Respiratory diseases, where we are and where we want to be in clinical science and medicines development: unmet needs, challenges and opportunities

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November, 13, 2015

Agenda

- Respiratory Diseases: medical, social and economic burden, overview
- Clinical science and medicines development, where we are: Asthma ,COPD and IPF
- Clinical endpoints, surrogate endpoints, biomarkers: challenges and opportunities
- Collaboration efforts and consortia programs
- Summary & Discussion

ERS

€380bn

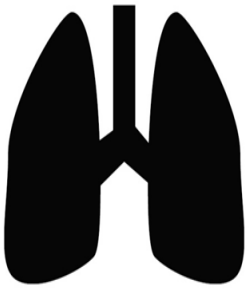
The total cost of respiratory disease in the EU exceeds 380 billion euro

ELF

€200bn

Greatest burden is from COPD and asthma – over 200 billion euro

600,000 people die every year in the EU from respiratory disease

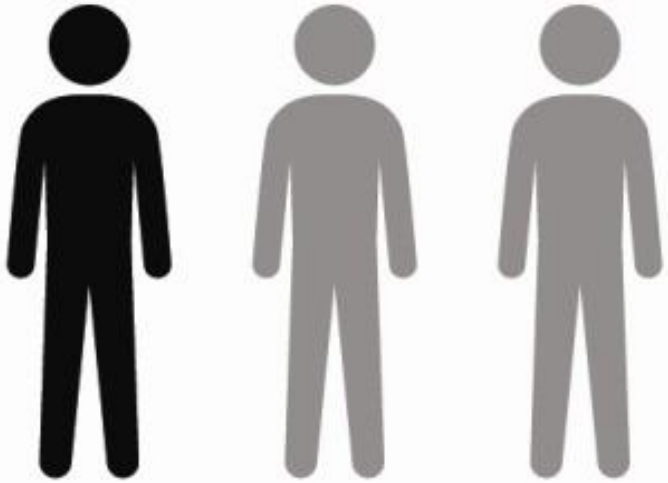


6 million hospital admissions per year are due to respiratory diseases

european respiratory society every breath counts

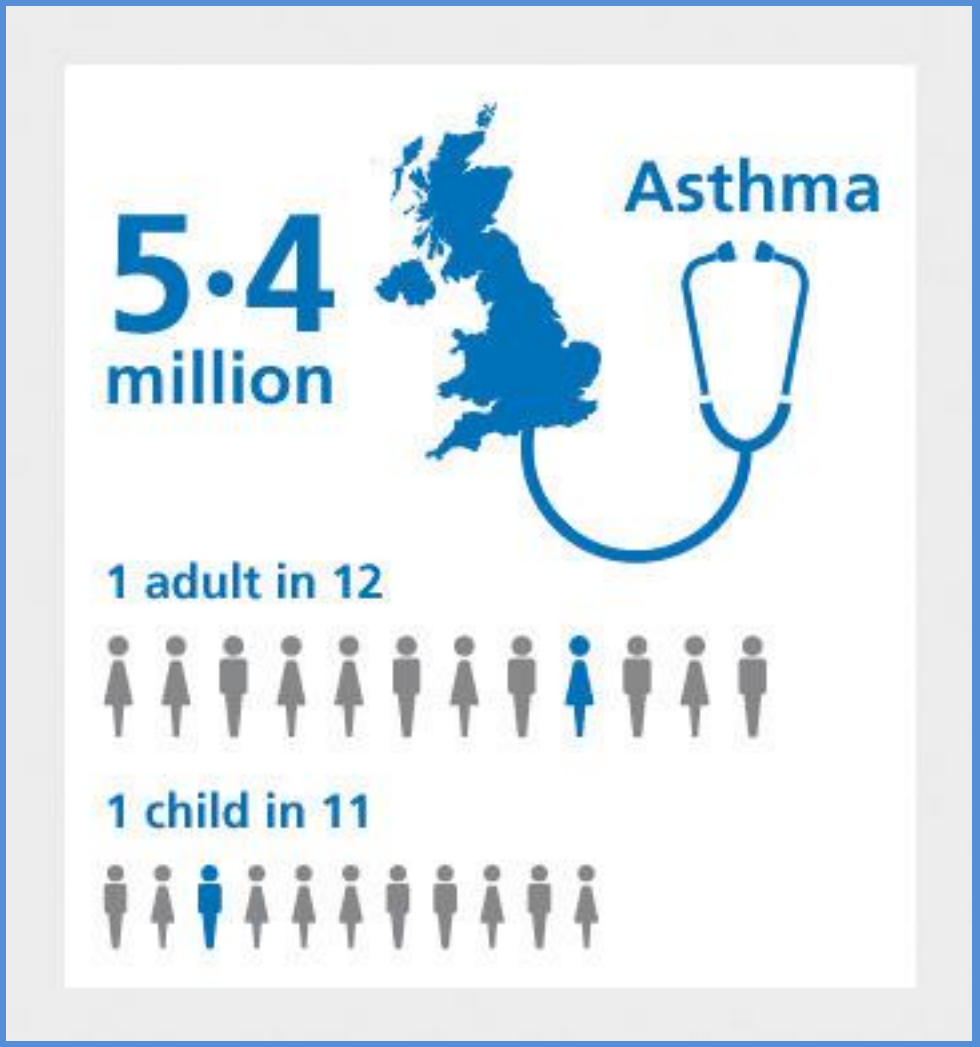
ERS

ELF



Approximately one third of the population will develop asthma at some time between the ages of 5 and 80 years, most before the age of 20 years

UK Asthma Prevalence



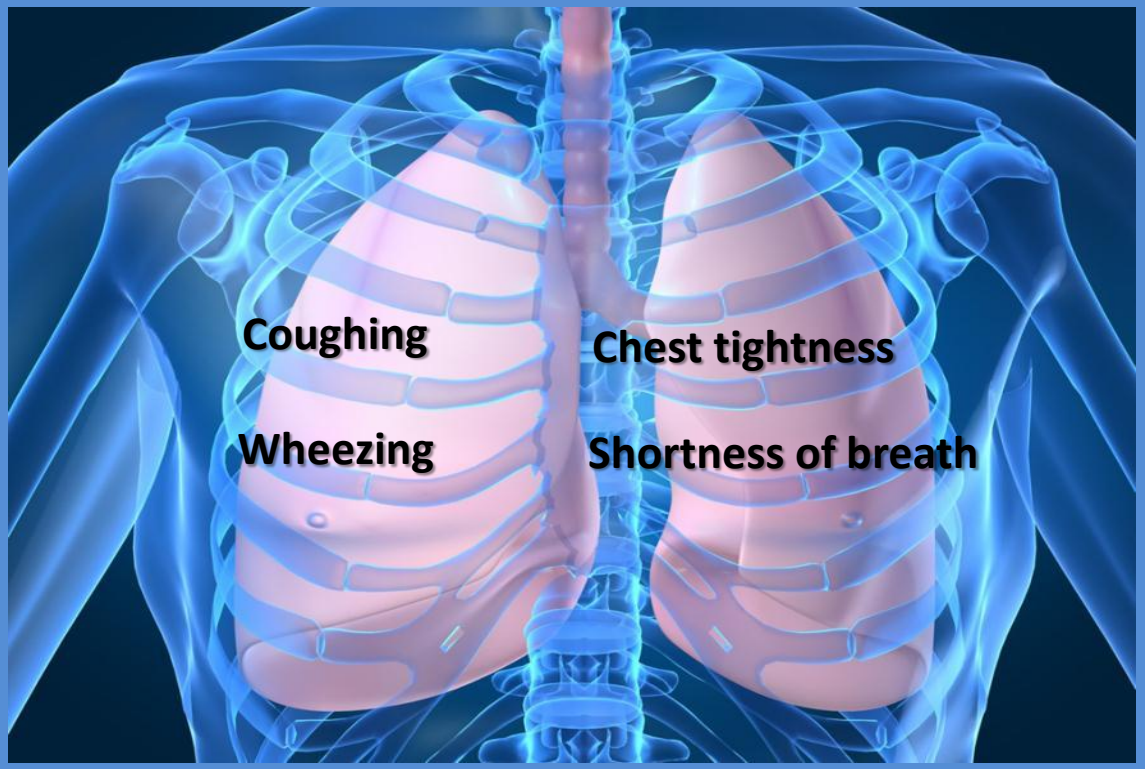
There were 1,167 deaths from asthma in the UK in 2011

