만성기침 - 놓치지 말아야 할 것들

2021년 일선진료의를 위한 호흡기질환 심포지엄

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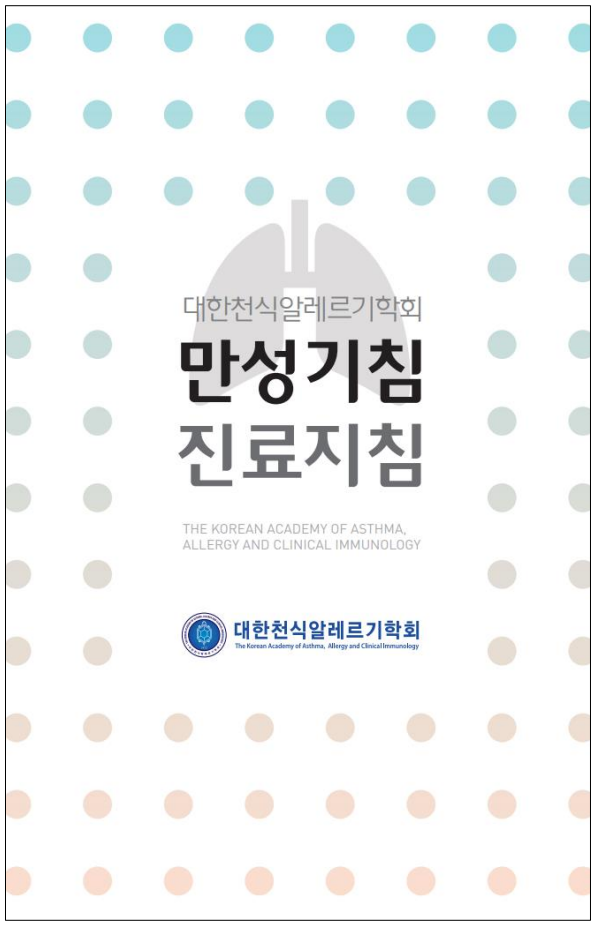
김 이 형

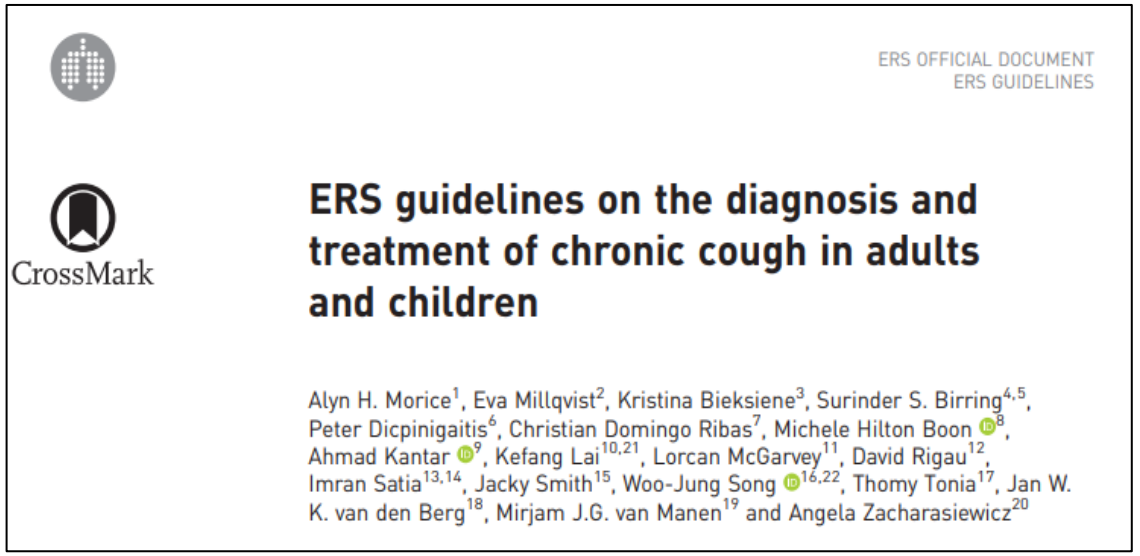
Contents

Mostly, based on Expert opinion and low-quality studies

호흡기학회 진료지침
2020



천식알레르기학회
2018



유럽호흡기학회 지침
2020

만성 기침이란?

- 자연 호전을 기대할 수 없을 정도로 오래 지속된 기침

  (성인 > 8주, 소아 > 4주)

- 만성 기침 ≠ 감기
- Unmet need : 약제 효과가 별로 없다 (50%), 확실하지 않은 진단명 (30%)*
  - 대학병원 의뢰의 10%
- More unpleasant situation in COVID-19 era : 사회적 시선

*Lung 2019:197:635

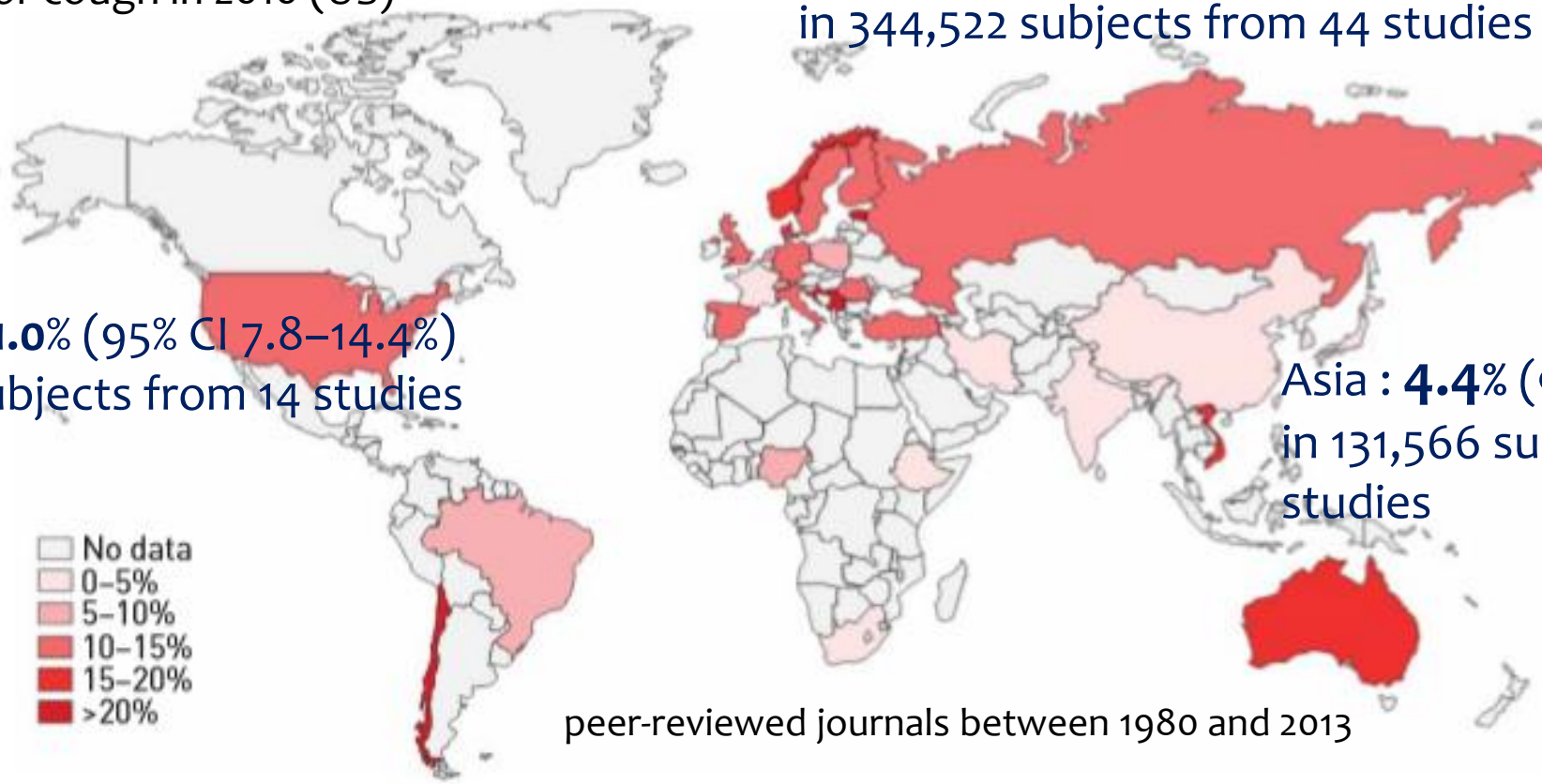
Pooled prevalence of chronic cough

30 million visits, $600 million spent on medication for cough in 2010 (US)

Europe : **12.7**% (95% CI 10.4–15.2%)
in 344,522 subjects from 44 studies

America : **11.0**% (95% CI 7.8–14.4%)
in 60,585 subjects from 14 studies

Asia : **4.4**% (95% CI 1.8–7.4%)
in 131,566 subjects from 22 studies



peer-reviewed journals between 1980 and 2013

In the meta-regression analyses, the regional differences in chronic cough prevalence were independent of smoking

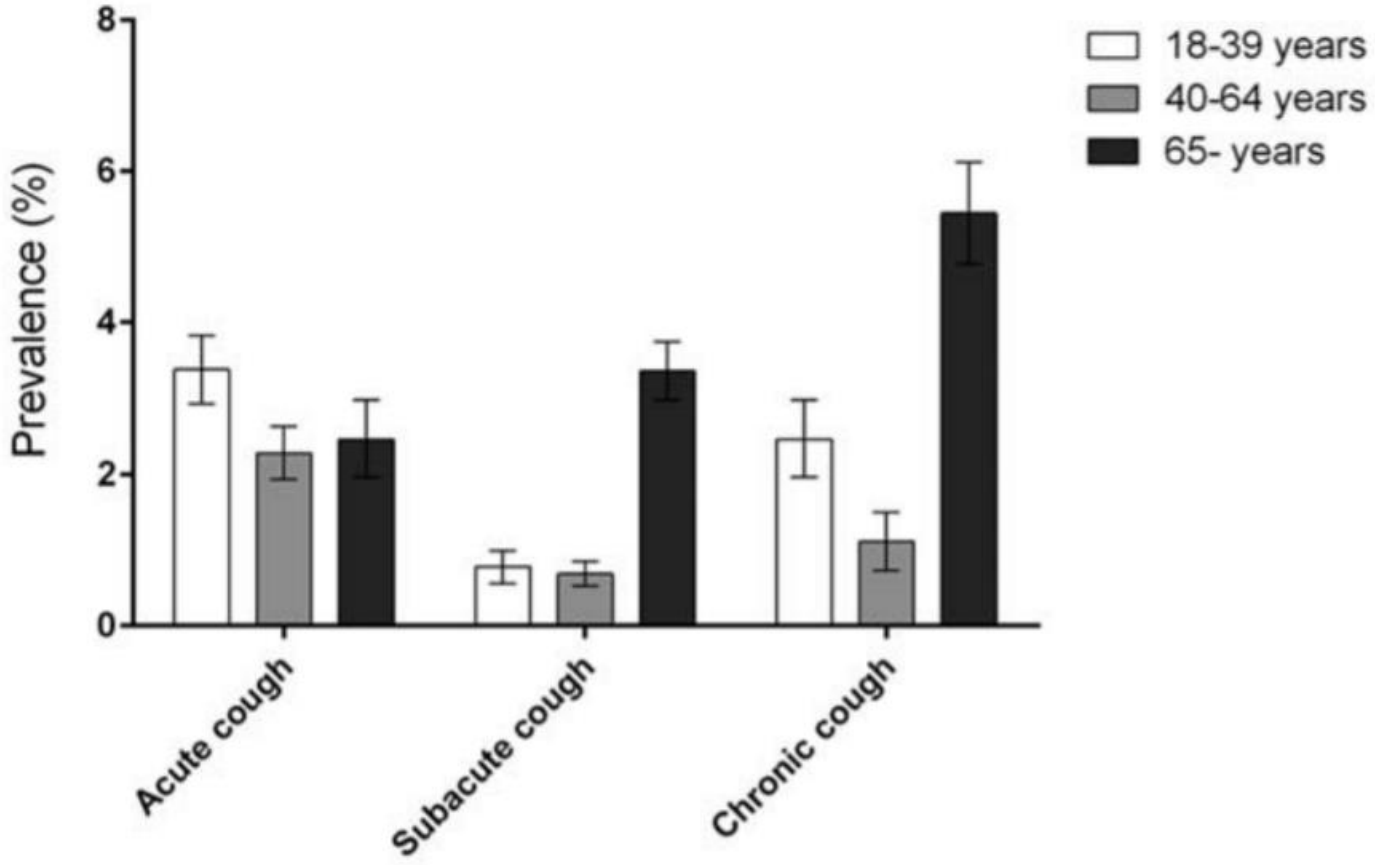
Song WJ et al, Eur Respir J 2015:45:1479

Prevalence of chronic cough in Korean community

Study	Population	Survey year	Definition of chronic cough	Cough duration	Prevalence of chronic cough
Kang et al (2017)	Participant of KNHANES (> 18 yrs)	2010-2012	Point prevalence of chronic cough (current cough lasting more than 8 weeks)	1.6% had cough lasting for more than one year	**2.6%**
Won et al (2020)	Participant of KNHANES (> 40 yrs)	2010-2016	Point prevalence of chronic cough (cough on most days for 3 months and more in the past year)	Mean duration of chronic cough: 7.8 yrs	**3.5%**

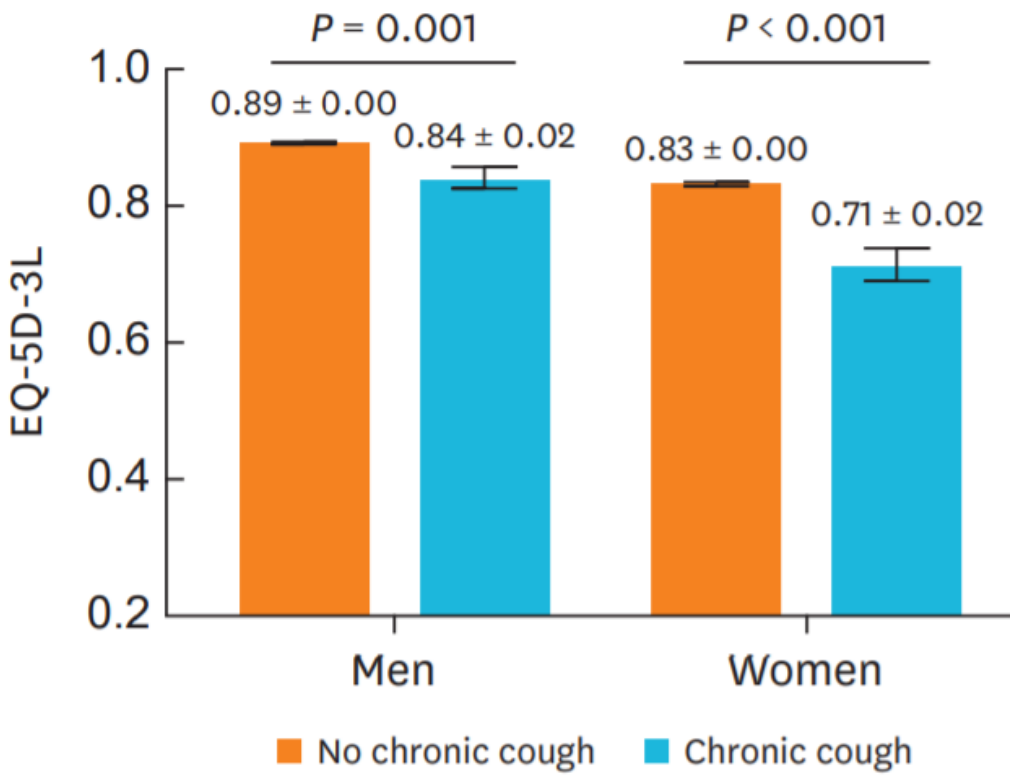
Medicine (Baltimore) 2017;96:e6486.
Allergy Asthma Immunol Res 2020;12:964-79

