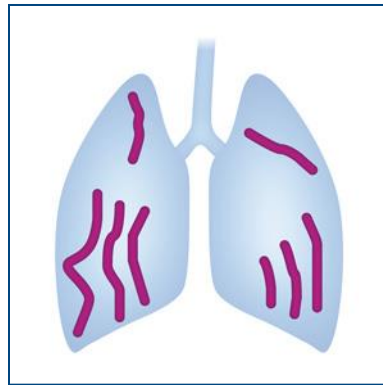


Pneumo Update Europe 2017

9-10 June, Vienna

Interstitial Lung Diseases



Luca Richeldi, Italy

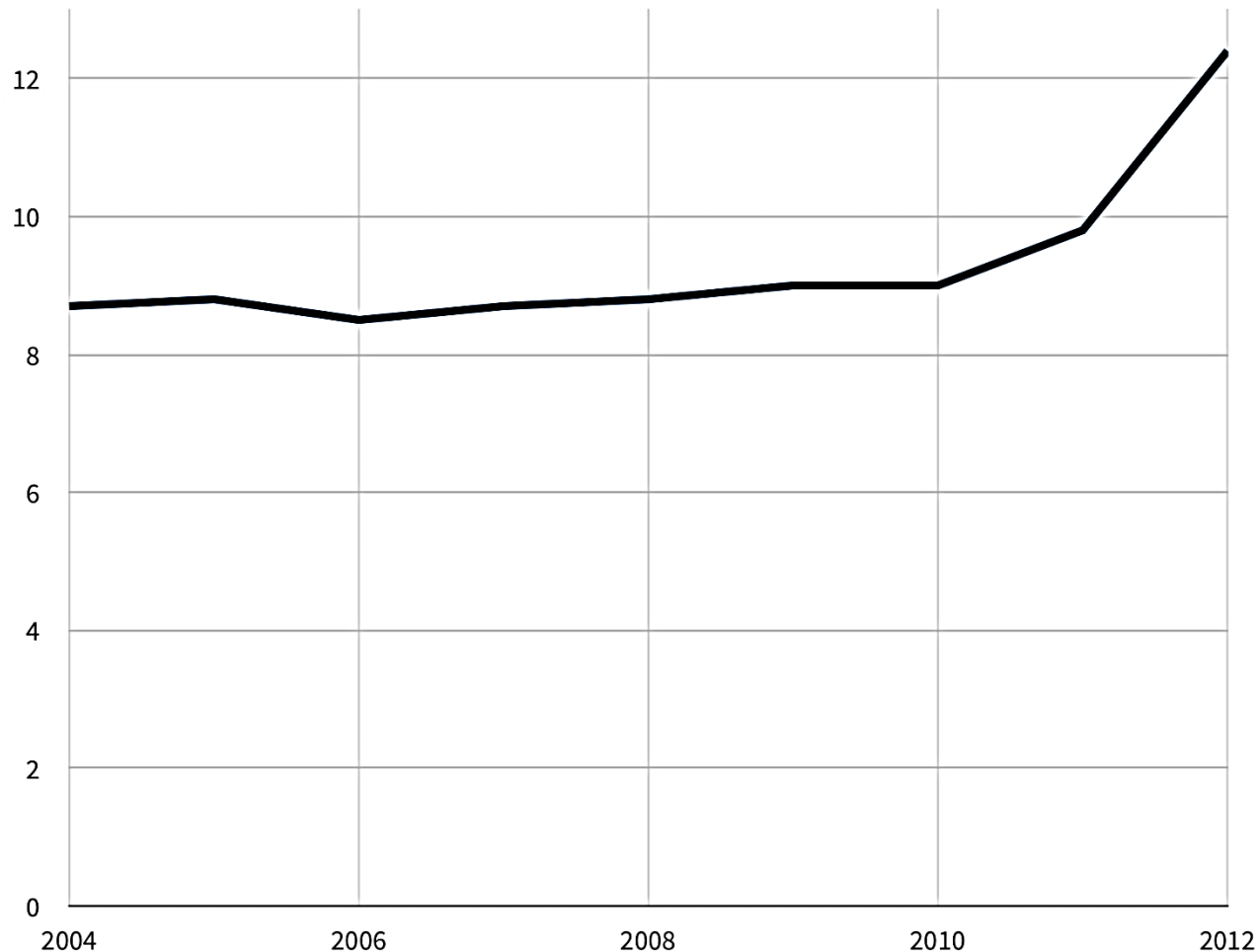
Idiopathic Pulmonary fibrosis

Idiopathic pulmonary fibrosis statistics

Our statistics about the prevalence, incidence and mortality of IPF in the UK, and how they affect different demographics.

