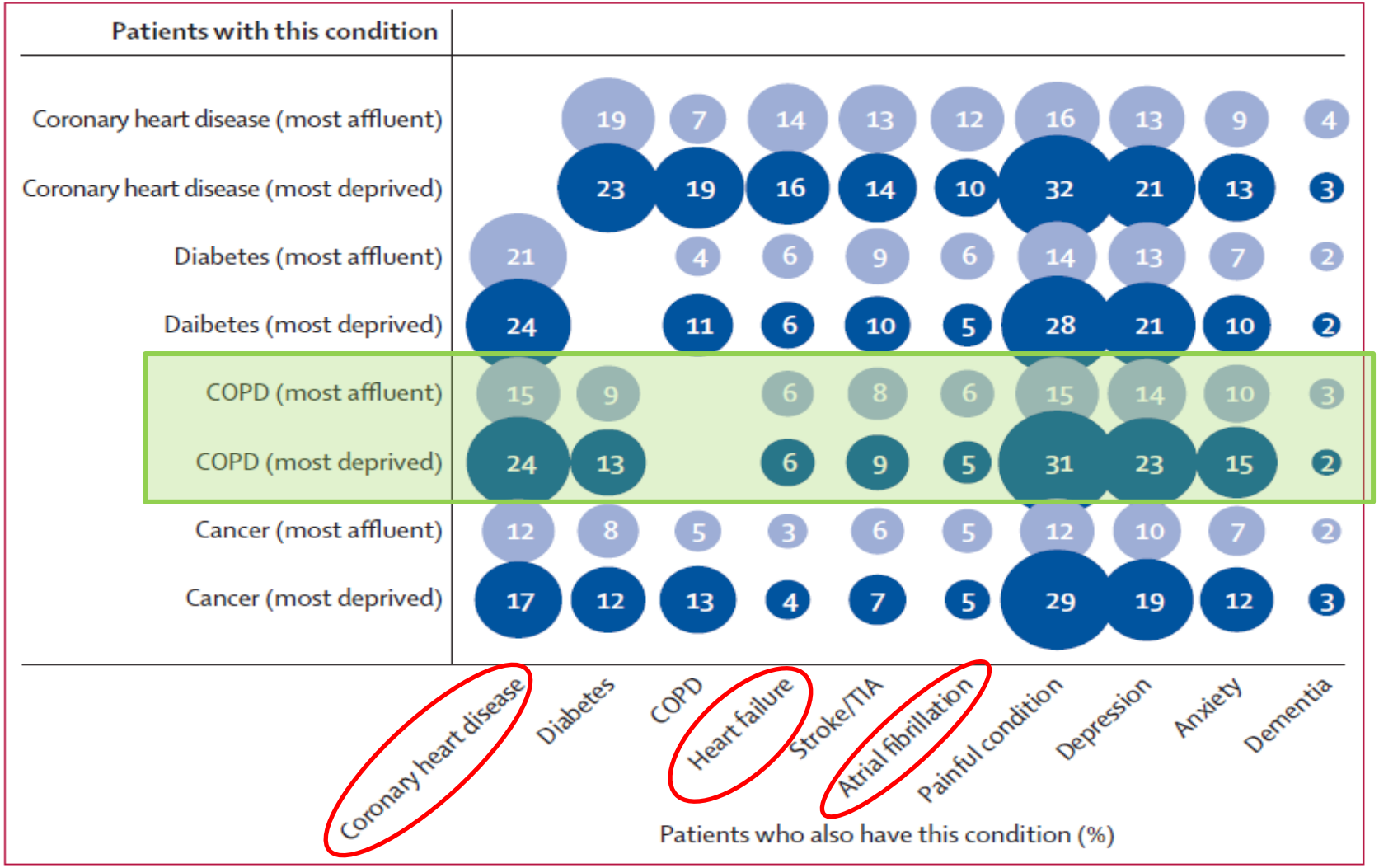



***Figure 4:*** **Selected comorbidities in people with four common, important disorders in the most affluent and most deprived deciles**

COPD=chronic obstructive pulmonary disease. TIA=transient ischaemic attack.

Barnett et al. Lancet 2012

# And, How long it could be EFFECTIVE and/or SAFE ???

- No study with “really long-term” treatment
- No study with adequate concern about economic burden
- Large differences in the CV risk among different countries
- Different susceptibility of community bacteria to various antibiotics
- The “ aging population ” problem…

# 요약 및 제언

- COPD 환자의 치료에서 급성악화의 예방은 매우 중요하며, 예방적 항균제 요법은 과거 잦은 세균성 급성 악화를 보인 환자들에서 시도되어왔다.

- 잦은 급성 악화, 중증 악화 및 만성 기관지염 동반 환자들을 대상으로 한 최근의 몇몇 대규모 무작위 대조군 연구 및 이들을 포함한 메타분석 연구들은 장기 예방적 항균제 요법의  효과에 대해 긍정적인 연구 결과들을 보여주었다.

- 그러나, 각 연구의 입적 기준은 COPD 환자 전반에 일반적으로 적용할 수 없으며, 장기간의 항균제 치료에 따라 이독성  증가 및 항균제 내성 증가 등의 부작용 또한  관찰되었다.

# 요약 및 제언

- 장기간 항균제 예방 치료에 대한 최근의 대규모 연구 결과와는 대조적으로, 실제 항균제 처방 예를 대상으로 한  후향적 분석 연구에서는 부정맥의 발생 및 심혈관계 사망률의 증가가 보고되었다.

- 치료 효과가 입증된 환자군의 조건이 매우 제한적이며, 장기간 치료의 결과에 대한 선행 연구가 없고, 중요한 부작용의 발생이 예견되므로, 경제성 및 유효성, 안정성의 포괄적인 분석이 먼저 국내에서도 이루어져야 할 것이다.

*Thank you for your attention !!*