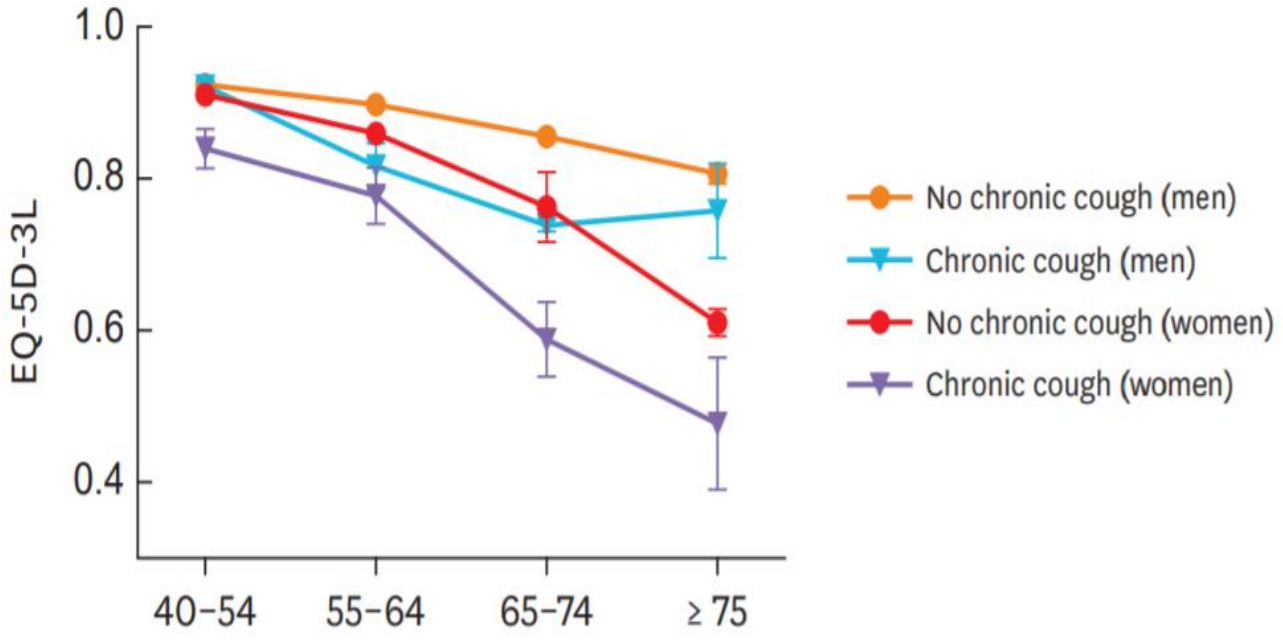
Prevalence according to age (Korea)



- Medicine (Baltimore) 2017;96:e6486

Health-related QoL and chronic cough





EQ-5D-3L, 3-level EuroQoL 5-dimension component
(1: perfect health, 0: health state equivalent to death)

Allergy Asthma Immunol Res 2020;12:964-79

Classification of cough and main causes

arbitrary cut-off in cough duration & overlap (+)

acute

- 상기도 감염
- 급성기관지염

subacute

- 감염 후 기침 (m/c)
- causes of chronic cough

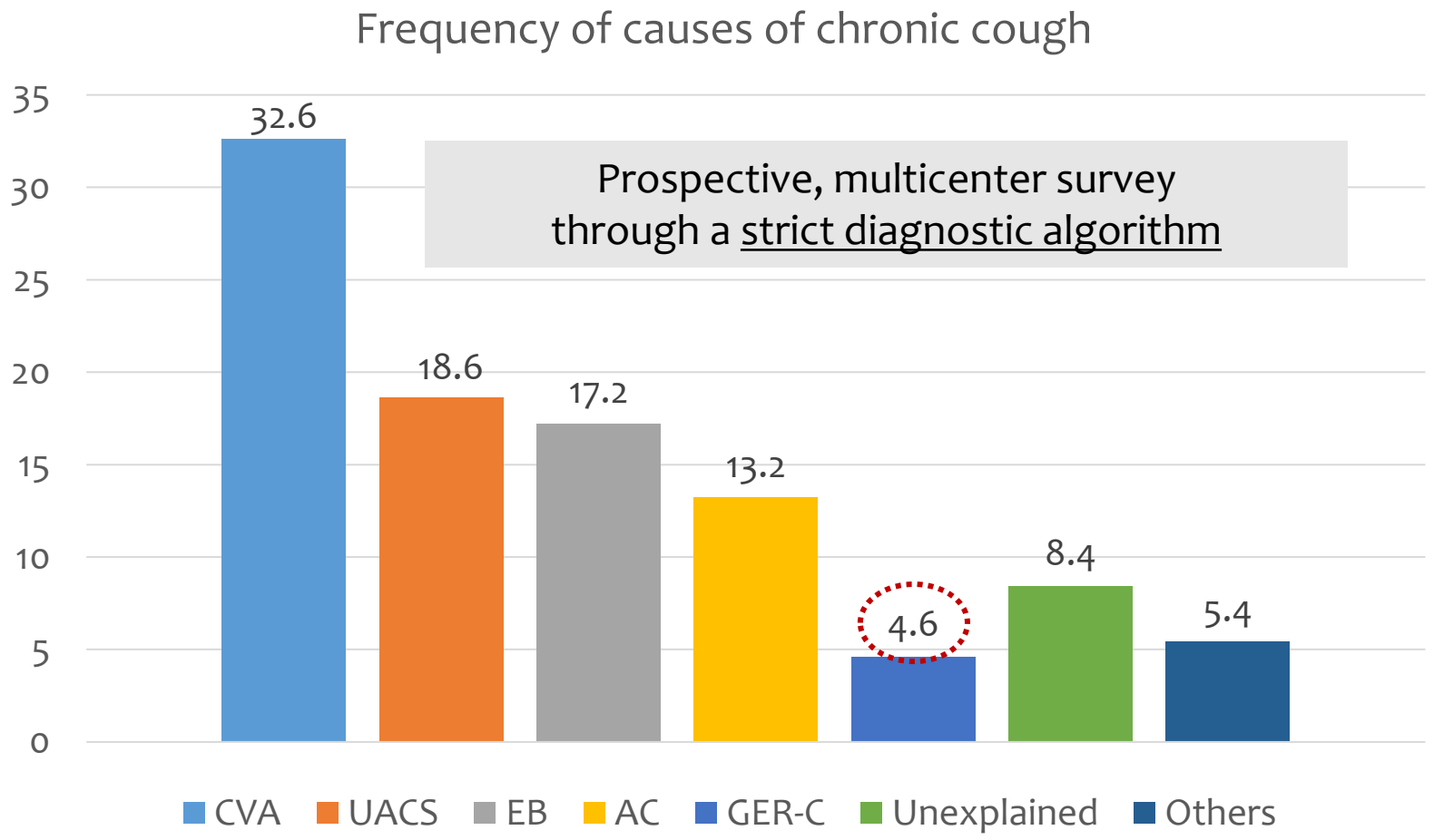
3대 원인

chronic

- **기침형천식 (CVA) & 호산구성 기관지염 (EB)**
- **상기도기침증후군 (UACS)**
- **위식도역류질환 (GERD)**
- 약물, 흡연, TB, BE, COPD ……

CVA : cough variant asthma, EB : eosinophilic bronchitis, GERD : gastroesophageal reflux disease
BE : bronchiectasis, UACS: upper airway syndrome (post-nasal drip syndrome)

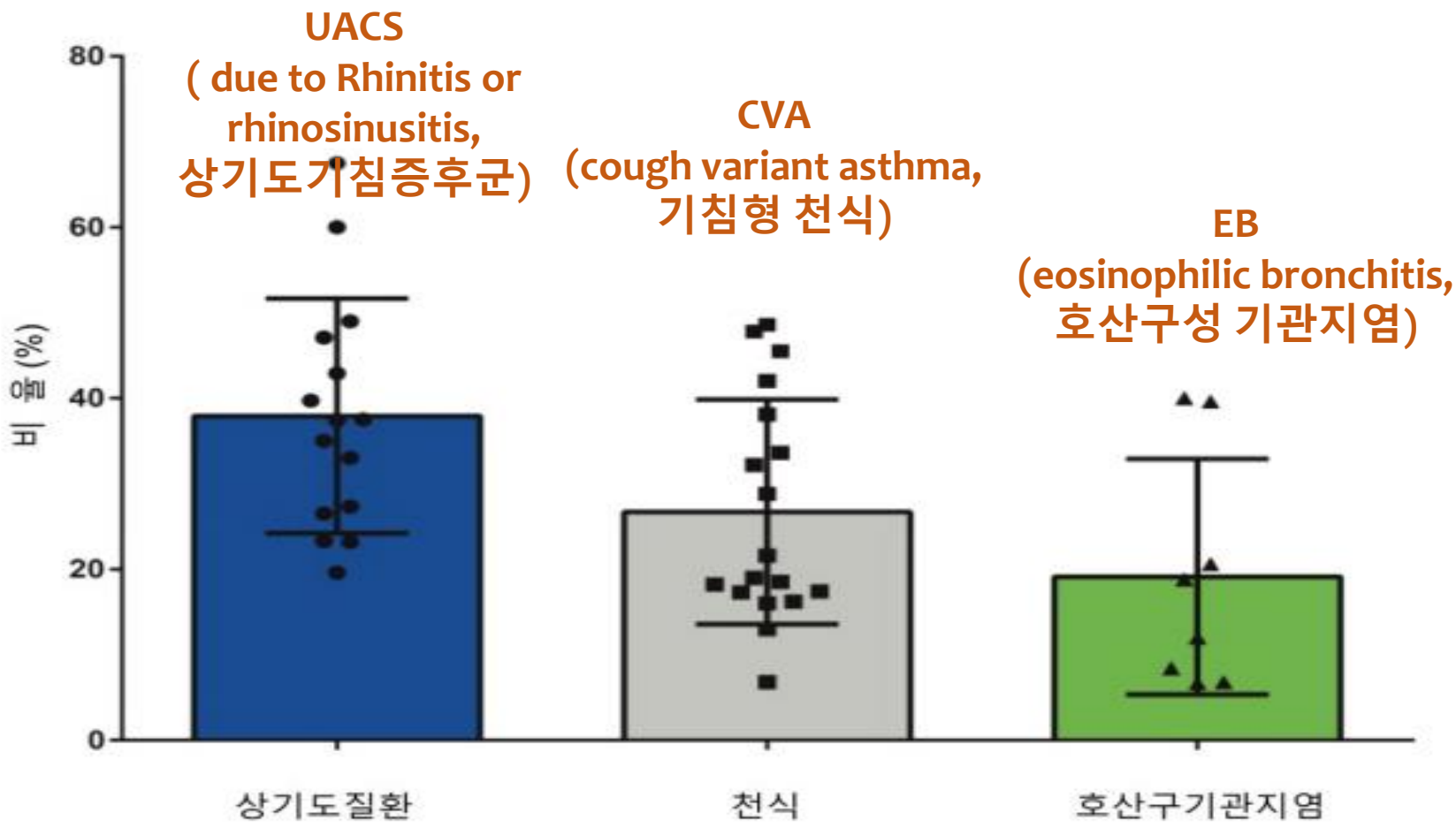
Causes of chronic cough in China



CVA (cough-variant asthma), UACS (upper airway cough syndrome), EB (eosinophilic bronchitis), AC (atopic cough), GER-C (gastroesophageal reflux-related cough)

CHEST 2013:143:613

한국 성인 만성기침환자에서의 주요질환



UACS: Upper airway cough syndrome

Kang SY et al, Asia Pacific Allergy 2016:6(4):198 (18 studies)

만성 기침 환자의 접근 첫 단계

표 2. 간편기침평가검사(COugh Assessment Test: COAT)

기침이 얼마나 심하십니까?

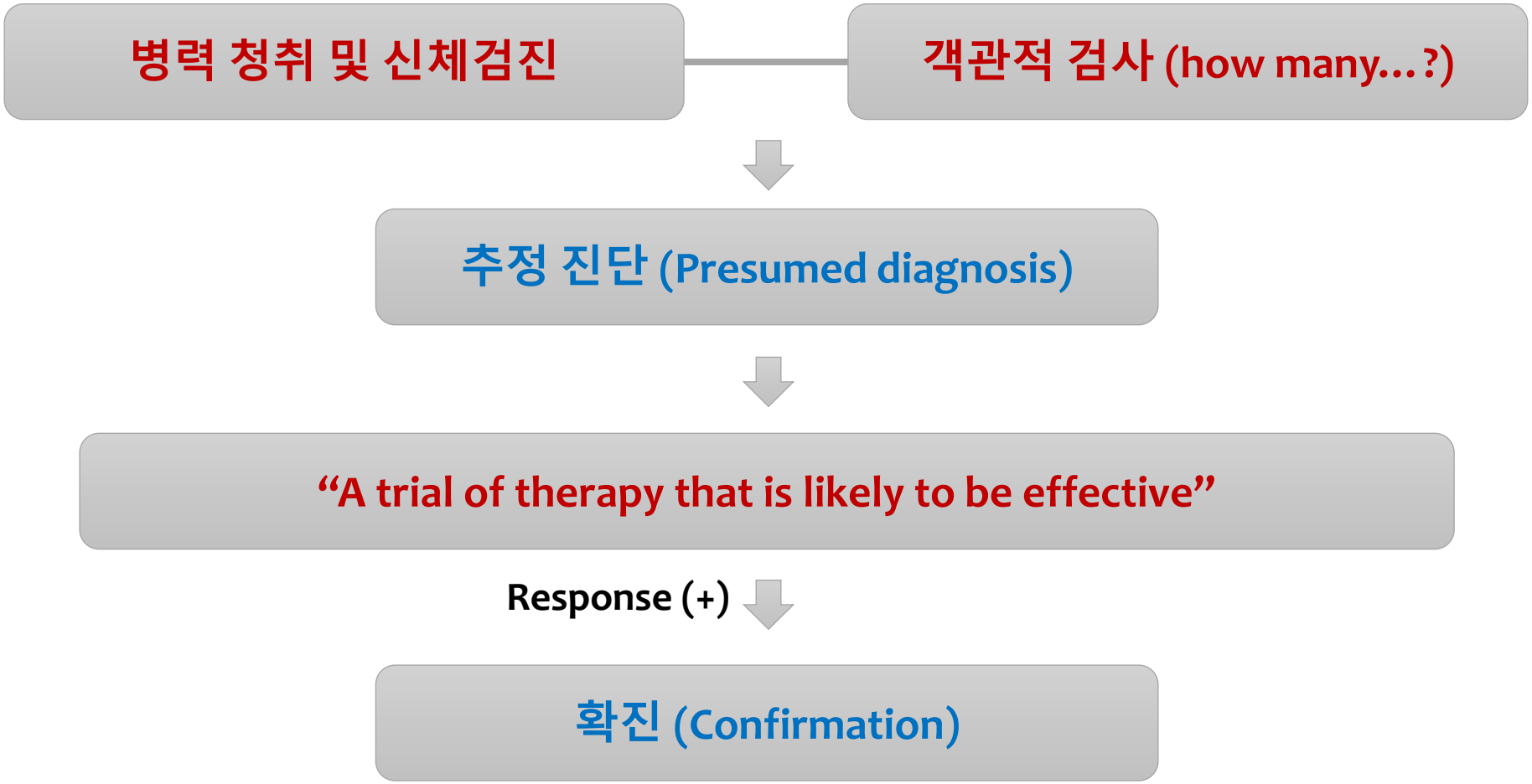
다음 질문들은 기침이 얼마나 심한지 귀하의 육체적, 정신적 건강 상태와, 기침으로 인한 일상 생활에 미치는 영향을 평가하기 위한 것입니다. 아래의 각 항목마다 최근 3일 간의 귀하의 상태에 해당하는 점수에 **체크 표시(√)**를 해주십시오.

	없음	약함	보통	심함	매우심함
기침을 얼마나 자주 하나요?	⓪	①	②	③	④
기침 때문에 일상생활에 지장이 있나요?	⓪	①	②	③	④
기침 때문에 잠자기 힘든가요?	⓪	①	②	③	④
기침 때문에 피곤한가요?	⓪	①	②	③	④
먼지 많을 때, 자극성 냄새, 찬공기를 마실 때 기침이 심해지나요?	⓪	①	②	③	④
총점					점

COAT : cough assessment test 간편기침평가도구 (5문항, 0~20점)

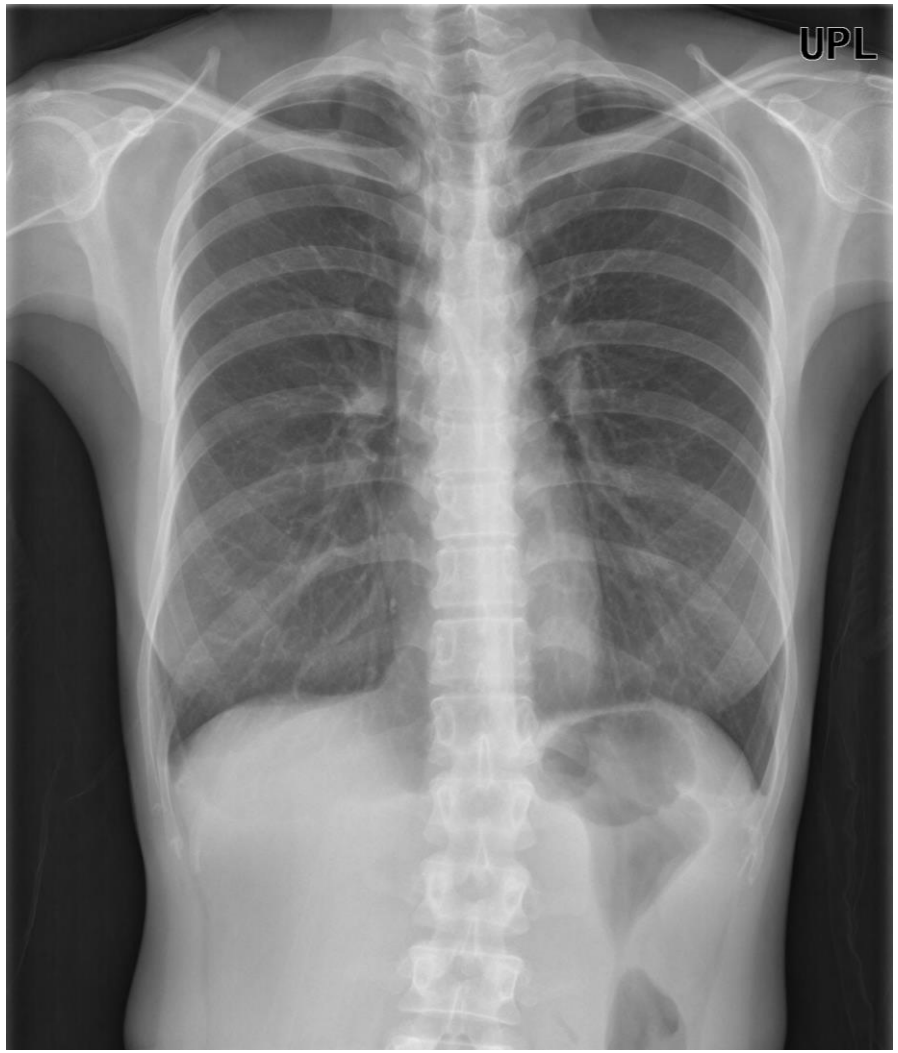
Allergy Asthma Immunol Res, 2018:10(6):591-613
기침진료지침 2020 (대한결핵 및 호흡기학회)
Eur Respi J, 2020:55(1):1901136

전통적인 만성 기침 진단 및 치료



Example 1.