AsthmaUK

Asthma: definition and symptoms

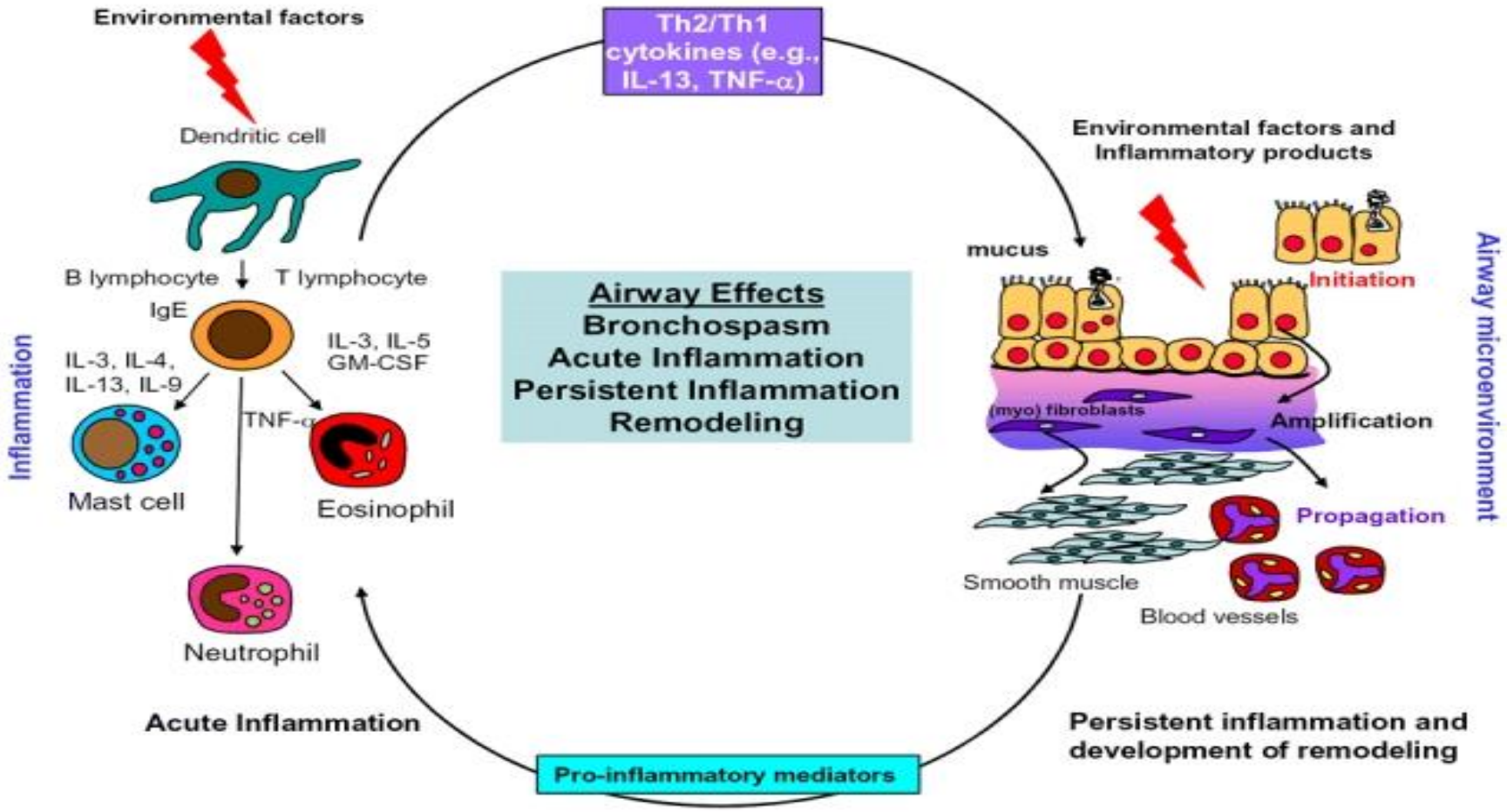
- Asthma is characterized by variable airflow limitation, airway hyperresponsiveness (AHR, increased sensitivity of the airways to an inhaled constrictor agonist) and inflammation, as well as underlying structural changes to the airways, which all contribute to airway narrowing

- Symptoms may culminate in a life-threatening situation known as an asthma exacerbation



GINA 2015, Airway hyperresponsiveness. Chest Airway hyperresponsiveness.O'Byrne PM, Inman MD.Chest. 2003 Mar;123(3 Suppl):411S-6S

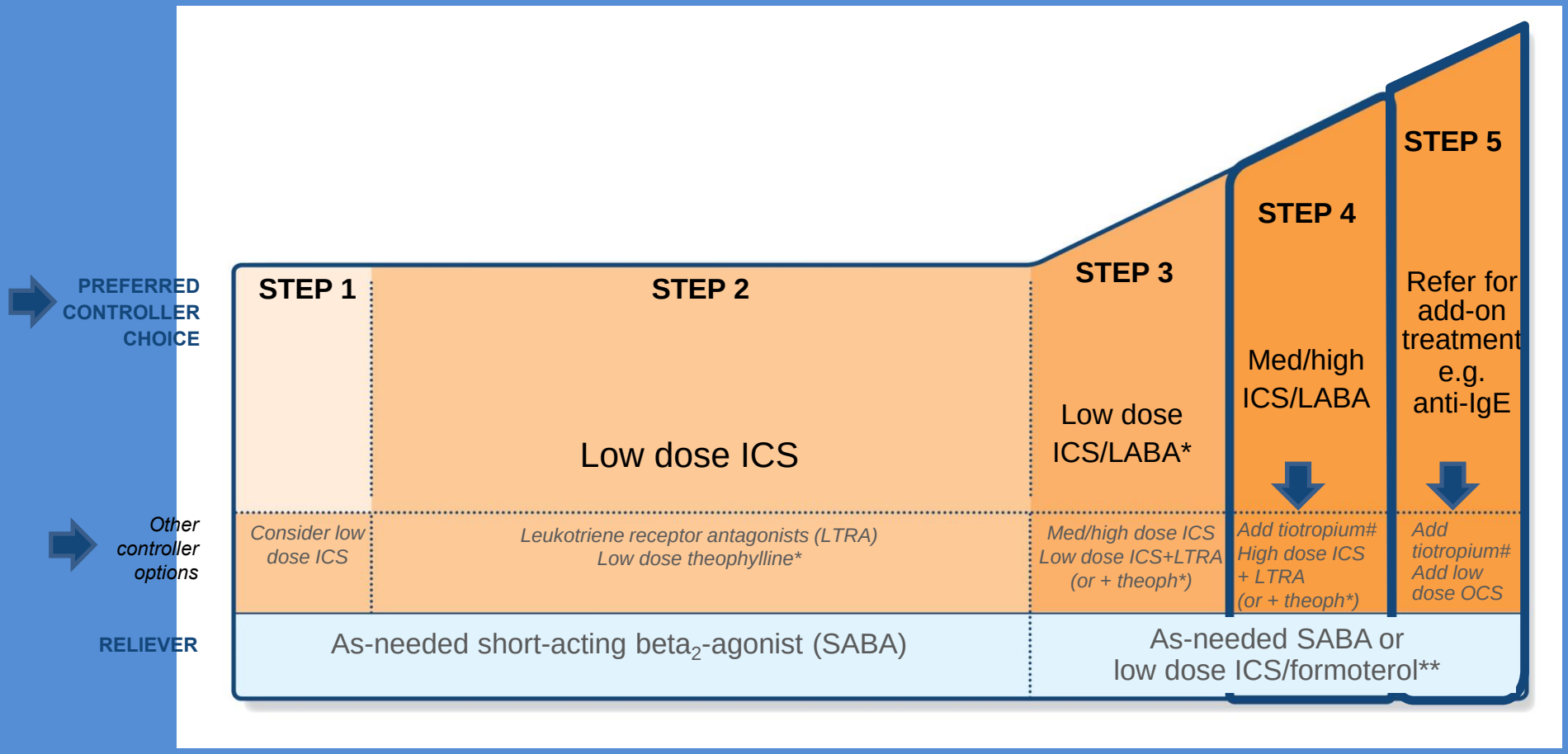
FACTORS LIMITING AIRFLOW IN ACUTE AND PERSISTENT ASTHMA