- F/37, cough lasting **for 6 weeks**
- non-smoker, no medication, no previous TB, no travel Hx ⇨ r/o drugs, smoking
- No recent respiratory infection ⇨ r/o post-infectious cough
- BMI = 25.1
- Post-nasal drip (+) : aggravation on supine position
- Nasal congestion : sometimes
- Frequent FB sensation or secretion in throat ⇨ r/o GER-cough ?
- dyspnea (-), GE reflux Sx (-)
- Fever (-), no wheezing/rale on auscultation



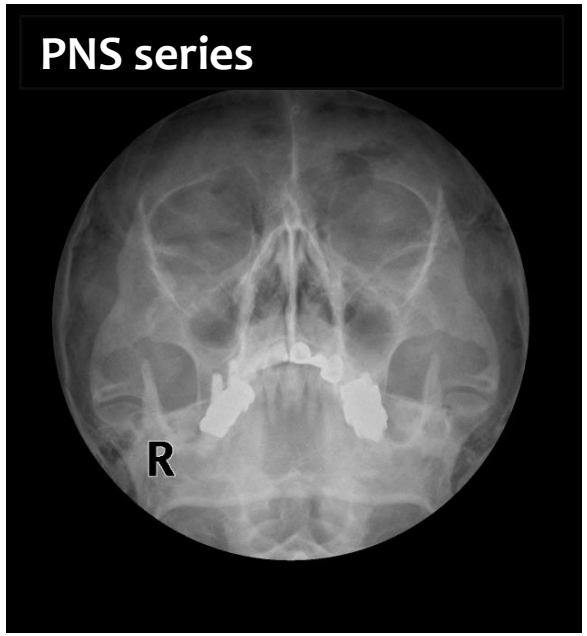
Normal chest PA

점막비후, 혼탁, 공기-수면상

Spirometry result ： within normal limits

	Ref	Pre (Meas)	Pre (% Pred)	Post (Meas)	Post (% Pred)	Post (% Chg)
FVC (liters)	3.85	3.67	95	3.73	97	2
FEV1 (liters)	3.02	2.82	93	2.90	96	3
FEV1/FVC (%)	76	77		78		
FEF25-75 (L/sec)	3.40	2.42	71	2.66	78	10
PEF (L/sec)	6.55	6.07	93	5.85	89	-4

Example 1.



점막비후, 혼탁, 공기-수면상

+

Relevant symptoms or signs

Exclusion of other diseases or triggers

Presumed Dx : cough due to rhinosinusitis

Trial of therapy
(**항히스타민 + 비충혈제거제**, 비강분무스테로이드, if indicated antibotics)

Response (+)

Confirmation : **상기도 기침증후군 (UACS)***

*UACS: upper airway syndrome (old term : post-nasal drip syndrome)

Upper airway cough syndrome (UACS)

- ACCP definition ： chronic cough coexisting with upper airway Sx.
- Most common cause of chronic cough
- Sensory neuropathic process attributed by upper airway
  - Formerly, postnasal drip syndrome
- Dx ： Response to empirical anti-histamine or nasal decongestant

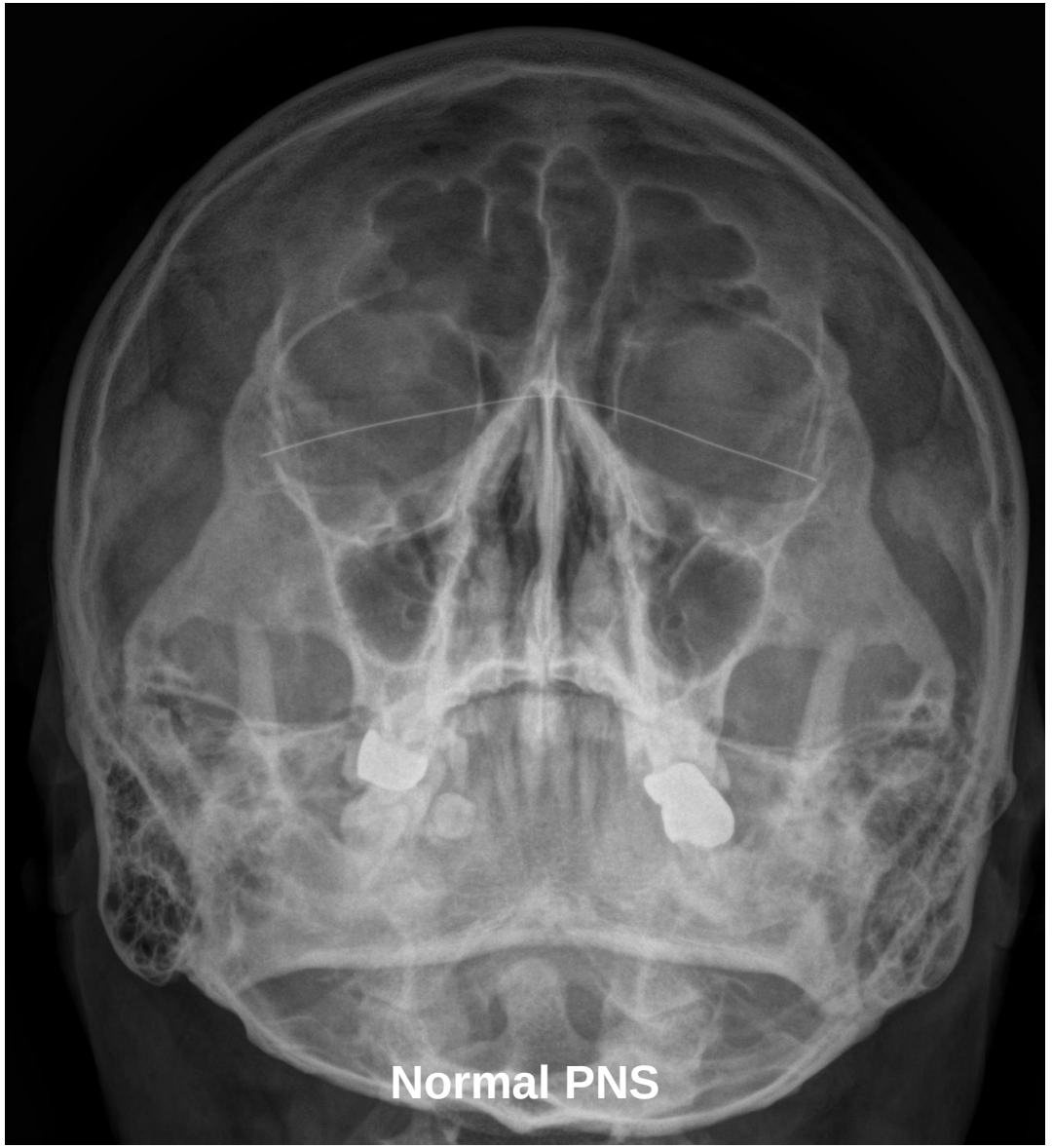
Chest 2006:129:638

Example 2.

- F/63, Chronic dry cough lasting **for 12 weeks (aggravation at night)**
- non-smoker, no medication, no previous TB, no travel Hx ⇨ r/o drugs, smoking
- No recent respiratory infection, atopy (-)

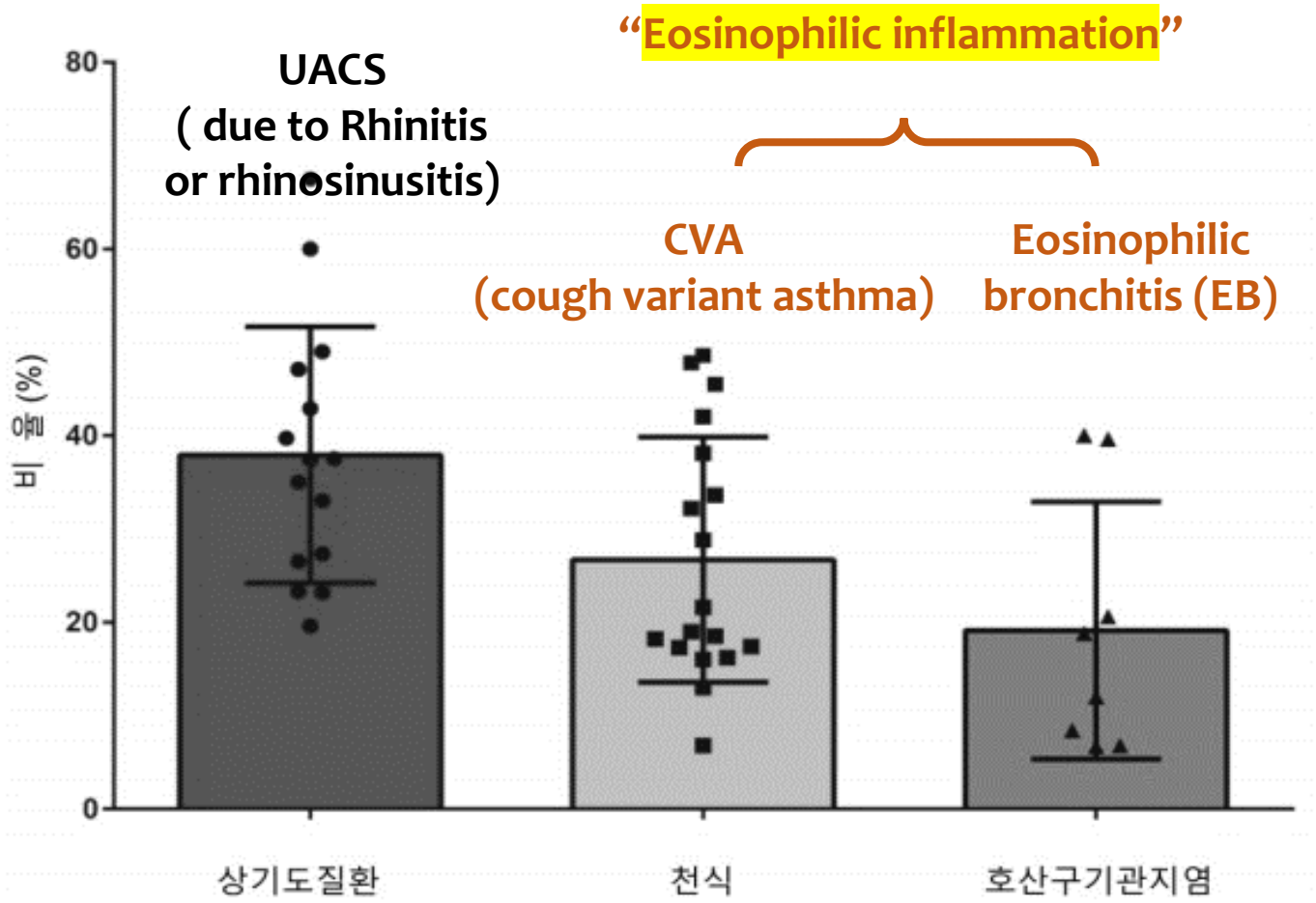
- Post-nasal drip (-), Nasal congestion (-) ⇨ r/o UACS
- Frequent FB sensation or secretion in throat (-) ⇨ r/o GER-cough
- GE reflux-associated Sx (-)
- dyspnea (-), productive sputum (-)
- Fever (-), no wheezing/rale on clinic visit

Normal chest PA



Normal PNS

한국 성인 만성기침환자에서의 주요질환



UACS: Upper airway cough syndrome

Kang SY et al, Asia Pacific Allergy 2016:6(4):198

천식 및 호산구기관지염 여부를 확인하기 위한 검사

검사 종류	특 징
메타콜린 기관지유발 검사	• 천식 진단 및 배제를 위한 목적으로 사용 • 경험 많은 전문가와 필요 : **1차 의료기관에서 시행에 어려움** • 양성 소견 후 천식 약물 치료 후 호전됨이 확인될 때, 천식으로 최종확진
유도객담검사 (induced sputum analysis)	• 호산구성 기관지염 (EB) 진단목적으로 사용 • 항히스타민 치료와 메타콜린 기관지 유발검사 음성인 환자에서 추천됨 • 객담 내 호산구 증가(>3%) 시 진단 가능 • **2, 3차 의료 기관에서만 가능**
호기산화질소 검사 (FENO)	• 위의 두 검사를 시행할 수 없는 경우, 이 검사가 활용가능 • 기도 내 **Th2 inflammation** 정도를 반영 (호산구성 기도염증) • **1차 의료 기관에서도 사용가능 (간단한 장비와 짧은 검사시간)**

FENO=Fractional exhaled nitric oxide measurement

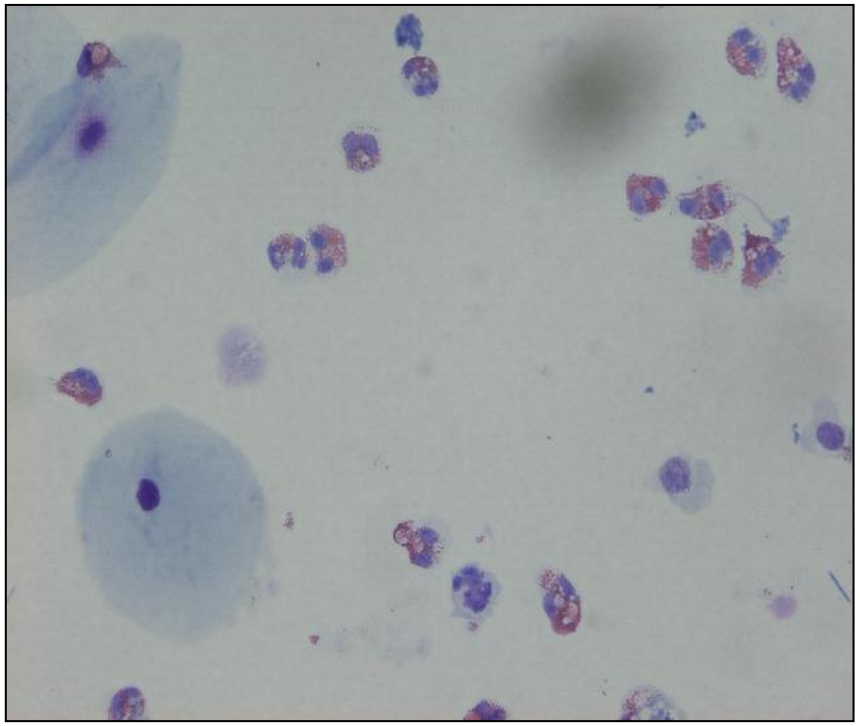
유도객담검사 (induced sputum analysis)

1. 기관지확장제 흡입

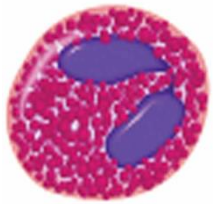
2. 4.5% Saline 흡입

3. 코 풀기 (오염 줄임)