Key: GM-CSF, granulocyte-macrophage colony-stimulating factor; IgE, immunoglobulin E; IL-3, interleukin 3 (and similar); TNF-α, tumor necrosis factor-alpha

NAEPP, EPR-3, pg. 15, The Lancet, 368, Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults, 780–93 .

Asthma treatment



*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy
Tiotropium by soft-mist inhaler is indicated as add-on treatment for patients with a history of exacerbations; it is not indicated in children <18 years.

ICS: Inhaled Corticosteroids (Anti-Inflammatory)
LABA: Long-Acting β2-agonist (Bronchodilators)

GINA 2015, Box 3-5, Steps 4 and 5

Current asthma treatment landscape: limitations of treatment paradigm

Despite management by SOC therapies:

- 1/3 of asthma patients never achieved total control
- 1/3 severe asthma patients have limited clinical response to escalating doses of ICS
  - Up to 30% of patients are reported to be steroid insensitive
- Frequent OCS use has significant risk factors (e.g. fractures, bruising, cataracts, muscle weakness)

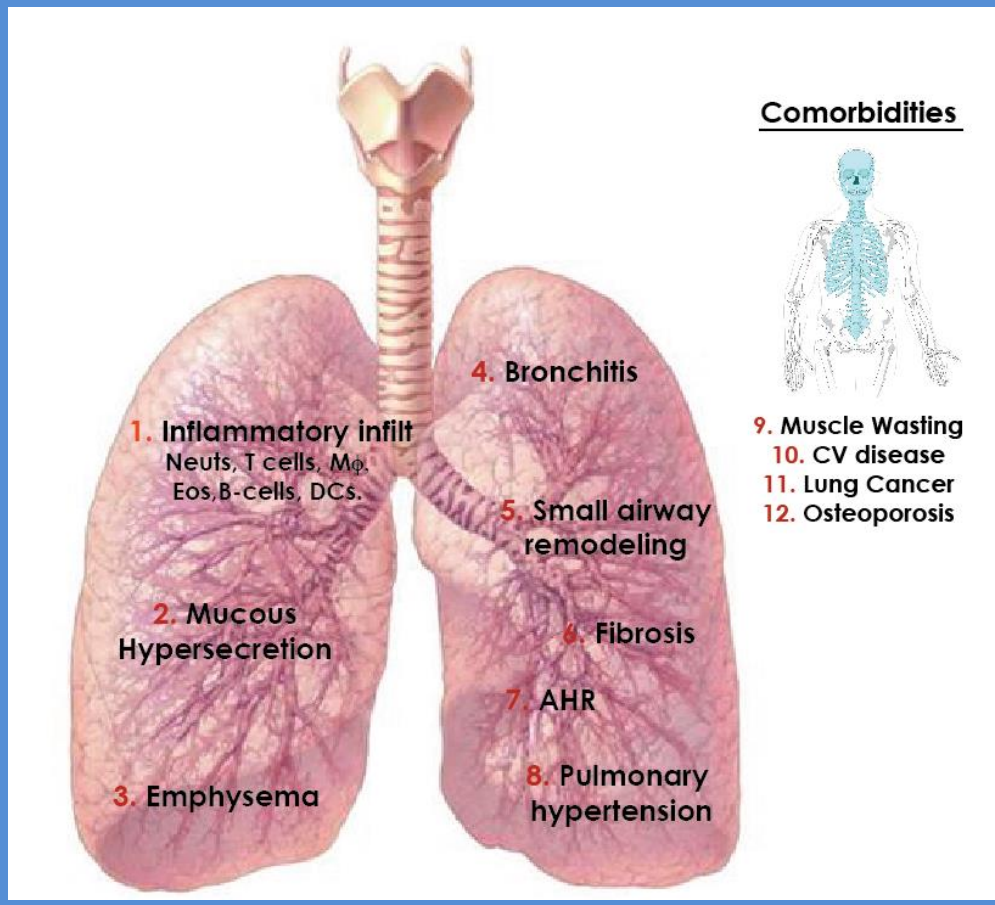
Overview of sources:

1. *Stephen P. Peters, MD, PhD,a Craig A. Jones, MD,b Tmirah Haselkorn, PhD,c, David R. Mink, MS,d David J. Valacer, MD,c and Scott T. Weiss, Mde. Real-world Evaluation of Asthma Control and Treatment (REACT): Findings from a national Web-based survey resistance J Allergy Clin Immunol 2007;119(6):1454-1461*
2. *Eric D. Bateman, Homer A. Boushey, Jean Bousquet, William W. Busse, Tim J. H. Clark, Romain A. Pauwels,Søren E. Pedersen for the GOAL Investigators. Group Can Guideline-defined Asthma Control Be Achieved? The Gaining Optimal Asthma ControL Study: Am J Respir Crit Care Med Vol 170. pp 836–844, 2004*
3. *Holt S, Suder A, Weatherall M, Cheng S, Shirtcliffe P, Beasley R. Dose-response relations of inhaled fluticasone propionate in adolescents and adults with asthma:meta analysis, BMJ 2001;323 (7307);253-256*
4. *Broder MS, Chang EY, Kamath T,Sapra S. Poor disease control among insured users of high dose combination therapy in asthma. Allergy Asthma Proc. 2010;31(1) 60-67*
5. *Donald Y. M. Leung, MD, PhD, John W. Bloom, MD. Update on glucocorticoid action and resistance J Allergy Clin Immunol 2003;111:3-22*
6. *Matsumoto H, Ishihara K, Hasegawa T, Umeda B, Niimi A, Hino M. Effects of inhaled corticosteroid and short courses of oral corticosteroids on bone mineral density in asthmatic patients: a 4-year longitudinal study. Chest. 2001;120:1468-1473. 3. Walsh LJ,*
7. *Wong CA, Oborne J, et al. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. Thorax.*