4. 흡입 5분 후 객담 채집



Eosinophil > 3%



FENO measurement tool

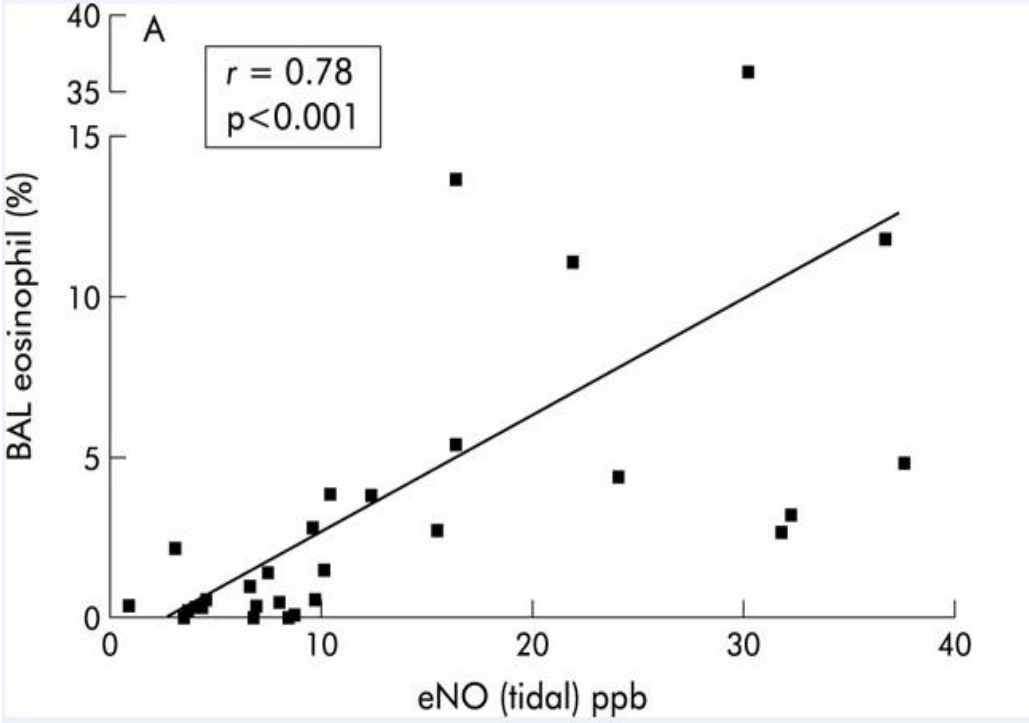
FENO = Fraction of exhaled nitric oxide

비보험 (강동경희대병원 : 5만원)

Filter ： 17,000 원
Device ： 600-700 만원

FENO (호기산화질소) 검사

- Non-invasive and needs much less efforts than induced sputum analysis
  - Standardized
  - Comfort
  - Needs less time and technician's labor
- Examination within a day, without reservation!
  - FeNO, spirometry, chest X-ray / PNS view , rhinoscopy
- Effect of smoking, respiratory infection, food

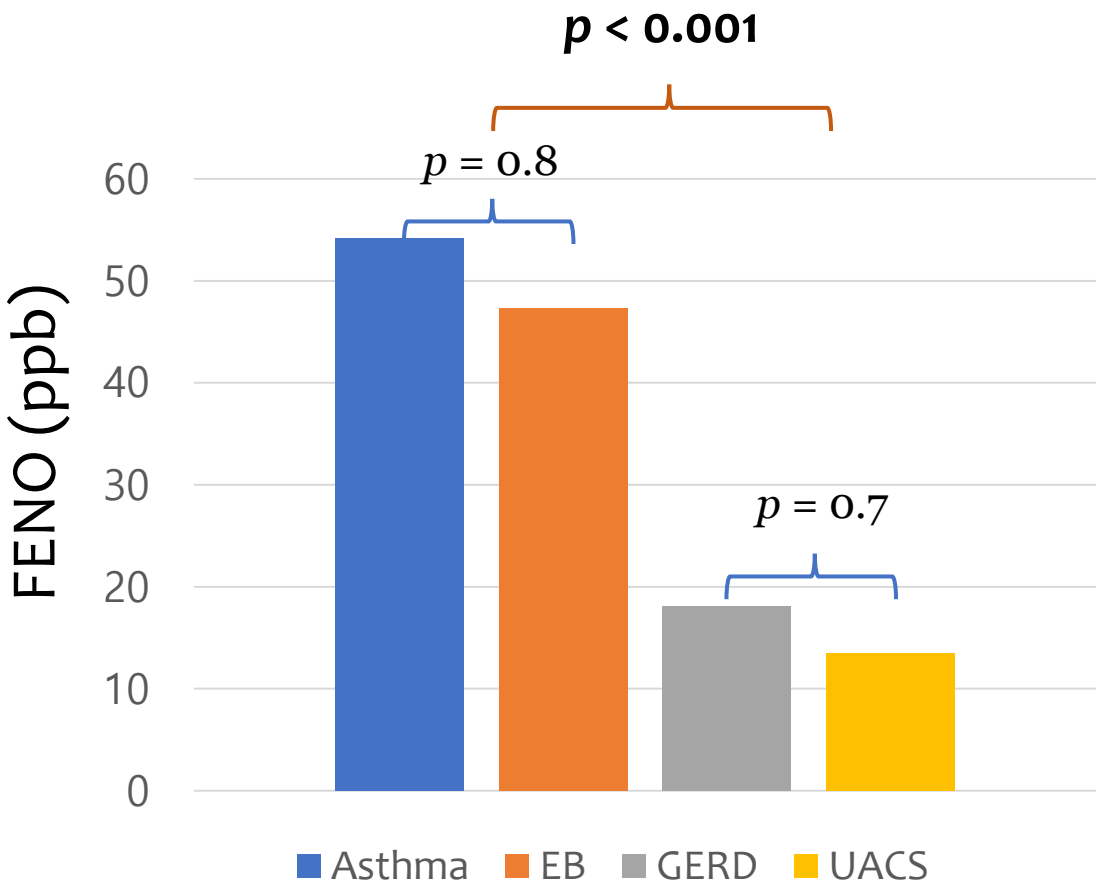


FENO as a predictor of response to steroid

- Easy to use in private clinic (portable device), Non-invasive tool
- Increased FENO (> 30~35 ppb)
  - Eosinophilic inflammation-associated cough (asthma or EB) … !!
  - Expectation of **favorable response to steroid** … !!
- Limitation
  - Higher specificity (89%) and moderate sensitivity (73%)*
  - 천식 진단배제 목적으로는 유용하지 않음

* J Allergy Clin Immunol, 2017:!40:701 (from 15 studies, 2187 patients with chronic cough)

Exhaled NO (FENO) in screening of adults with chronic cough



EB : eosinophilic bronchitis
GERD : gastroesophageal reflux disease
UACS: upper airway syndrome (post-nasal drip syndrome)

Respir Med, 2015:109:970

Example 2.

호기 산화질소(FENO) = 55 ppb

Serum eosinophil (5%)

+

F/33, no smoker, no medication

No post-nasal drip

No GER-associated Sx, dyspnea (-)

No wheezing/rale, aggravated cough at night

Presumed Dx : cough due to eosinophilic bronchitis or CVA

Trial of therapy (흡입스테로이드)

Response (+)

Confirmation : eosinophilic bronchitis (EB) or CVA

Differentiation of asthma and EB

Asthma	Eosinophilic bronchitis
객담 호산구 증가, FENO 상승	객담 호산구 증가, FENO 상승
호흡곤란, 천명 동반될 수 있음	호흡곤란, 천명 없음
기도 과민성 (+)	기도 과민성 (-)
메타콜린 기관지유발검사 : 양성	메타콜린 기관지유발검사 : 음성
치료 : ICS	치료 : ICS

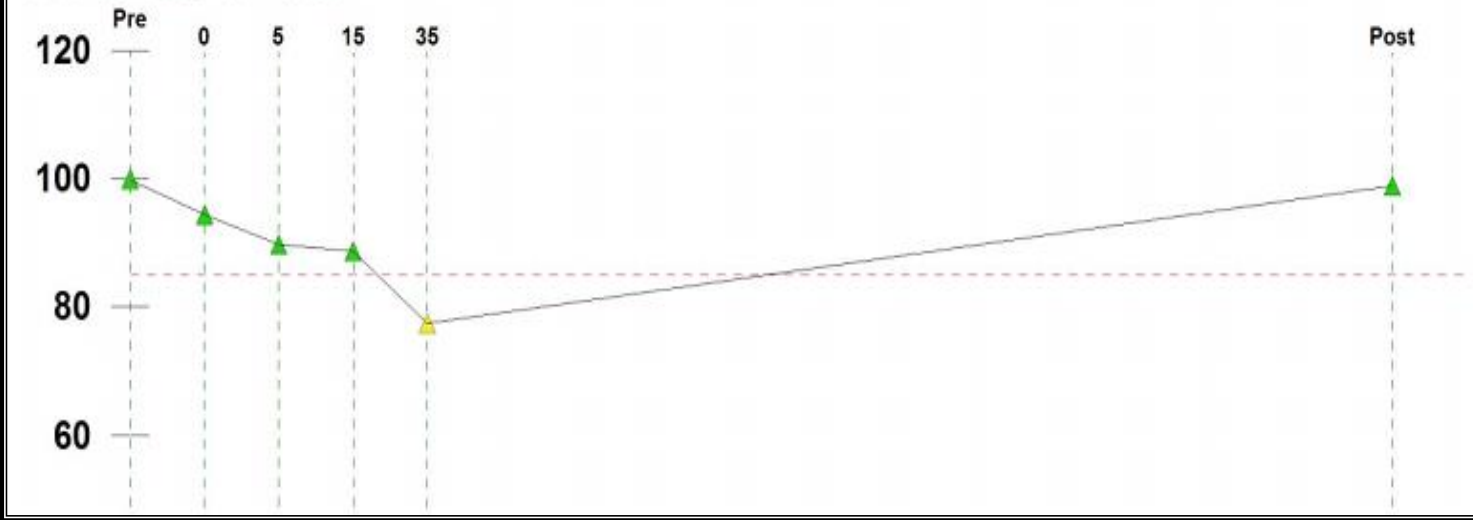
Example 2.

기관지유발검사
(Bronchial provocation test)

감별
Cough-variant asthma

	Ref	Pre Meas	Pre % Ref	Level 1 Meas	Level 2 Meas	Level 3 Meas	Level 4 Meas	Level 5 Meas	Level 6 Meas	Level 7 Meas	Level 8 Meas	Level 9 Meas	Post Meas
Dose				0	5	15	35						
FVC Liters	5.20	4.00	77	4.04	3.95	3.71	3.31						3.88
% Chg				1	-1	-7	-17						-3
FEV1 Liters	4.10	3.00	73	2.84	2.70	2.67	2.33						2.97
% Chg				-6	-10	-11	-22						-1
FEF25-75%	4.36	2.32	53	1.98	1.85	2.03	1.72						2.53
% Chg				-15	-21	-13	-26						9
PEF L/sec	9.39	7.73	82	7.06	6.11	5.58	5.21						7.27
% Chg				-9	-21	-28	-33						-6

PC 15 FEV1: 19.9



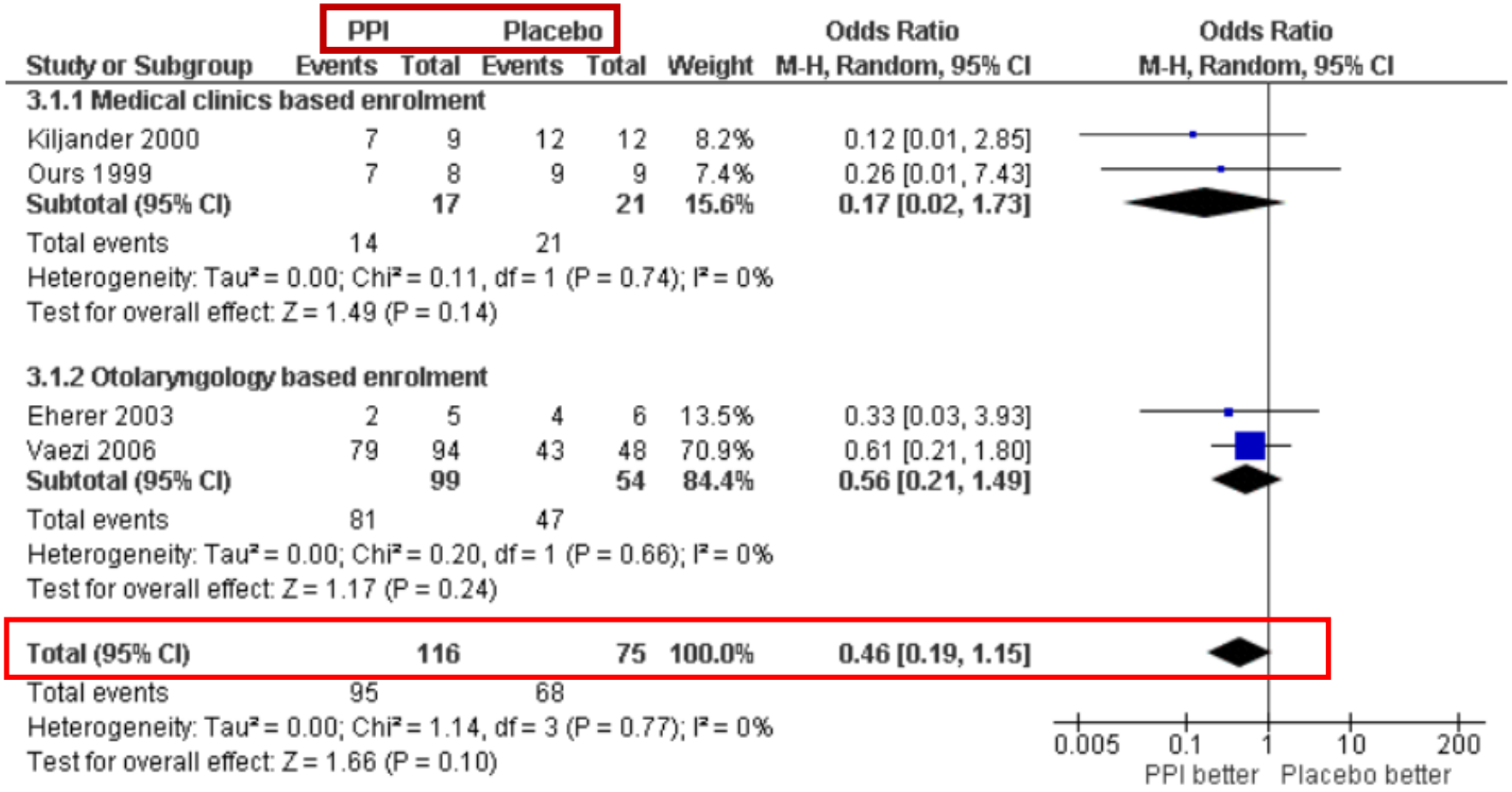
Example 3.

- M/55
- Ex-smoker, no medication, cough lasting **for 3 months** ⇨ r/o drugs, smoking
- BMI = 31, no definite infectious events ⇨ r/o post-infectious cough
- Dyspnea (-), Nasal congestion or post-nasal drip (-) ⇨ r/o UACS ?
- GER-related Sx. like Heart burn (-) ⇨ r/o GER-cough ?
- Wheezing/rale (-/-), normal PFT ⇨ r/o COPD
- Normal PNS and CXR, FENO = 22 ppb ⇨ r/o CVA or EB ?

What would you do for this patient … ?

24-hr pH monitoring or PPI trial ?

PPI use is effective in the treatment of GER-Cough?



Study or Subgroup	PPI Events	PPI Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
3.1.1 Medical clinics based enrolment						
Kiljander 2000	7	9	12	12	8.2%	0.12 [0.01, 2.85]
Ours 1999	7	8	9	9	7.4%	0.26 [0.01, 7.43]
Subtotal (95% CI)		**17**		**21**	**15.6%**	**0.17 [0.02, 1.73]**
Total events	14		21			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.49 (P = 0.14)						
3.1.2 Otolaryngology based enrolment						
Eherer 2003	2	5	4	6	13.5%	0.33 [0.03, 3.93]
Vaezi 2006	79	94	43	48	70.9%	0.61 [0.21, 1.80]
Subtotal (95% CI)		**99**		**54**	**84.4%**	**0.56 [0.21, 1.49]**
Total events	81		47			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Total (95% CI)		**116**		**75**	**100.0%**	**0.46 [0.19, 1.15]**
Total events	95		68			
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 3 (P = 0.77); I² = 0%						
Test for overall effect: Z = 1.66 (P = 0.10)						

Insufficient evidence to conclude ***definitely*** that GERD treatment with PPI is ***universally*** beneficial.

Cochrane Database Syst Rev 2011

Expert consensus* about a trial of PPI

Cough and reflux

Question 12

양전자펌프억제제 (PPIs)가 GER-Cough 에 효과적인 치료인가?

A+	Agree strongly	4
A	Agree with minor reservations	13
A-	Agree with major reservations	9
D-	Disagree with major reservations	7
D	Disagree with minor reservations	7
D+	Disagree strongly	3

38.6% (17/44)

Task Force does NOT support that a trial of PPI should be used in routine Mx.