COPD

Chronic disease of lung characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response

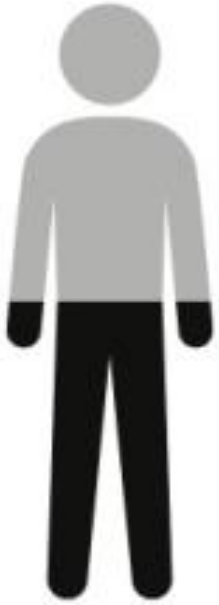
- Major risk factor is smoking; occupational or biomass exposures may account for ~10%
- Symptoms include cough, excess sputum production, shortness of breath, and exercise limitation
- COPD overlaps with traditional diagnostic terms such as chronic bronchitis and emphysema
- Many patients also have systemic effects and co-morbidities that add to burden of disease



The 10 most common causes of death in 2008. Source: World Health Organization (WHO) World Health Statistics 2011., GOLD 2015, Guarascio et al The clinical and economic burden of chronic obstructive pulmonary disease in the USA, Clinicoecon Outcomes Res. 2013; 5: 235–245

ERS

ELF



40-50% of lifelong smokers will develop COPD, compared with 10% of people who have never smoked

The burden of various respiratory diseases, around 2010, in the 28 countries of the European Union

COPD
Deaths
150 000
Hospital admissions
1.1 million per year
Prevalence
23 million with COPD
Adults aged ≥40 years
260 million

Lung cancer
Deaths
188 000
Hospital admissions
521 000 per year
Incidence
234 000 new cases per year
Population all ages
505 million

Tuberculosis
Deaths
5500
Hospital admissions
105 000 per year
Incidence
80 000 new cases per year
Population all ages
505 million

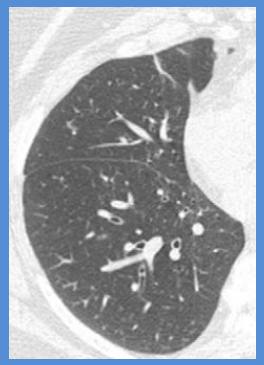
ERS ELF White Book

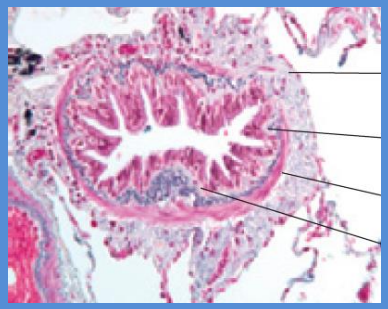
WHO, most common causes of death in 2008

Deaths attributed to	Worldwide	WHO European Region
Ischaemic heart disease	7.3 million (12.8%)	2.40 million (24.7%)
Cerebrovascular disease	6.2 million (10.8%)	1.40 million (14.0%)
Lower respiratory infections	**3.5 million (6.1%)**	**0.23 million (2.3%)**
COPD	**3.3 million (5.8%)**	**0.25 million (2.5%)**
Diarrhoeal diseases	2.5 million (4.3%)	0.03 million (0.3%)
HIV/AIDS	1.8 million (3.1%)	0.08 million (0.8%)
Trachea/bronchus/lung cancer	**1.4 million (2.4%)**	**0.38 million (3.9%)**
Tuberculosis	**1.3 million (2.4%)**	**0.08 million (0.8%)**
Diabetes mellitus	1.3 million (2.2%)	0.17 million (1.7%)
Road traffic accidents	1.2 million (2.1%)	0.12 million (1.2%)

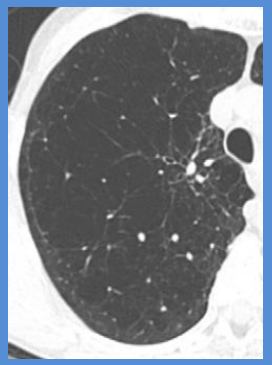
The 10 most common causes of death in 2008. Source: World Health Organization (WHO) World Health Statistics 2011.

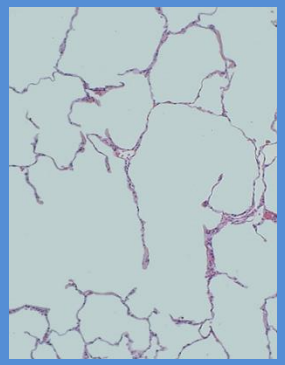
COPD is far more heterogeneous than asthma





Wide spectrum of disease





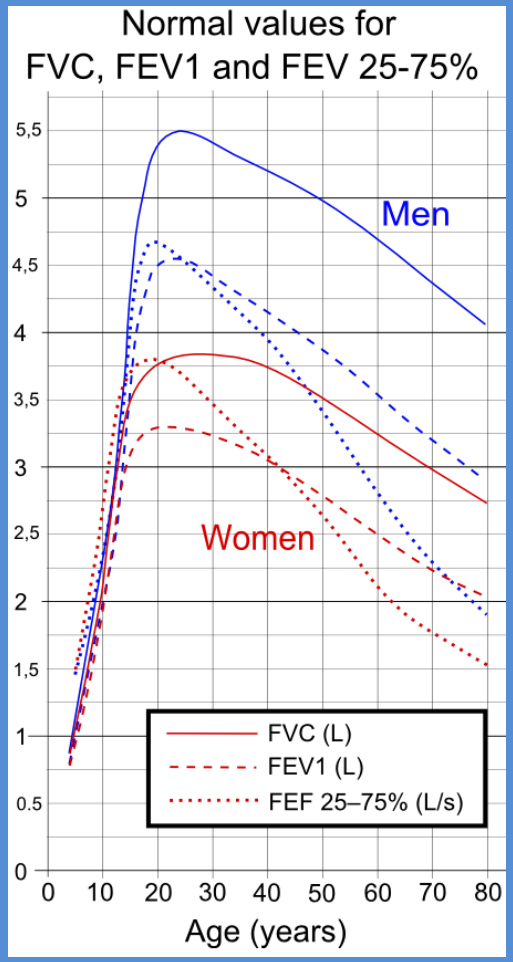
Chronic bronchitis "asthma-like" phenotype