*호주, 벨기에, 캐나다, 미국, 중국, 덴마크, 그리스, 아일랜드, 이탈리아, 리투아니아, 스페인, 네덜란다, 영국, 미국의 기침 전문가 대상

ERS Task Force Report, ERJ 2014:44:1132

Changes in international guideline

Chest 2006
Patients with chronic cough who have GI symptoms that are consistent with GERD should be considered to have a high likelihood of having GERD and should be prescribed antireflux treatment **even when they have no GI symptoms.**
Chest 2016 (the US)
In adult patients with suspected chronic cough due to reflux-cough syndrome, but **without heartburn or regurgitation, we recommend against using PPI therapy alone** because it is unlikely to be effective in resolving the cough.
ERS 2020 (Europe)
We suggest that clinicians **do not routinely prescribe anti-acid drugs in adult patients with chronic cough**

GERD and PPI use in chronic cough

- Only 1.7% of patients with chronic cough : GERD-related cough*
- Pathophysiology is still controversial : reflux may have a minor role (reflux ---> reflex theory)
- Empirical PPI use : less effective than expected, controversies on efficacy among experts

- 성인 만성기침 환자에서 **양성자펌프억제제 (PPI)**의 경험적 사용이 기침을 감소시킬까?

- 제한적으로만 사용할 것을 권고 (acid reflux 증상이 명확한 경우)
- 남용의 문제가 크고 장기 복용 시 부작용의 해가 큼 (pneumonia, fracture, hypomagnesemia, dementia, anemia, CDAD …)

Ther Adv Respir Dis 2019;13:1753466619891520
Chest 2013:143:605

Example 3. (Continued)

- M/55
- Ex-smoker, cough lasting **for 3 months**
- BMI = 31
- Dyspnea (-), Nasal congestion or post-nasal drip (-)
- GER-related Sx. like Heart burn (-)
- Wheezing/rale (-/-), No previous respiratory infection Hx.
- Normal PNS and CXR, FENO = 22 ppb,
- **No response to PPI**

Next, what would you do for this patient … ?

검사가 만성 기침의 원인확인에 얼마나 도움이 될까?

검사법 종류	Positive predictive values for cause of chronic cough
PNS x-ray	48 ~ 69%
ENT exam with rhinoscopy	63 ~ 75%
Esophageal pH monitoring	68 ~ 84%
Bronchial provocation test	22 ~ 88%
Spirometry	25 ~ 66%

Thorax 1998:53:738, Chest 1999:116:281, Arch Intern Med 1998:158:1222, Am Rev Respir Dis 1990:141:640

비특이적 만성기침

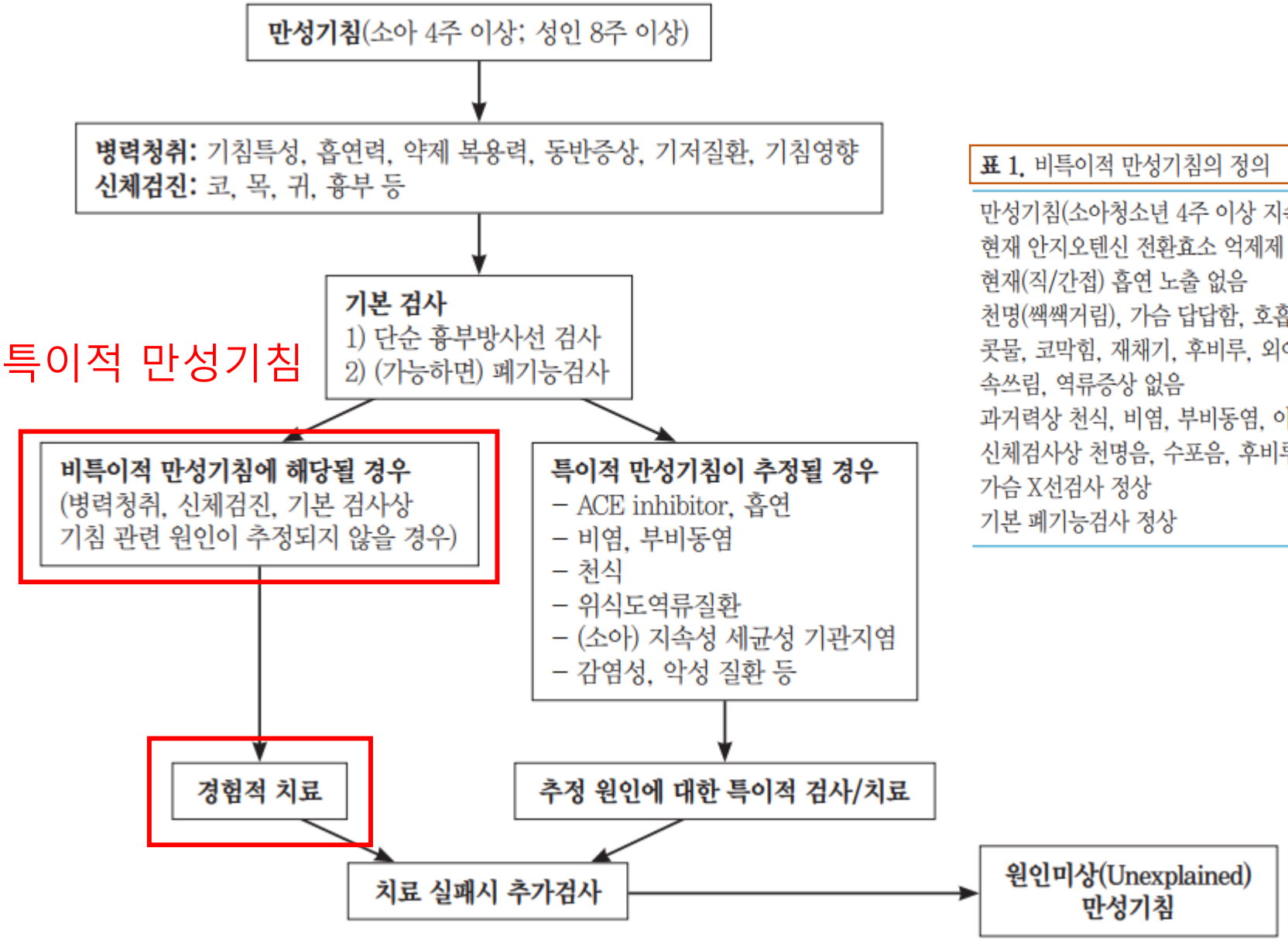


표 1. 비특이적 만성기침의 정의

만성기침(소아청소년 4주 이상 지속된 기침/성인 8주 이상 지속된 기침)
현재 안지오텐신 전환효소 억제제 복용 없음
현재(직/간접) 흡연 노출 없음
천명(쌕쌕거림), 가슴 답답함, 호흡곤란 없음
콧물, 코막힘, 재채기, 후비루, 외이도 이상소견 없음
속쓰림, 역류증상 없음
과거력상 천식, 비염, 부비동염, 아토피, 위식도역류질환, 기관지질환, 폐질환 병력 없음
신체검사상 천명음, 수포음, 후비루, 조약돌 모양 없음
가슴 X선검사 정상
기본 폐기능검사 정상

만성기침진료지침 (천식알레르기학회)

만성 기침에 대한 경험적 치료

- 항히스타민제 : 모든 환자에게 권고
- 흡입스테로이드 (Inhaled corticosteroids, ICS)
  - 천식 및 호산구성 기관지염의 유병율이 높아 권장됨
  - 경험적 투여의 경우, high-dose ICS for 2-4 weeks 사용하고, 4 주 이상 사용 후에도 호전이 없으면 중단
- 항류코트리엔제 (leukotriene receptor antagonists, LTRA)
  - ICS을 사용할 수 없을 경우에 차선책으로 사용
- Proton-pump inhibitor (PPI)
  - 남용의 문제가 크고 장기 복용 시 부작용의 해가 커서 Reflux 증상이 있을 때만 사용

Example 4.

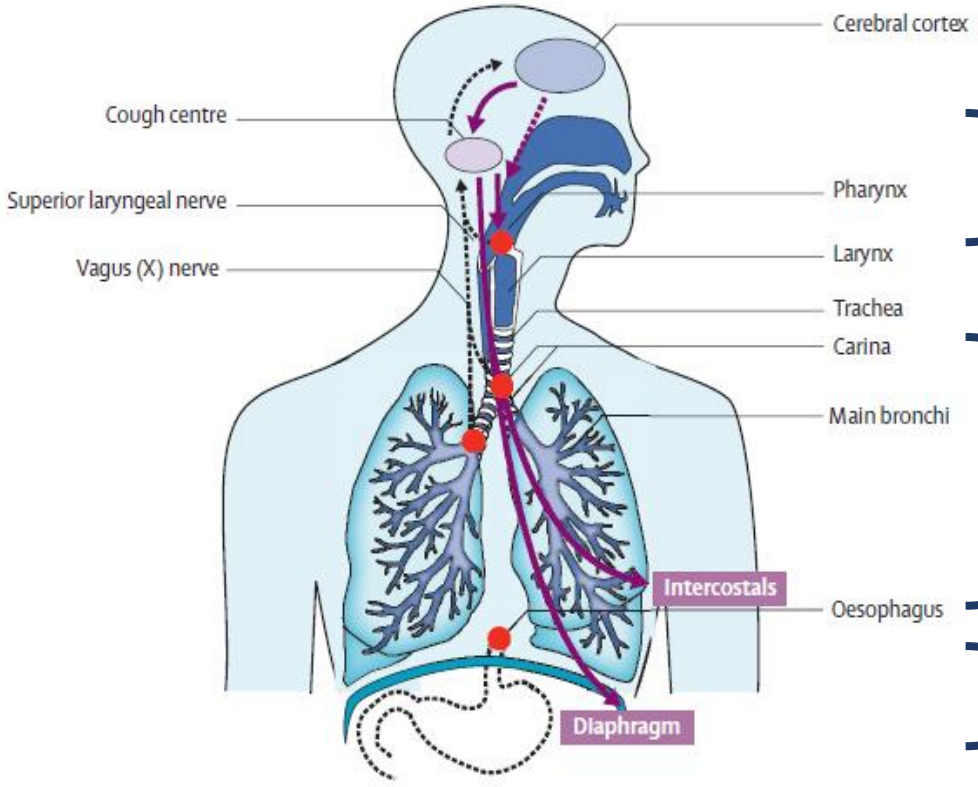
- F/58, cough lasting **for 6 months**
- No medication, Non-smoker, No previous respiratory infection Hx.
- BMI = 22.6
- Dyspnea (-), Nasal congestion or post-nasal drip (-), GER-related Sx (-)
- Wheezing/rale (-/-), Normal PNS and CXR, FENO = 19 ppb
- Chest CT : no abnormalities, Methacholine provocation test (-) : 2차 병원의뢰
- **suboptimal response to PPI, ICS, and anti-histamine for 4 weeks**

☞ **Unexplained/Refractory/idiopathic cough**

Concept … Paradigm …!!

30년 이상 유지해 온 만성기침에 대한 개념과 진단적 접근법으로는 한계

Conventional concept for chronic concept
"anatomical diagnostic protocol"



"Finding the cause and treating it"

UACS	Post-nasal drip
CVA/EB	Eosinophils
GER-C	Acid

Based on anatomical distribution of cough receptors and vagal afferent pathways

The Cough Hypersensitivity Syndrome: A Novel Paradigm for Understanding Cough

Alyn H. Morice

Abstract For many years patients with chronic cough have been investigated in an attempt to diagnose the cause of the cough. Here I suggest that the overwhelming majority of patients with chronic cough have a single diagnosis: cough hypersensitivity syndrome. This is demonstrated by the homogeneous nature of the clinical history and investigational results of patients attending cough clinics. The hypersensitivity facet of the syndrome is demonstrated by objective testing with capsaicin and other protussive agents. Within the cough hypersensitivity syndrome there are different phenotypes. Those patients with a predominantly Th2-type immune response will develop eosinophilic inflammation and either cough-variant asthma or eosinophilic bronchitis. Those with predominantly heartburn symptoms will have a phenotype that reflects GERD and cough. However, the similarities between the different phenotypes far outweigh differences in a unifying diagnosis of the cough hypersensitivity syndrome, providing a more rational understanding of chronic cough.

"Umbrella" concept

Alyn H. Morice, Lung, 2010:188:S87

Model 1. (Anatomincal diagnostic protocol)

Factors + Normal cough reflex → **Chronic Cough**

강력한 원인

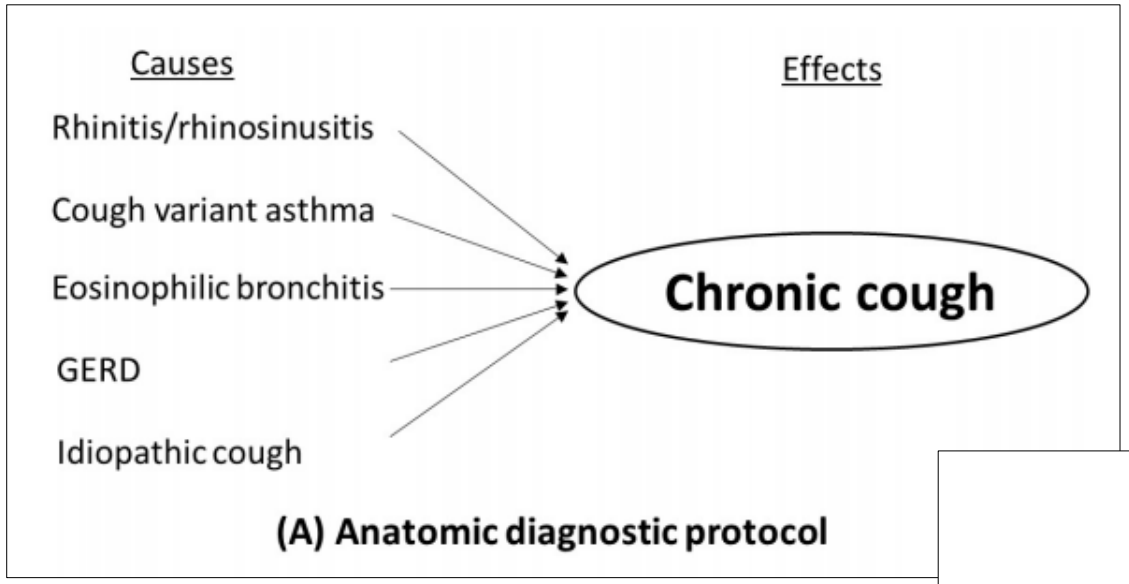
Model 2. (Cough hypersensitivity : Neuropathy)

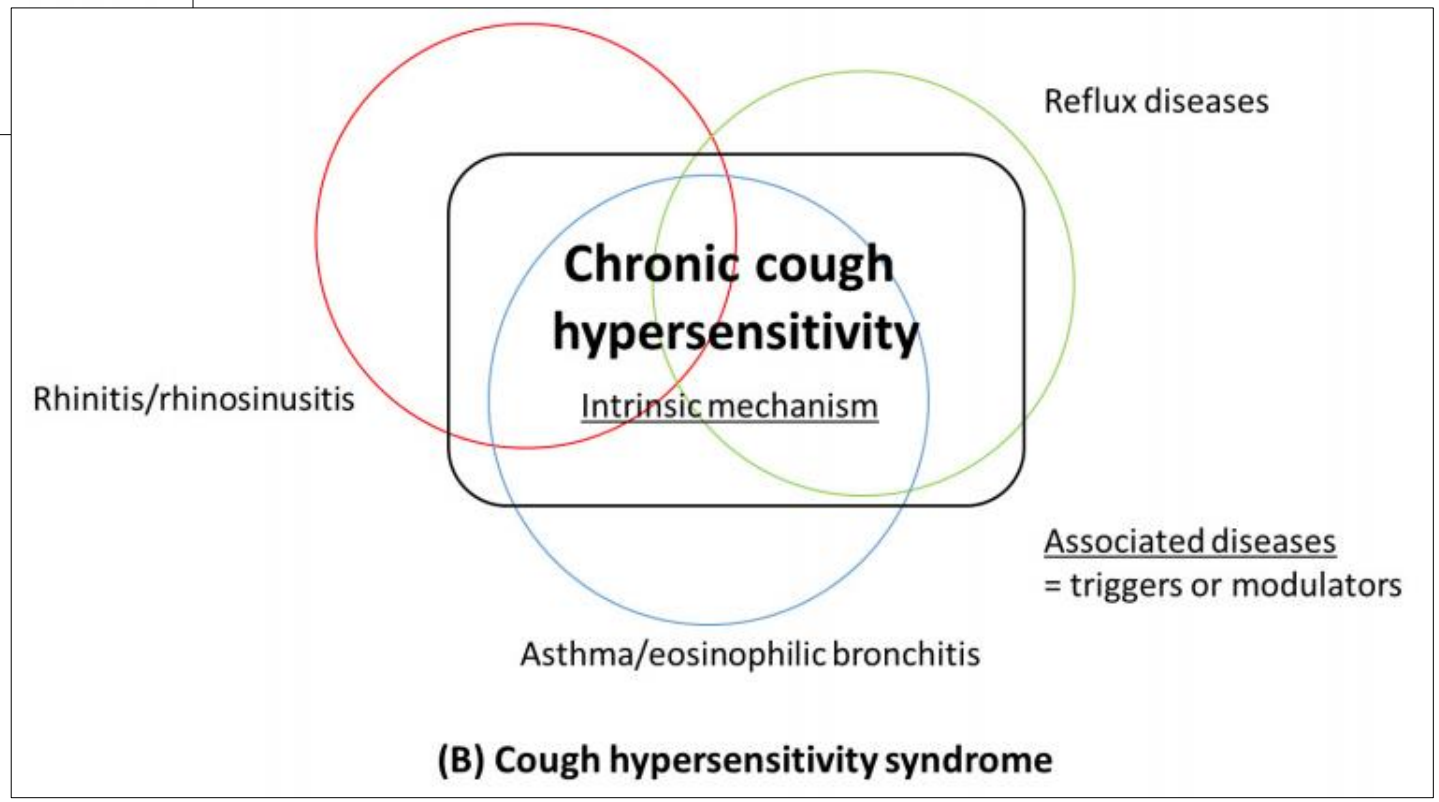
Factors + ***abnormal cough reflex*** → **Chronic Cough**

단순한 trigger/modulator

Too sensitive, disorganized alarm

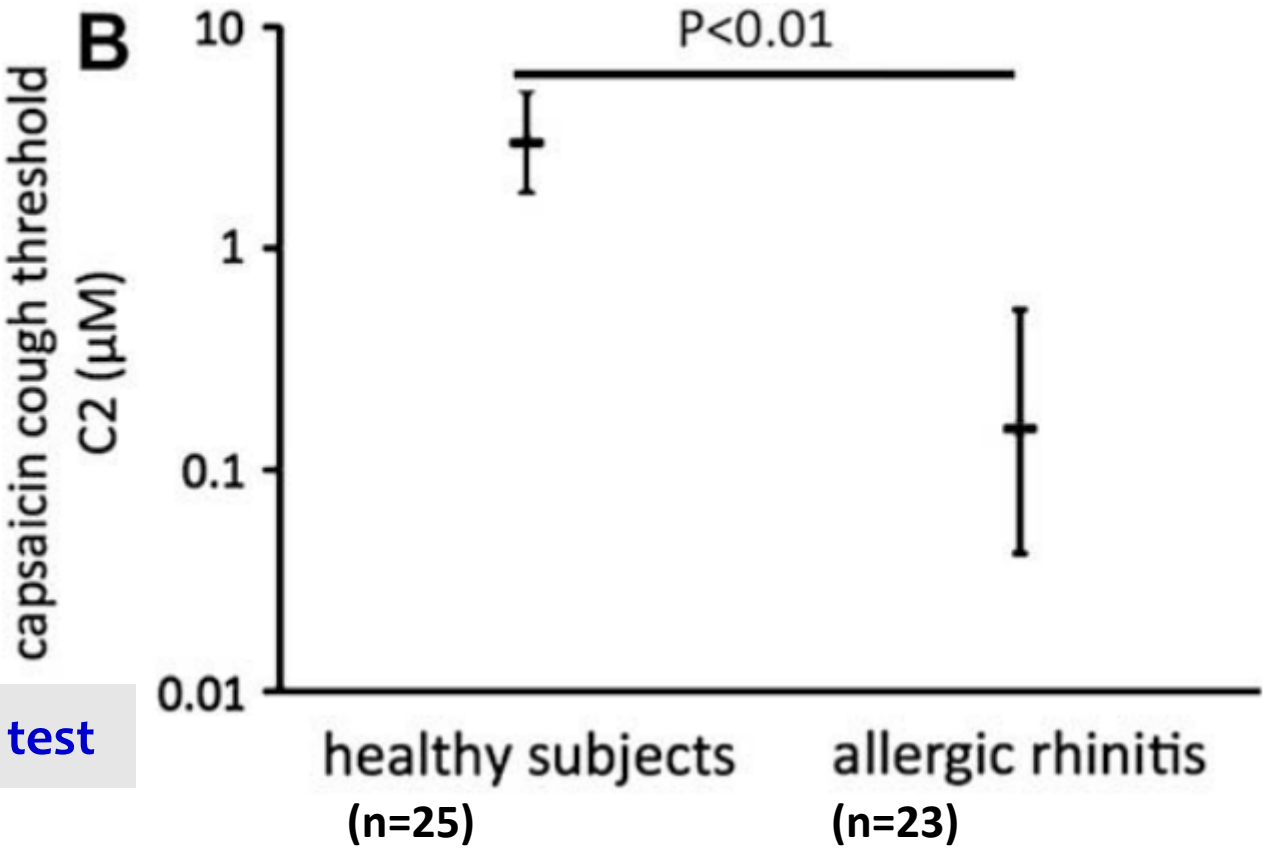
Paradigm for chronic cough





Asia Pac Allergy 2014;4:3-13 (modified)

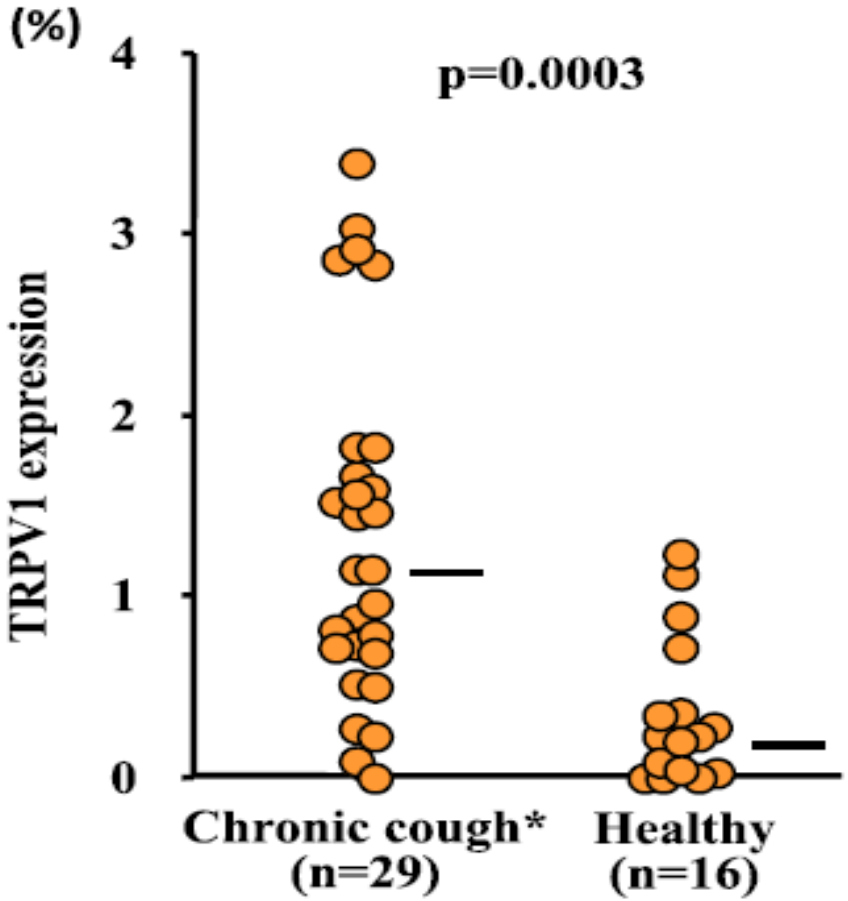
Increased cough reflex in allergic rhinitis



Cough provocation test

Pulm Pharma Ther, 2009:22:121

Upregulation of TRPV1 in intraepithelial nerves in chronic cough



Increased expression of TRP norciceptors in airway epithelium

↓

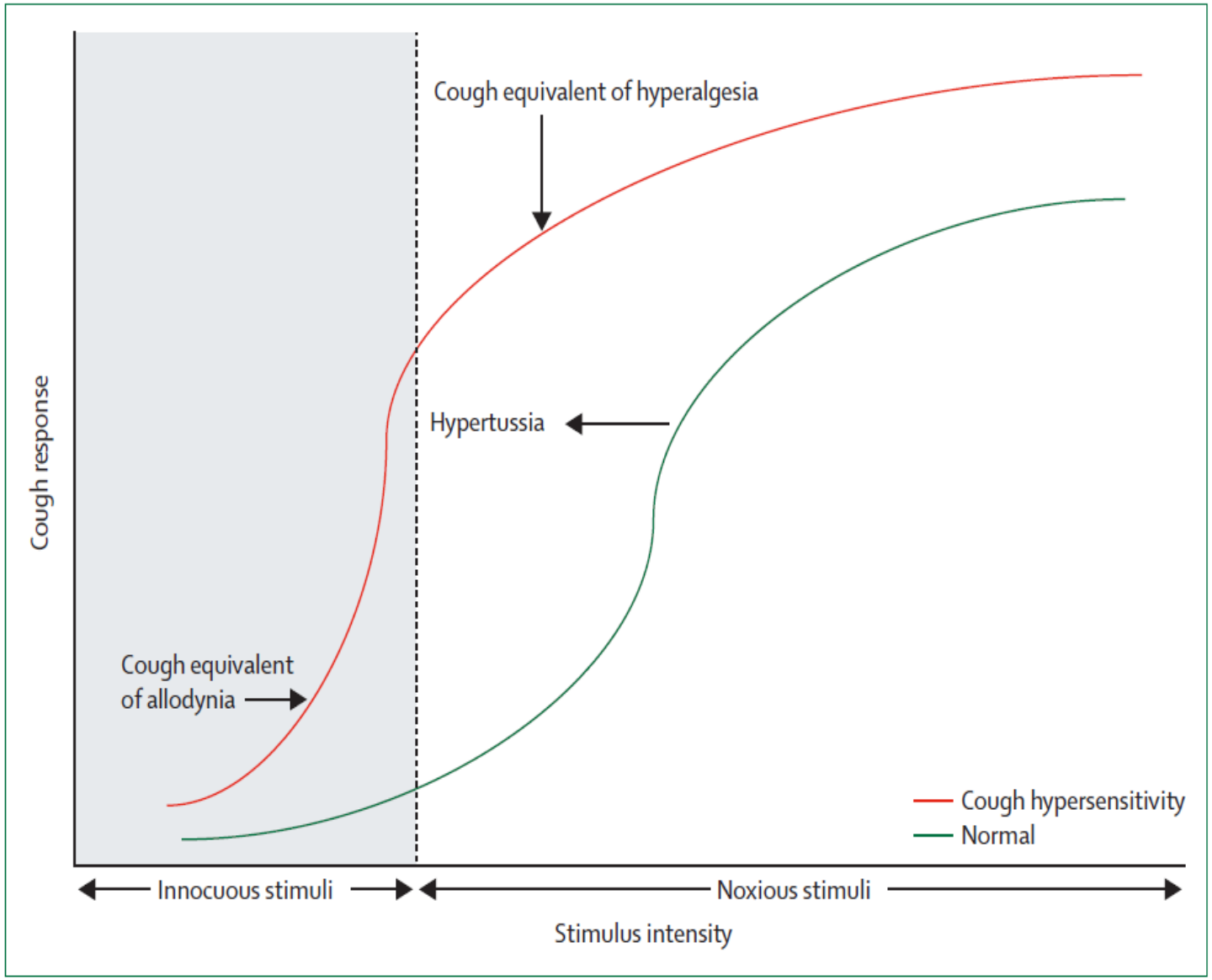
Neuronal hypersensitivity*

TRPV1 = Transient Receptor Potential Vanilloid 1

Am J Respir Crit Care Med, 2004:170:1276
*Thorax 2014:69:46

Concept of cough hypersensitivity syndrome proposed (2014)

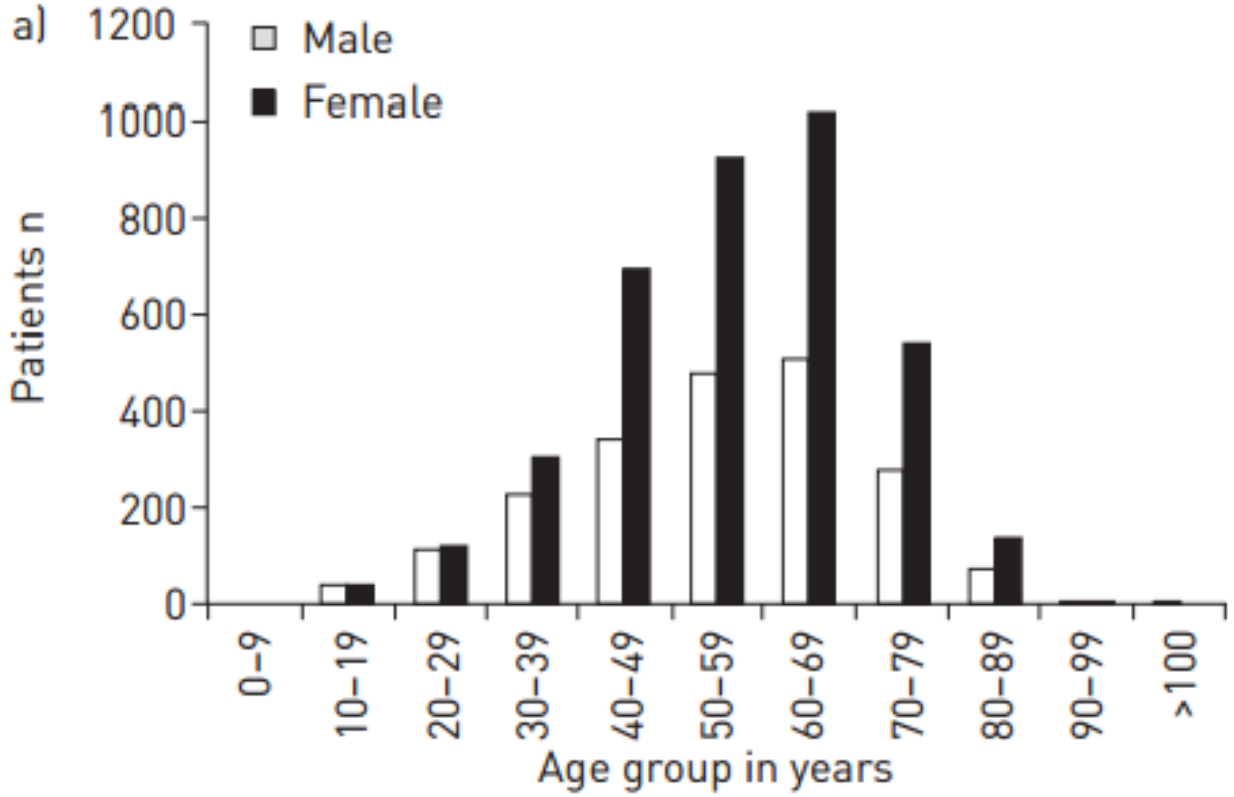
triggered by low levels of thermal, mechanical or chemical exposure

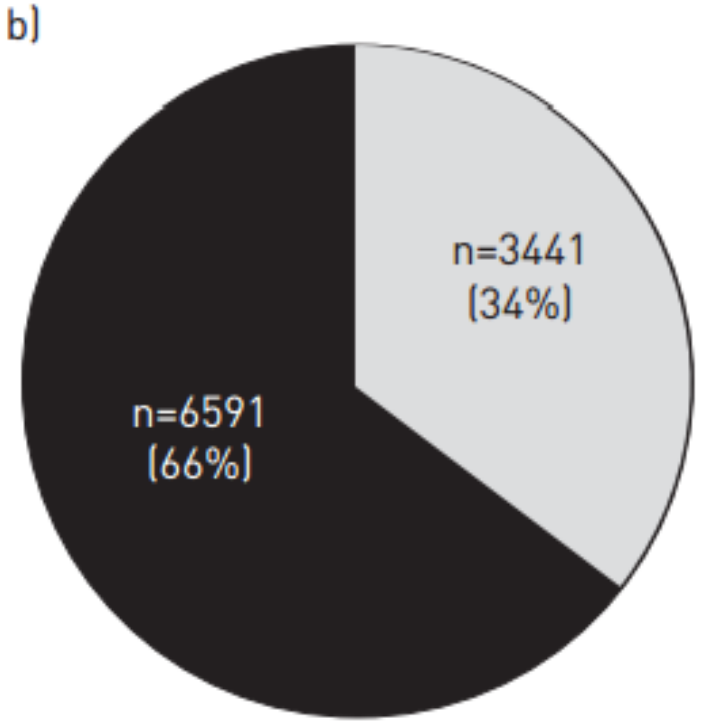


Hyperalgesia (통각과민), allodynia (무해자극통증)