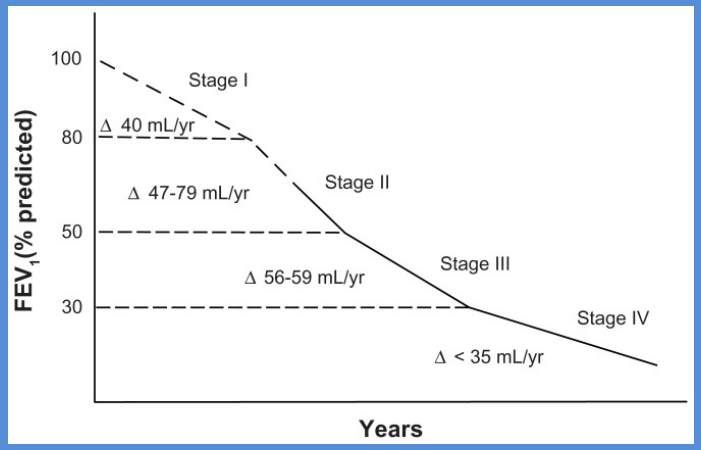
Emphysema phenotype

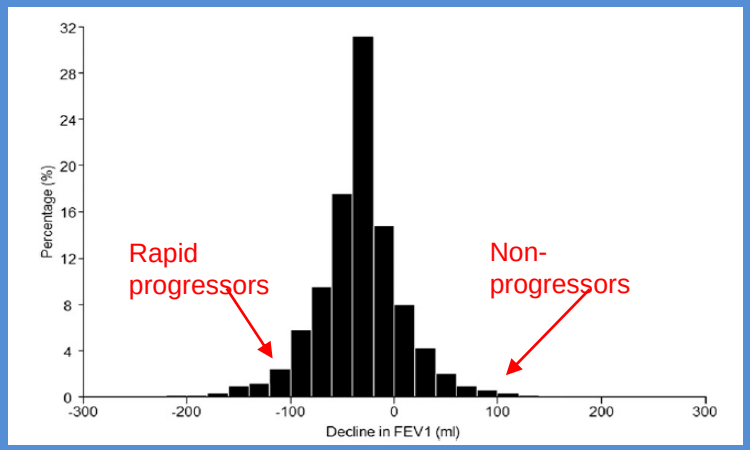
Clinical-radiographic-histopathological manifestations vary from pure **airway disease (e.g. chronic bronchitis)** to extensive **alveolar destruction (e.g. emphysema)**

Lung function decline in COPD. antucci C, Modina D - Int J Chron Obstruct Pulmon Dis (2012, GOLD 2015,) Chronic obstructive pulmonary disease: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases. Ann Am Torac Soc2014 Drummond MB et al

Patients with COPD experience **accelerated loss of lung function**, but the rate of decline varies widely (e.g. **not all patients progress**)







Lung function decline in COPD. antucci C, Modina D - Int J Chron Obstruct Pulmon Dis (2012, GOLD 2015,) Chronic obstructive pulmonary disease: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases. Ann Am Torac Soc2014 Drummond MB et al, Stanojevic S, Wade A, Stocks J, et al. (February 2008). "Reference ranges for spirometry across all ages: a new approach". Am. J. Respir. Crit. Care Med. 177 (3): 253–60

COPD Classification & Treatment

Classification of Airflow Severity (GOLD Grade)

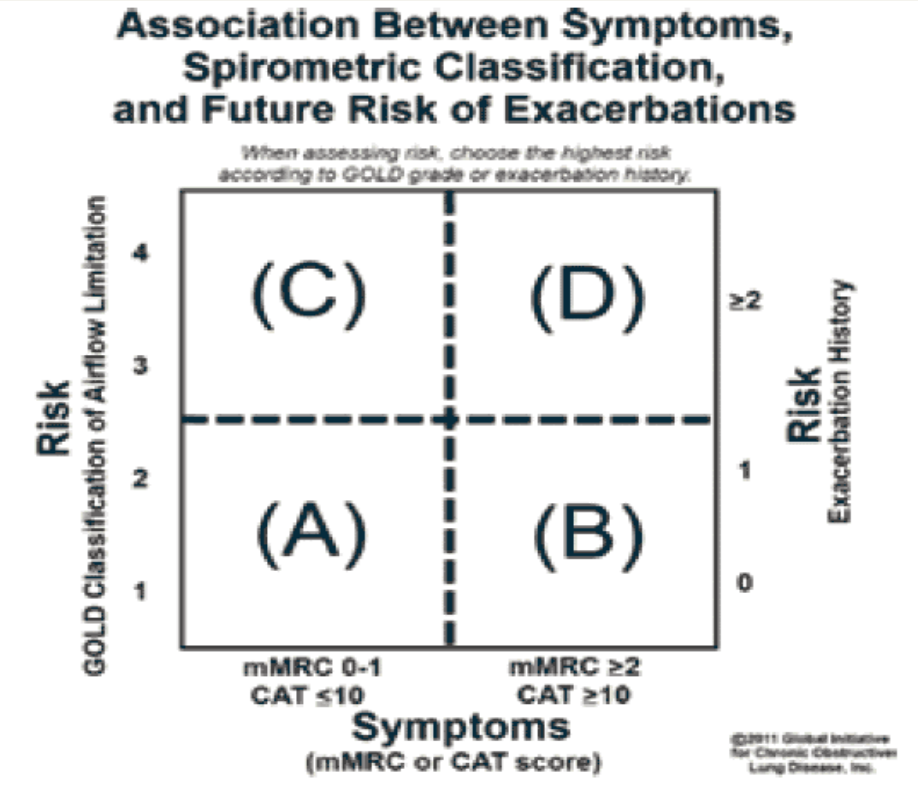
Table 2.5. Classification of Severity of Airflow Limitation in COPD (Based on Post-Bronchodilator FEV_1)

In patients with $FEV_1/FVC < 0.70$:

GOLD 1:	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4:	Very Severe	$FEV_1 < 30\%$ predicted

Combined Symptom-Risk Assessment

FIGURE 1



CAT = COPD (chronic obstructive pulmonary disease) Assessment Test; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = Modified Medical Research Council.
Reprinted with permission from reference 1.

GOLD, 2015, https://www.pharmacytimes.org/landing/282

Management of Stable COPD: Pharmacologic Therapy

- Treatment algorithm with well-defined stepwise approach to therapy is not available in COPD
- Existing medications for COPD treatment have not been conclusively shown to modify the long-term lung function decline

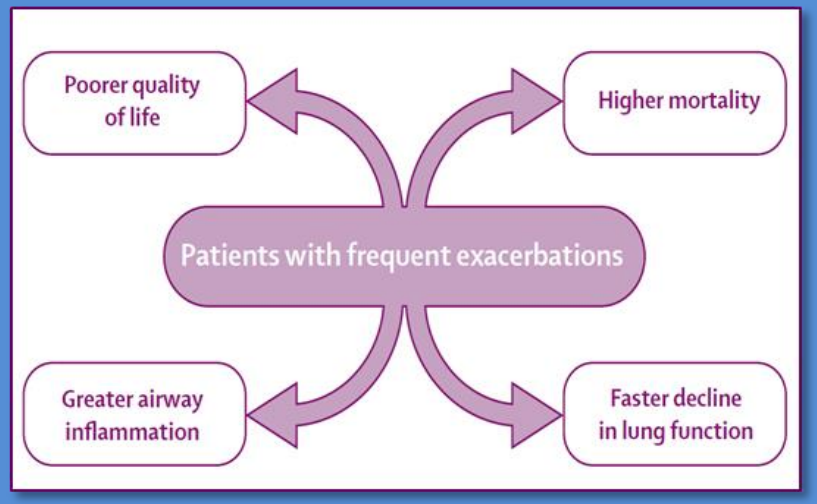
Main Pharmacologic Management:
SABA = Short-acting beta-agonist
SAMA = Short-acting anti-muscarinic
LABA = Long-acting beta-agonist
LAMA = Long-acting anti-muscarinic
ICS = Inhaled corticosteroid

GOLD Group	1st choice	Alternative
A	SABA *or* SAMA	LAMA *or* LABA *or* SABA + SAMA
B	LABA *or* LAMA	LAMA/LABA
C	ICS/LABA *or* LAMA	LAMA/LABA *or* LAMA + PDE_4I *or* LABA + PDE_4I
D	ICS/LABA *and/or* LAMA	ICS/LABA + LAMA *or* ICS/LABA + PDE_4I *or* LAMA/LABA *or* LAMA + PDE_4I

Adapted from GOLD 2015; PDE_4I, phosphodiesterase-4 inhibitor (Roflumilast)

Unmet Medical Need in Moderate to Severe COPD

COPD is a leading cause of mortality and morbidity and the burden of disease is substantial and increasing and COPD exacerbations account for the greatest proportion of this burden



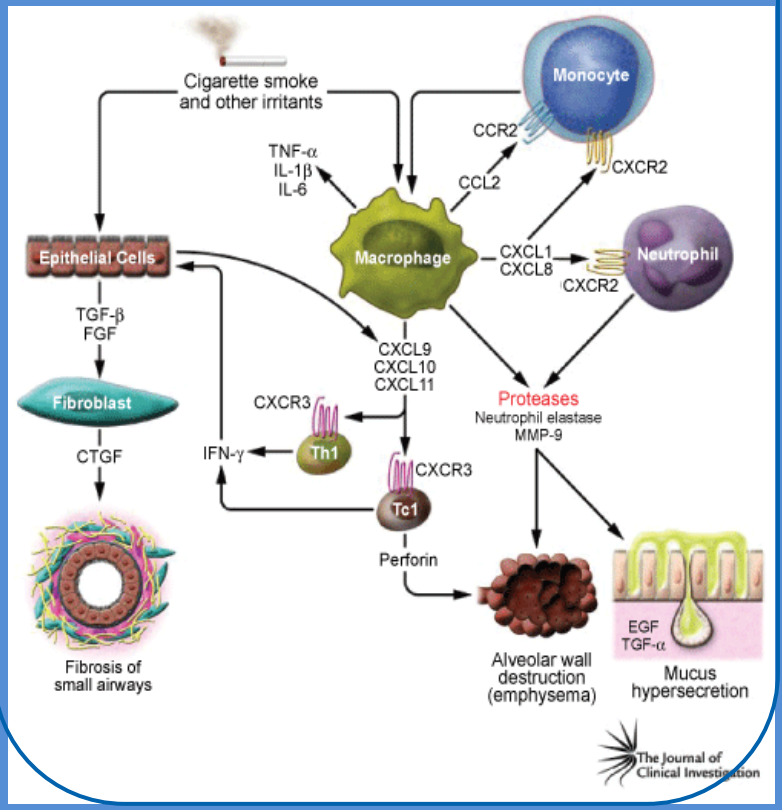
Currently available treatment options are effective in achieving bronchodilation and reducing symptoms for many patients, the effect on the risk of exacerbations is modest.

Mathers CD et al, 2006, Burge et al. 2000, Jones et al. 2003, Griffiths et al. 2000, Casaburi et al. 2002, Vincken et al. 2002, Calverley et al. 2003, Anzueto et al. 2013, GOLD, 2015)

The future of COPD will be untangling biologic heterogeneity

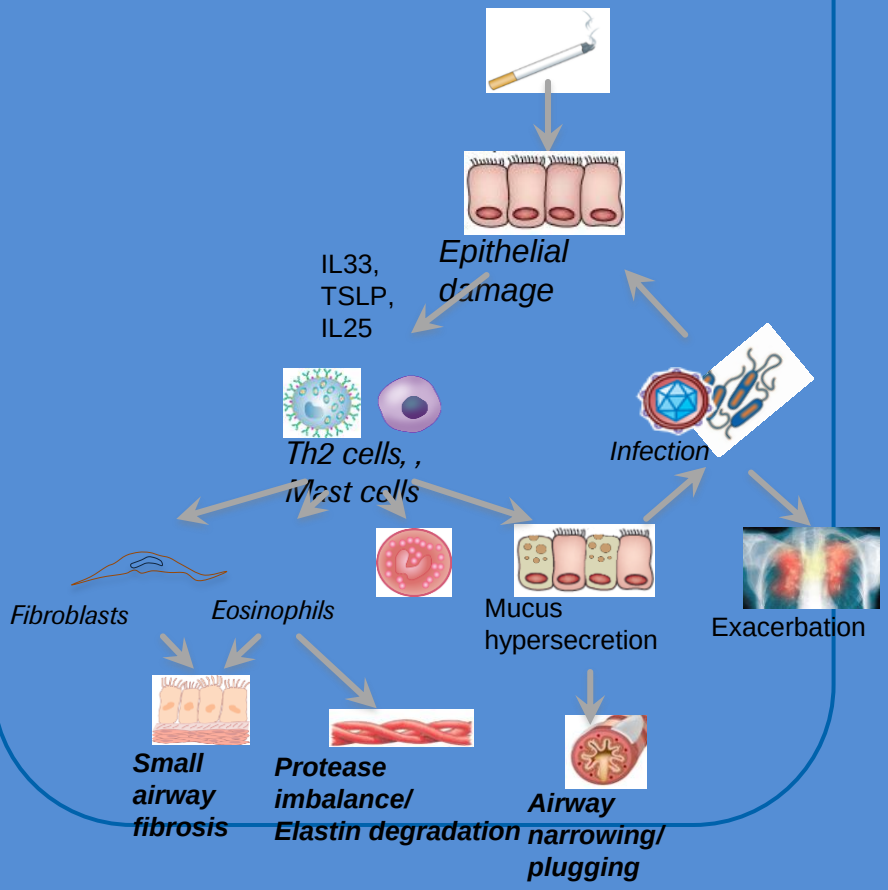
Current Paradigm

Neutrophils, macrophages and CD8+ lymphocytes are the key cell types causing inflammation in COPD.



Emerging Paradigm

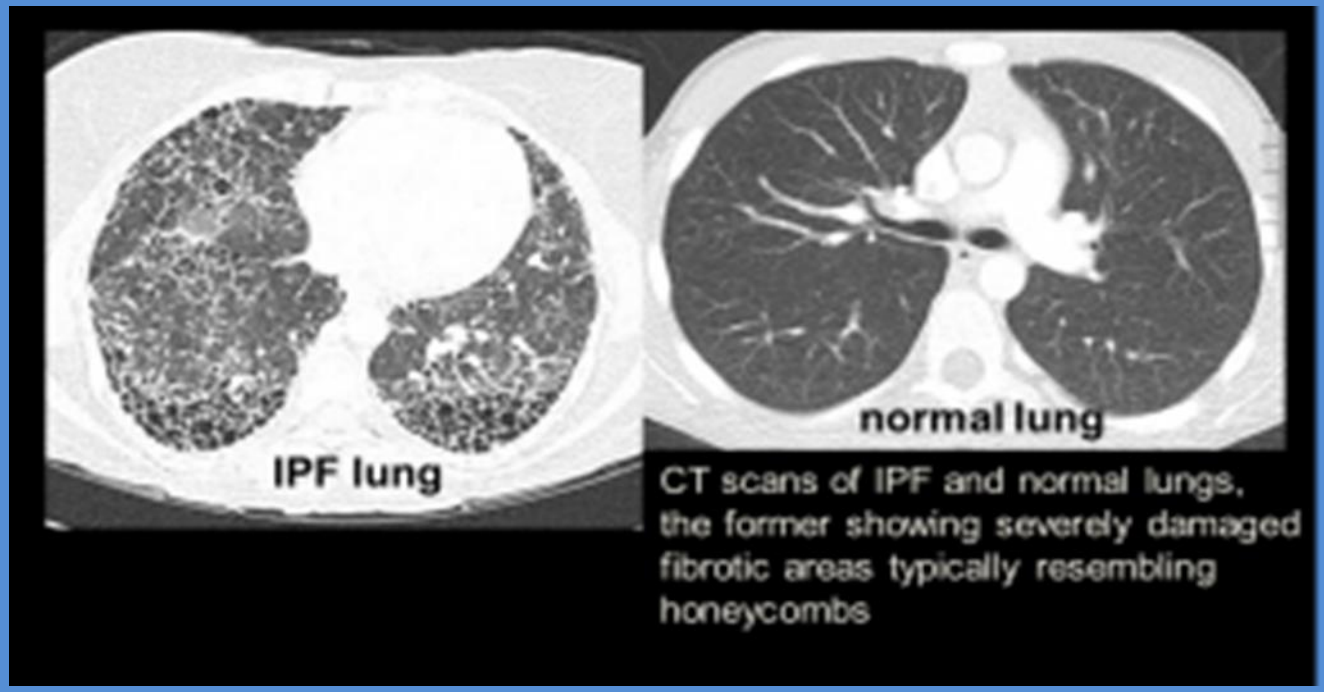
The key cell types vary. In some patients, eosinophils are activated in response to smoking or other insults.