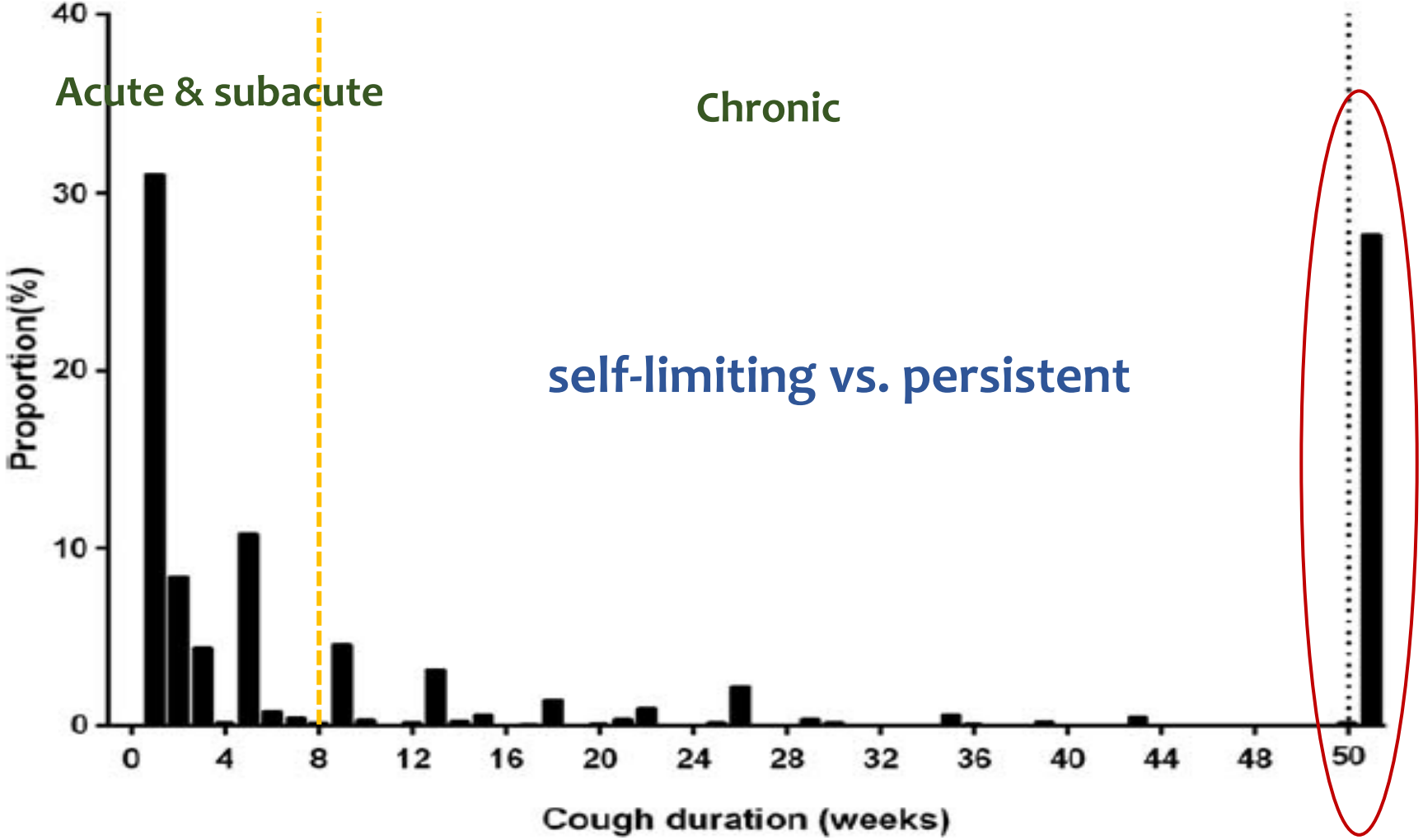
Greater susceptibility in women

영국, 미국, 네덜란드, 스웨덴, 한국, 중국으로 대상 만성 기침으로 의뢰된 환자의 성별, 나이별 분포



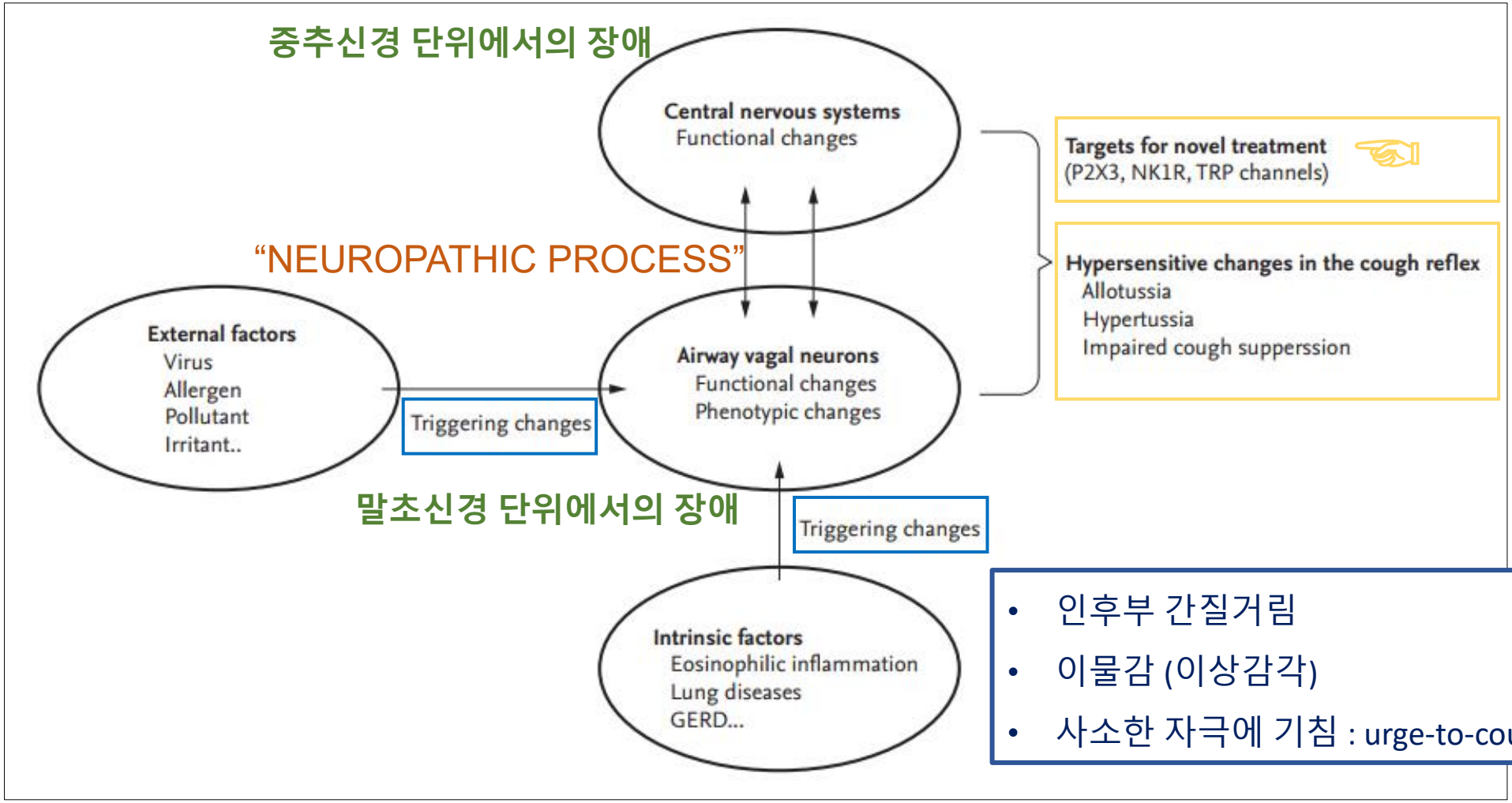


Eur Respir J, 2014:44:1149
Allergy Asthma Immunol Res, 2014:6:401



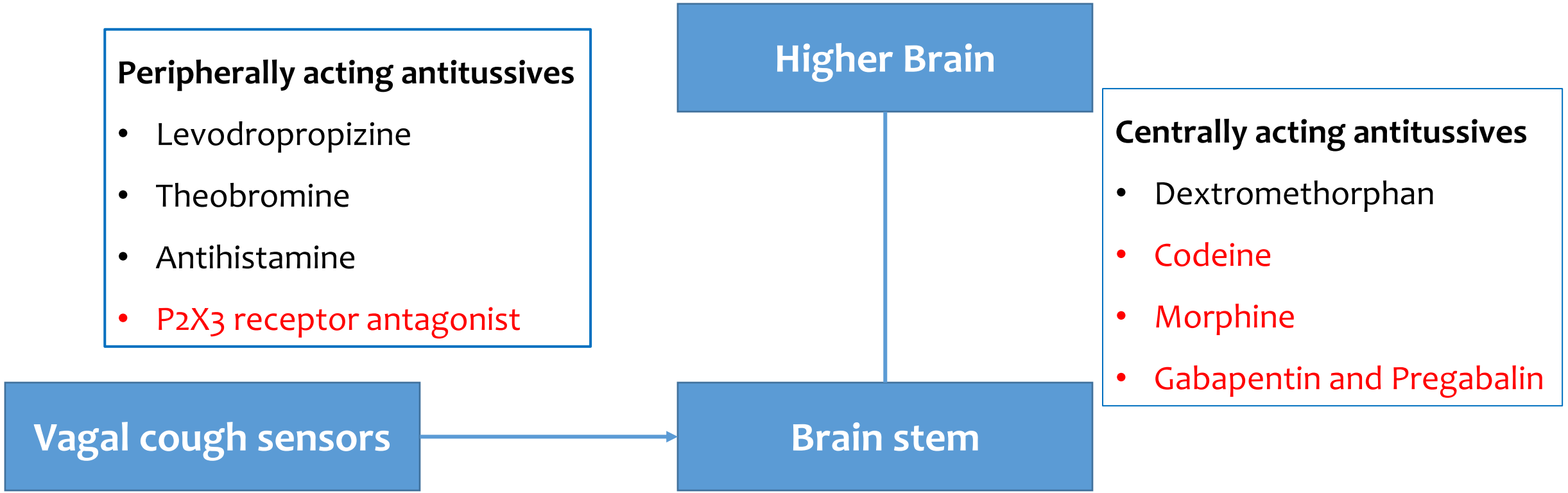
Medicine (Baltimore) 2017;96:e6486

Components of cough hypersensitivity syndrome



- 인후부 간질거림
- 이물감 (이상감각)
- 사소한 자극에 기침 : urge-to-cough

Korean J Intern Med 2020;35:811-822


Peripherally acting antitussives
• Levodropropizine
• Theobromine
• Antihistamine
• P2X3 receptor antagonist
Higher Brain
Centrally acting antitussives
• Dextromethorphan
• Codeine
• Morphine
• Gabapentin and Pregabalin
Vagal cough sensors
Brain stem

Pharmacological therapy for chronic refractory cough

- **Successful clinical trials**

Central acting

- Opioids (2007): low-dose SR morphine (5mg bid), codeine
- Gabapentin (2012)
- Pregabalin (2014)

Pph. acting

- P2X3 antagonist (Gefapixant) (2020)

Treatment for unexplained chronic cough

- Opioids
  - **Codeine** (morphine 의 prodrug), **Morphine**
    - 국내의 경우, Morphine 은 기침조절목적으로 허가 사항이 없음
    - Codeine : cytochrome P450에 의해 대사
    - Morphine may be more reliable than codeine
    - Marked variance in response
    - 변비(40%), 진정효과(25%) 에 대한 지속적인 모니터링 → 저용량으로 단기간 사용
    - **Codeine 20mg qid** : morphine 보다 의존성이 낮음
      - 간기능 저하자에서 주의, 신기능 저하자에서 용량 조절은 필요 없음
      - 유사체 : dihydrocodeine, pholcodine

Treatment for unexplained chronic cough

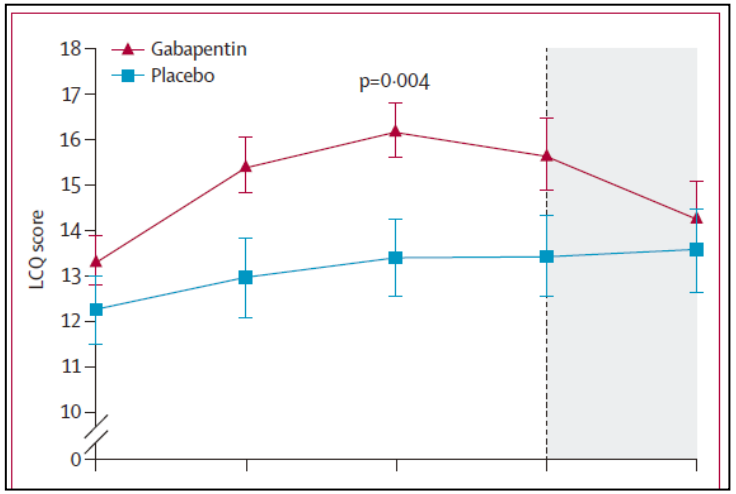
- Opioids
  - ERS guideline (2020) – Chronic refractory cough

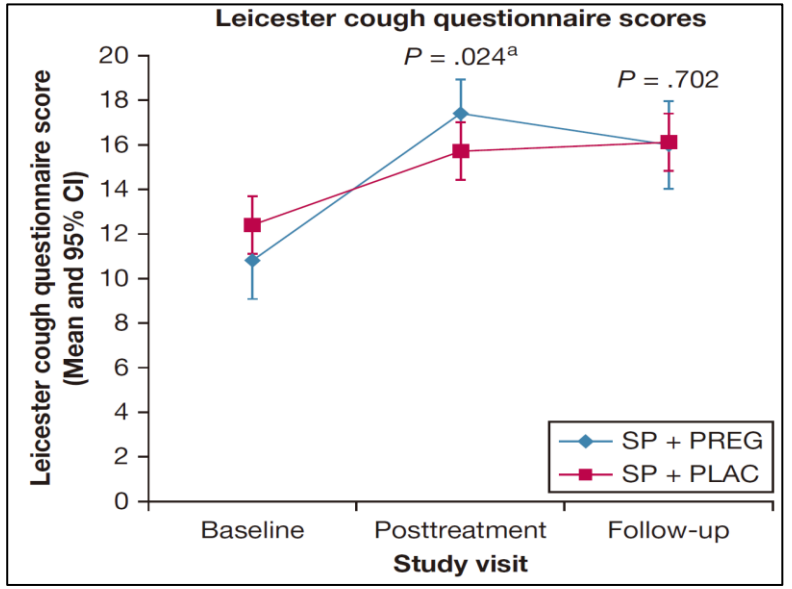
    - **Strong recommendation** / moderate level of evidence
    - **50%** of patients responded to opiates
    - Ceiling effect of therapeutic responses : ~ 20mg of daily dose (morphine)
    - **Stop if there is no response in 1~2 weeks**

Morice et al, Eur Respir J. 2020:55:1901136

Treatment for unexplained chronic cough

- Gabapentin and Pregabalin
  - Low quality and low quantity of studies, 국내에서는 임의비급여로만 처방가능
  - Gabapentin (300 ~ 1800 mg/day, gradual increase) : nausea, fatigue in 30%
  - Pregabalin (~ 300mg/day) : blurred vision, cognition disturbance, dizziness, weight gain