Barnes PJ *J Clin Invest* 2008; 118:3546;

IPF: Definition and Pathogenesis

A specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs



CT scans of IPF and normal lungs, the former showing severely damaged fibrotic areas typically resembling honeycombs

IPF likely results from dysregulated repair of unknown alveolar injury, leading to fibrocyte recruitment, fibroblast accumulation, myofibroblast differentiation, overproduction of extracellular matrix proteins, and, ultimately, destruction of lung architecture

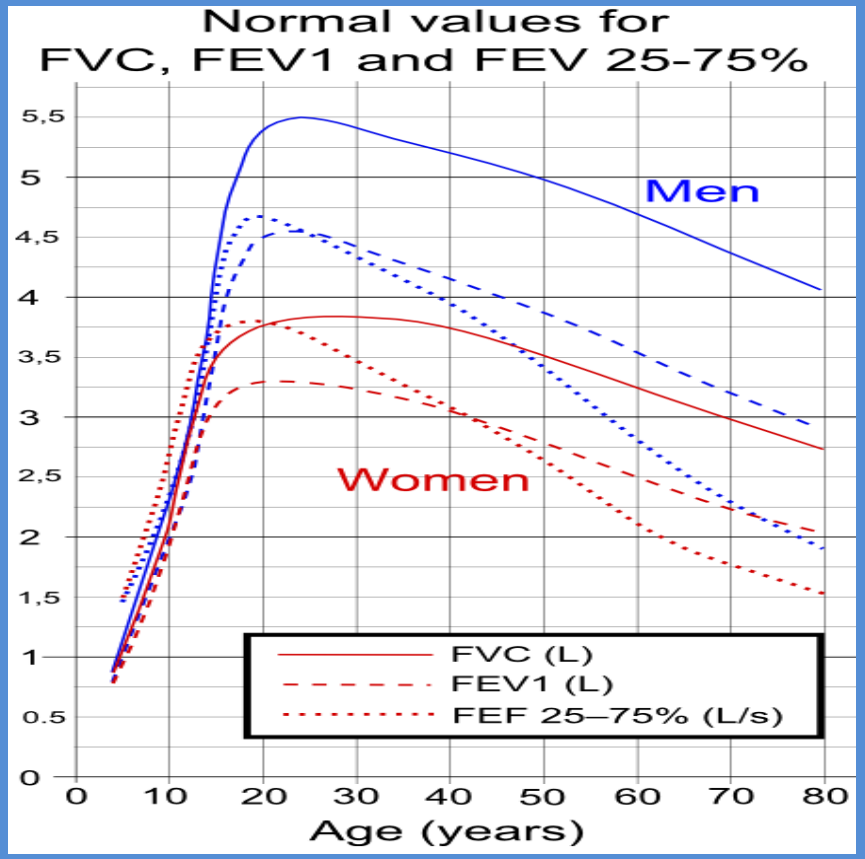
Naik P.K. et al. Periostin promotes fibrosis and predicts progression in patients with idiopathic pulmonary fibrosis, American Journal of Physiology - Lung Cellular and Molecular Physiology 2012 Vol. 303 no. L1046-L1056 Raghu G et al, An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management, Am J Respir Crit Care Med Vol 183. pp 788–824, 2011

More about IPF

- Affects about 250,000 in the United States and EU
- 50% patients die within 2-3 years of diagnosis, 10-year survival less than 15%
- Spontaneous remission does not occur

Respir Crit Care Med : Incidence and Prevalence of Idiopathic Pulmonary Fibrosis: Ganesh Raghu, M.D., Derek Weycker, Ph.D., John Edelsberg, M.D., M.P.H., Williamson Z. Bradford, M.D., Ph.D., Gerry Oster, Ph.D.: Published on June 29, 2006 as doi:10.1164/rccm.200602-163OC

FVC: Key lung function impact in patients with IPF



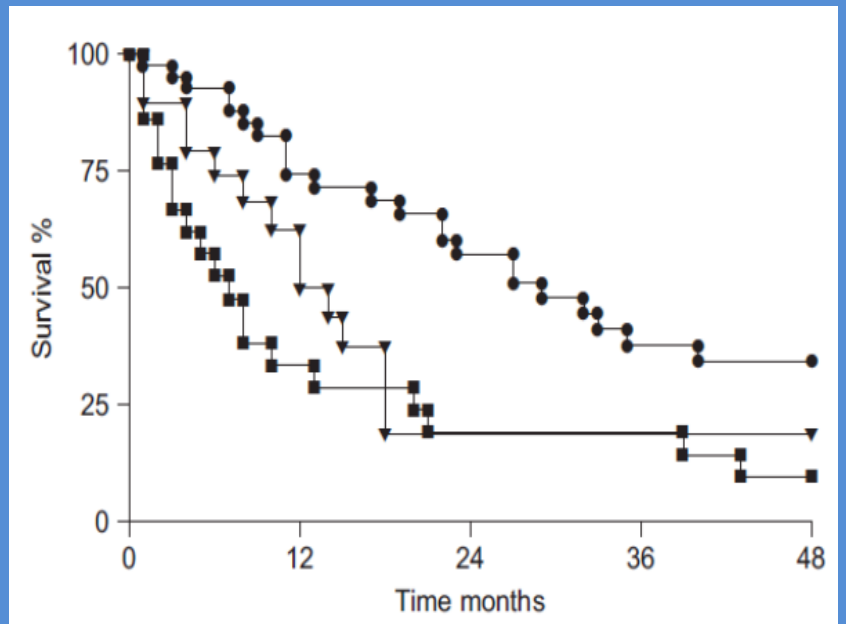


FIGURE 1. 4-yr survival in relation to the magnitude of serial change in forced vital capacity at 6 months in patients with idiopathic pulmonary fibrosis (n=84). Declines of 5–10% (marginal; ▼) and >10% (significant; ■) were both associated with a worse prognosis than stable disease (●) ($p<0.005$).

Substantial clinical evidence that a decline in FVC associated with increased mortality risk

Stanojevic S, Wade A, Stocks J, *et al.* (February 2008). *Am. J. Respir. Crit. Care Med.* **177** (3): 253–60,

Brett Ley, Harold R. Collard, and Talmadge E. King, Jr. "Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis", American Journal of Respiratory and Critical Care Medicine, Vol. 183, No. 4 (2011), pp. 431-440.

History of clinical studies in IPF – failure after failure…

Studies outcome: No meaningful difference between the intervention and placebo group:

Interferon γ-1B	(King et al lancet 2009)
Etanercept	(Raghu et al AJRCCM 2005)
Bosentan	(King et al AJRCCM 2008; AJRCCM 2011)
Imatinib	(Daniels et al AJRCCM 2010)
Sildenafil	(IPF net :NEJM 2010)

Studies outcome: Intervention worse than placebo:

- Warfarin increased mortality risk (AJRCCM 2012)
- Prednisolone+ NAC+ azathioprine increased mortality and hospitalisation risks (IPF net PANTHER study, NEJM 2012)

Finally, a glimpse of hope….

Recent breakthroughs advance the SOC: Esbriet® (Pirfenidone) and Ofev® (Nintedanib)

- Oral, small molecule drugs, with different MOAs, **approved simultaneously by FDA** for treatment of IPF on 15 October 2014
  - Ofev received EMEA approval on 19 January 2015, Esbriet approved in EU since 2011
  - Molecules had received FDA **Orphan, Fast Track, Breakthrough and Priority Review** designations
- Approvals based on **clinically meaningful** and **statistically significant changes in FVC** as well as mortality trends

Disease progression in IPF is unpredictable and medicines development is challenging

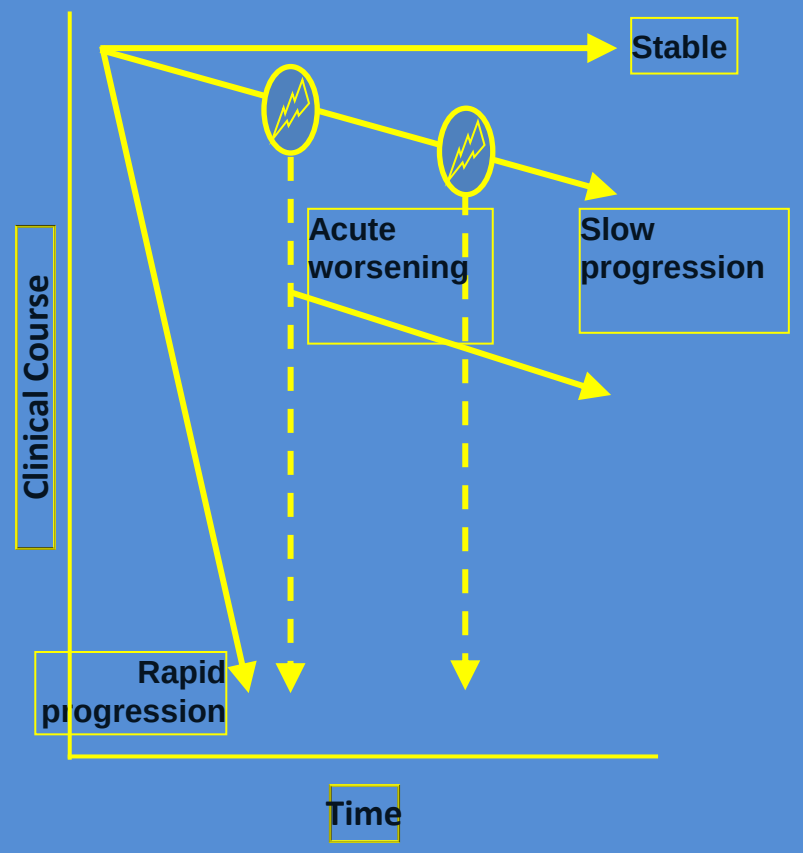
Preclinical models are not predictive of efficacy in humans

Lung fibrosis is thought to be largely irreversible

- possible efficacy ceiling

Clinical trials have been complex and lengthy

- Long treatment duration necessary to demonstrate clinical benefits
- Evolving standard of care limits options for comparators



Tools of the Trade

- Clinical endpoints
- Surrogate clinical endpoints
- Biomarkers
- Collaborations

http://armstrongclinical.com/service/clinical-study-design.html

Clinical Endpoints

	Clinical Endpoints	Clinical Surrogate Endpoints
Definition	Directly measure how a patient feels, functions or survives, e.g. PROs, exacerbations, mortality	An indirect measure intended to substitute for a clinically meaningful endpoint, e.g. Lung function parameter (e.g. FVC, DLCO), 6-minute Walk Test (6MWT), Imaging (e.g. quantitative HRCT)
Issues	Time needed to feasibly demonstrate treatment effect	Many indications or claims still with no validated surrogate endpoints Time needed to feasibly demonstrate treatment effect still may be long

Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89–95.
Temple RJ. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, editors. Clinical measurement in drug evaluation. New York: J. Wiley; 1995.
Raghu G. et al. Am J Respir Crit Care Med Vol 185, Iss. 10, pp 1044–1048, May 15, 2012 Idiopathic Pulmonary Fibrosis: Clinically Meaningful Primary Endpoints in Phase 3 Clinical Trials

Biomarkers

…an objectively measured indicators of a normal biological process, pathologic process, or pharmacologic response to a therapeutic agent

- **Prognostic biomarkers – information about the patient outcome**
- Selecting for rapid progressors ***may*** lead to shorter, smaller trials
- **Predictive biomarker – information about the effect of therapeutic intervention**
- Identify patients in whom the targeted pathway is active and that are most likely to respond

Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89–95.
Temple RJ. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, editors. Clinical measurement in drug evaluation. New York: J. Wiley; 1995.

What biomarkers can deliver?

- - Improve scientific understanding of biology
  - Increase likelihood of success in clinical trials

- **Issues and Challenges:**
  - Determination of threshold, particularly for biomarker candidates are that are continuous variables
  - Need for serial measurements in multiple cohorts for validation

Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89–95.
Temple RJ. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, editors. Clinical measurement in drug evaluation. New York: J. Wiley; 1995.

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Collaborative efforts and consortia, overview

- Subpopulations and intermediate outcome measures in COPD *study* (*SPIROMICS*) http://www.spiromics.net
- Non-interventional, observational, multicentre, three-year study in people with COPD (ECLIPSE) http://www.eclipse-copd.com/
- (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes) (U-BIOPRED) http://www.europeanlung.org/en/projects-and-research/projects/u-biopred/home

Collaborative efforts and consortia, overview, cont.

- COPDGene study
- a multicenter observational study designed to identify genetic factors associated with COPD
- one of the largest studies ever to investigate the underlying genetic factors of COPD (10,000 subjects)
- aims to find inherited or genetic factors that make some people more likely than others to develop COPD
- will also characterize the disease process using high resolution CT scans

http://www.copdgene.org/study-design

Collaborative efforts and consortia, overview, cont.

- FNIH Biomarkers Consortium: a public-private biomedical research partnership managed by the Foundation for the National Institutes of Health

  Biomarkers of Lung Function Decline in COPD:

  -Discover and replicate biomarkers that predict accelerated lung function decline in COPD patients

  -The project will also compare and contrast biomarker profiles related to lung function decline, acute exacerbation (AECOPD) risk, and recovered lung function

[http://www.biomarkersconsortium.org/projects_pipeline.php]

Summary: Key priorities for success in respiratory medicines development

- **Clinical Development**:
  - Small, efficient PoC designs needed to quickly evaluate new molecules
- **Endpoint Development**:
  - Novel exploratory endpoints needed to detect early efficacy (e.g., imaging)
- **Biomarker Development**

And always…

- follow the science
- efficiently collaborate, internally and externally
- …ask question (starting now!)