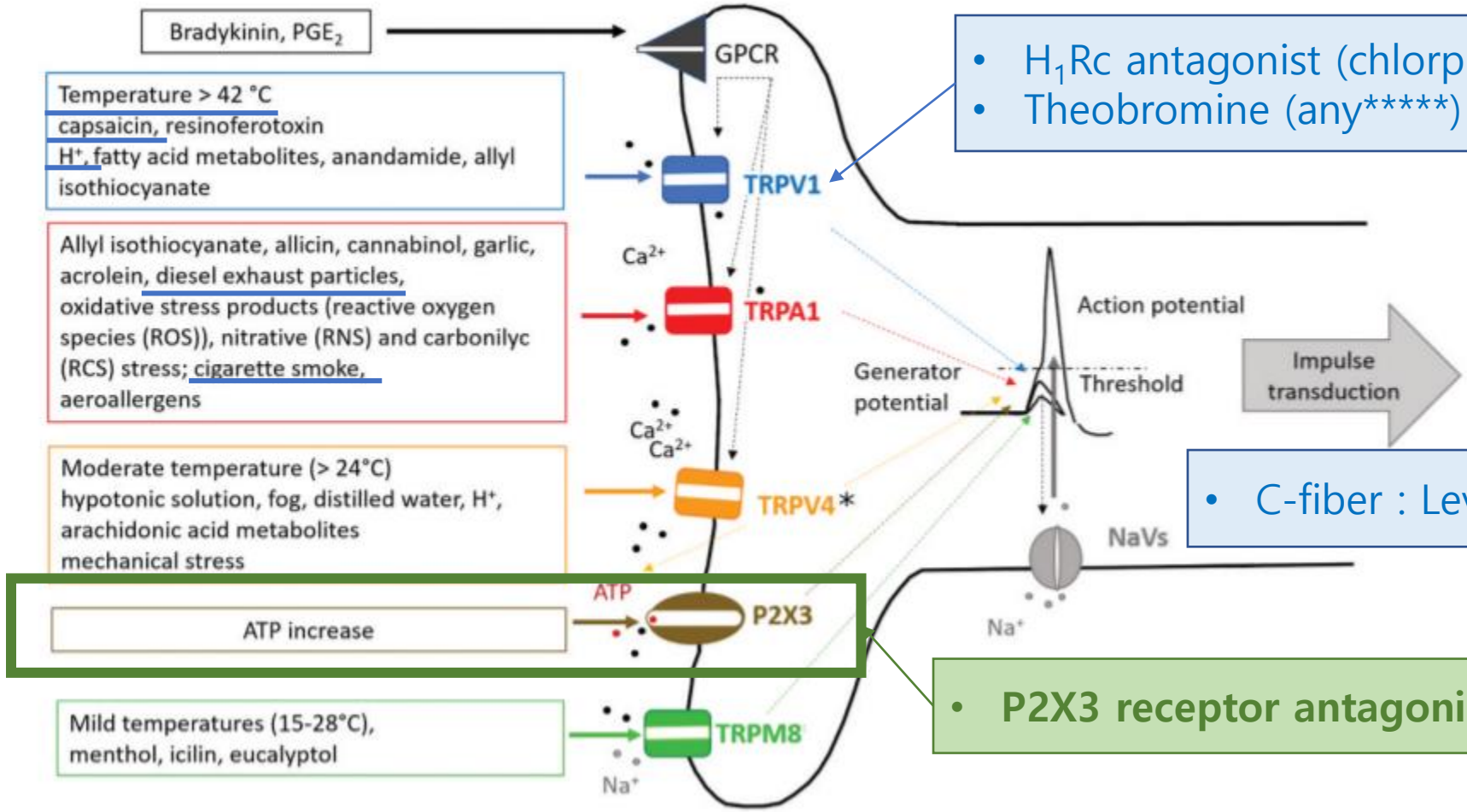
Ryan N et al. *Lancet 2012*, Vertigan AE et al. *Chest 2016*

Treatment for unexplained chronic cough

- Gabapentin and Pregabalin
  - ERS guideline (2020) – Chronic refractory cough
  - **Conditional recommendation / low level of evidence**

Morice et al, Eur Respir J. 2020:55:1901136

Novel therapy ： sensory nerve targeted



- H_1Rc antagonist (chlorpheniramine): co*** syrup
- Theobromine (any*****)

- C-fiber : Levodropropizine (levo*** syrup)

- **P2X3 receptor antagonist (Gefapixant)**

Expert Review of Respiratory Medicine, 2020:14:1217

P2X3 receptor antagonist (Gefapixant)

- Proof-of-concept study
- N=34, RCT
- Outcomes
  - Daytime cough frequency at two week
  - 75% reduced (p=0.0003)

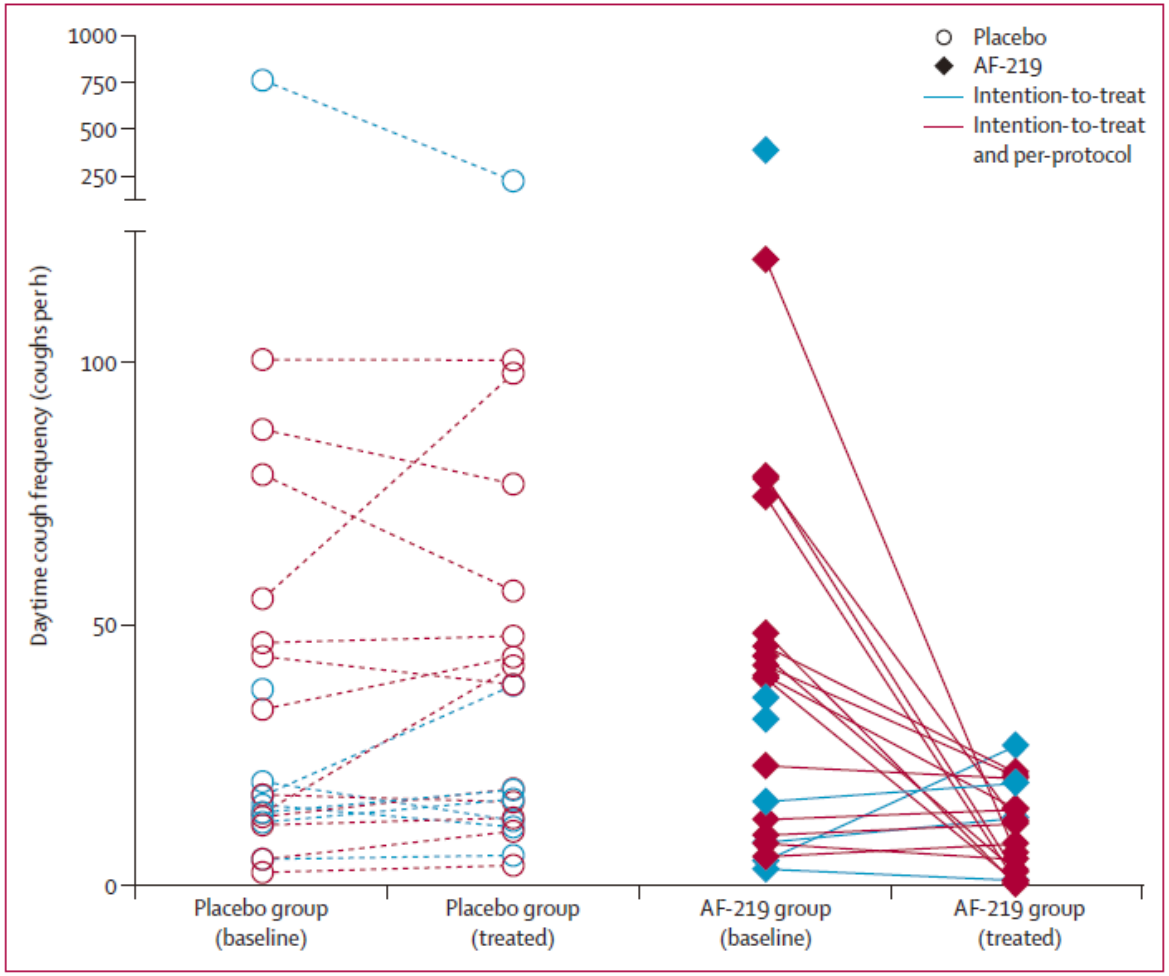
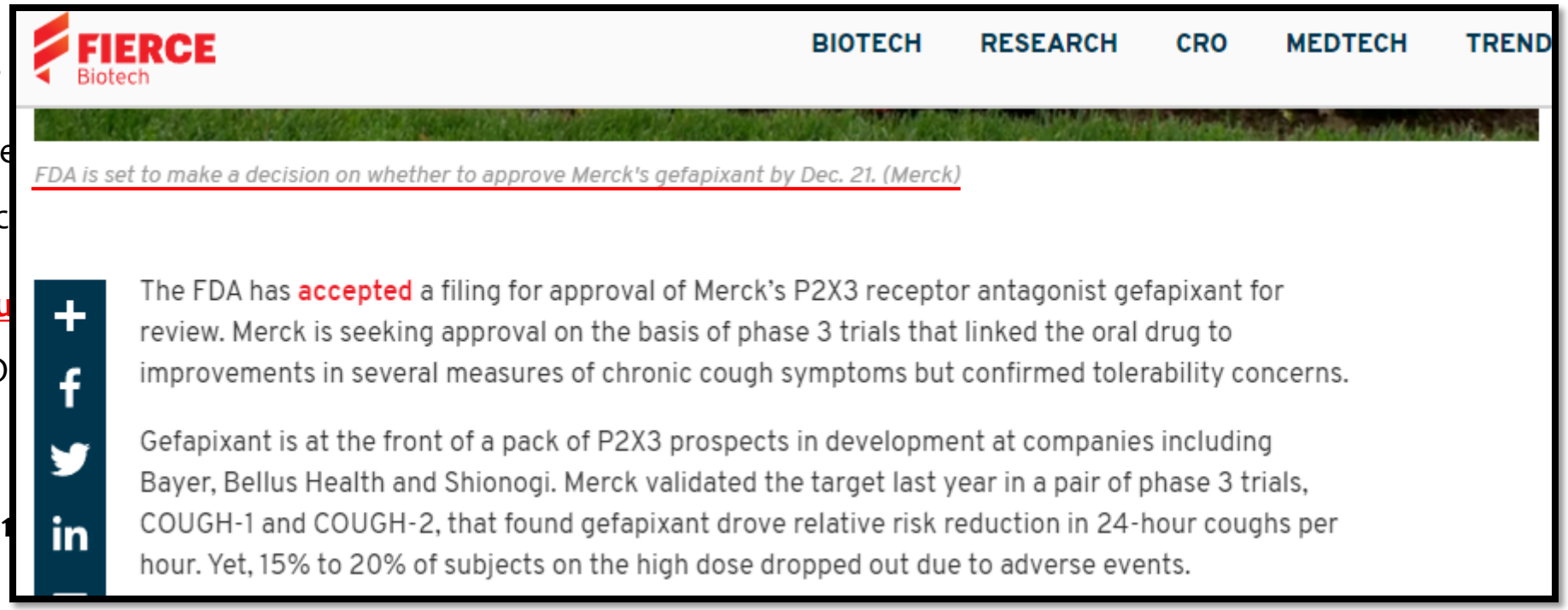


Figure 2: **Changes in objective daytime cough frequency from baseline to end of the treatment period**
Intention-to-treat analysis included the blue and red data points, whereas the per-protocol included data in red only.

Abdulqawi et al. *Lancet* 2014

Phase 3 study (Gefapixant) and FDA approval

- Age > 18, **more than 1 year with unexplained cough**
- **75% female, mean age=58, mean cough duration = 11 yr**
- COUGH-1 (n=730, 12 weeks),
- 24-hour cough frequency me
  digital audio recording devic
- 45mg bid of gefapixant **redu**
  frequency (COUGH-1 and CO
  compared with baseline.
- Discontinuation due to AE : **1**



FIERCE Biotech

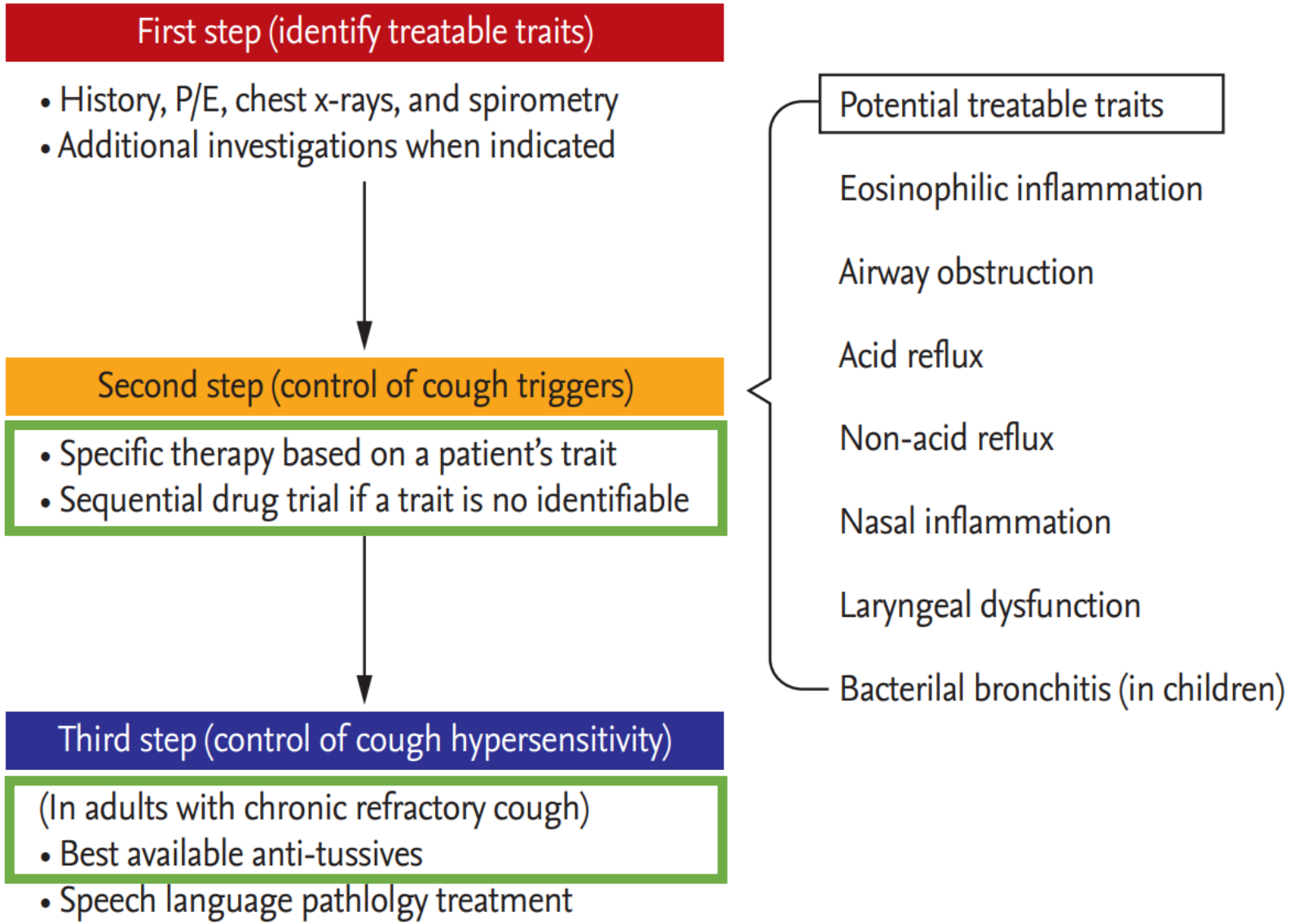
BIOTECH RESEARCH CRO MEDTECH TREND

FDA is set to make a decision on whether to approve Merck's gefapixant by Dec. 21. (Merck)

The FDA has **accepted** a filing for approval of Merck's P2X3 receptor antagonist gefapixant for review. Merck is seeking approval on the basis of phase 3 trials that linked the oral drug to improvements in several measures of chronic cough symptoms but confirmed tolerability concerns.

Gefapixant is at the front of a pack of P2X3 prospects in development at companies including Bayer, Bellus Health and Shionogi. Merck validated the target last year in a pair of phase 3 trials, COUGH-1 and COUGH-2, that found gefapixant drove relative risk reduction in 24-hour coughs per hour. Yet, 15% to 20% of subjects on the high dose dropped out due to adverse events.

Eur Respir J, 2020:56:3800 (Late Breaking Abstract)


First step (identify treatable traits)
• History, P/E, chest x-rays, and spirometry
• Additional investigations when indicated
Second step (control of cough triggers)
• Specific therapy based on a patient's trait
• Sequential drug trial if a trait is no identifiable
Third step (control of cough hypersensitivity)
(In adults with chronic refractory cough)
• Best available anti-tussives
• Speech language pathlolgy treatment
Potential treatable traits
Eosinophilic inflammation
Airway obstruction
Acid reflux
Non-acid reflux
Nasal inflammation
Laryngeal dysfunction
Bacterilal bronchitis (in children)

Example 4. (Unexplained refractory cough)

- F/58, cough lasting **for 6 months**
- No medication, Non-smoker, No previous respiratory infection Hx.
- BMI = 22.6
- Dyspnea (-), Nasal congestion or post-nasal drip (-), GER-related Sx (-)
- Wheezing/rale (-/-), Normal PNS and CXR, FENO = 19 ppb
- Chest CT : no abnormalities, Methacholine provocation test (-) : 2차 병원의뢰
- **No response to PPI, ICS, and anti-histamine for 4 weeks**

➔ **Try anti-tussive(s) that are expected to most effective and monitor their side effects**

Conclusions I

- Cough lasting for over 8 weeks in adults
  - Some of them can be **persistent** or **frequently recurrent**
  - Older > Younger, Female > Male
- **FENO can be a useful tool in primary clinics** (with CXR/PNS) during work-up

- Paradigm shift for chronic cough
  - Concept of "**hypersensitivity cough sydrome**" has emerged and been incorporated into **conventional anatomical protocol.**
  - Further studies for **neuropathophysiology** are required

Conclusions II

- **Triggers or associated diseases** should be controlled, if they are evident
  - CVA and EB : ICS
  - UACS : anti-histamine + anticongestant …
  - GERD with Sx : PPIs
  - **Sequential trial can be considered.**

  } Control of treatable traits

- **Unexplained refractory cough**
  - Peripherally or Centrally acting anti-tussives
  - Older drugs : inadequate efficacy & significant side effects ☞ monitoring
  - Novel drugs (Gefapixant) for specific cough receptors : promising

Thank you for listening!