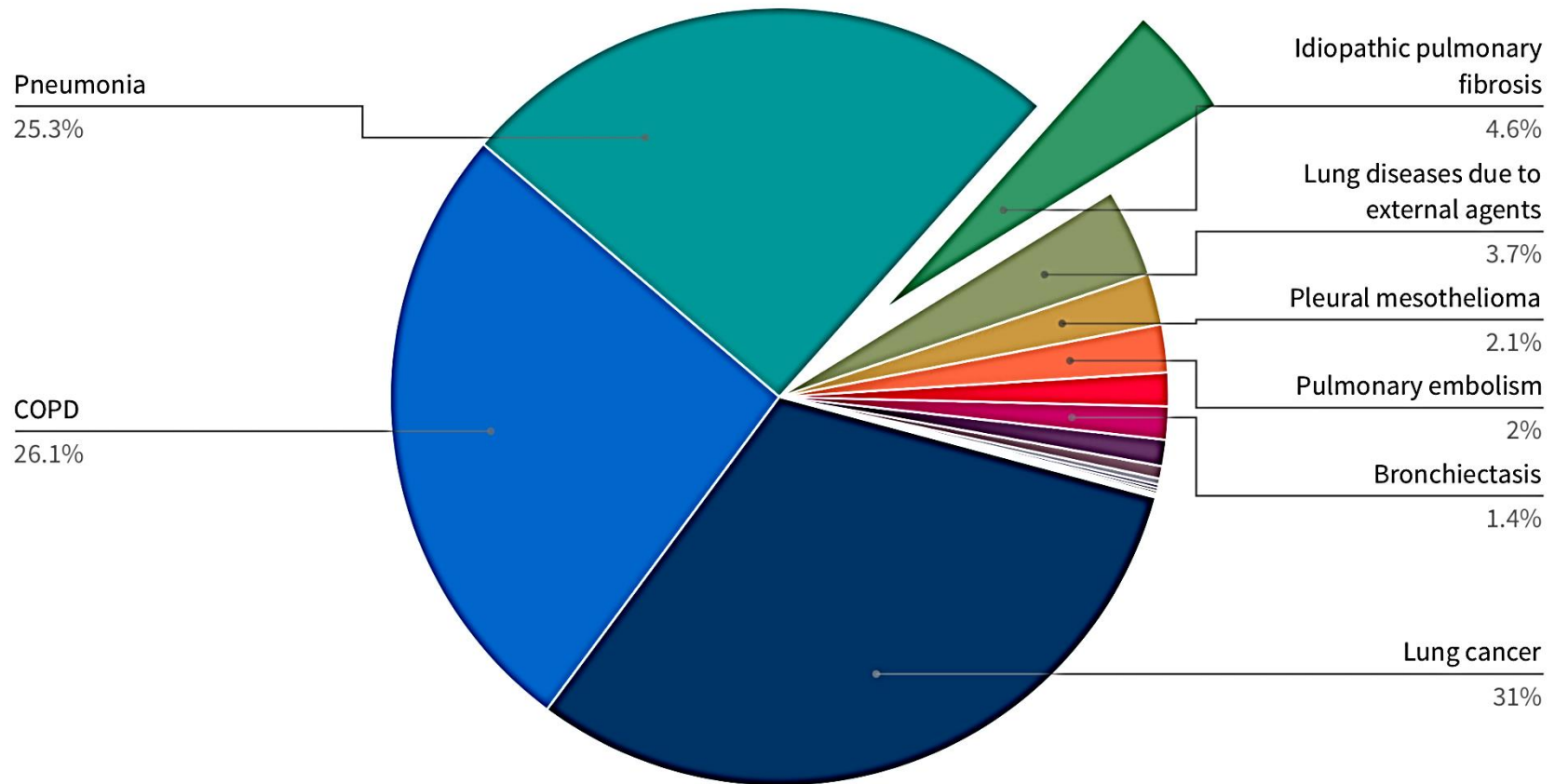
<https://www.blf.org.uk/support-for-you/idiopathic-pulmonary-fibrosis-ipf/statistics>

Number of people per 100,000 newly diagnosed with idiopathic pulmonary fibrosis, each year, 2004–12



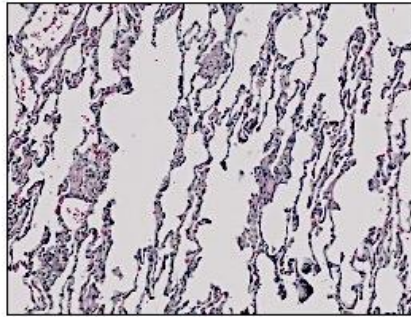
<https://www.blf.org.uk/support-for-you/idiopathic-pulmonary-fibrosis-ipf/statistics>

UK deaths from idiopathic pulmonary fibrosis compared with other lung diseases, 2012



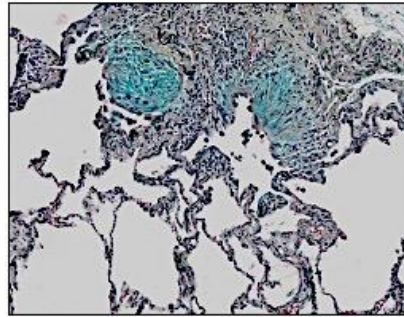
<https://www.blf.org.uk/support-for-you/idiopathic-pulmonary-fibrosis-ipf/statistics>

Dysfunctional epithelium



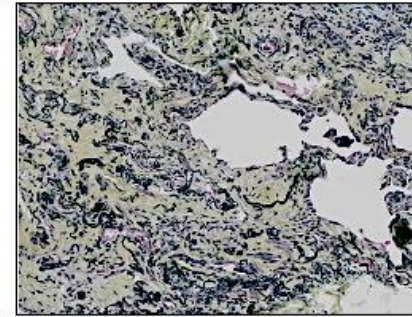
- Genetic susceptibility
- Ageing
- Recurrent microinjury

Fibrogenesis

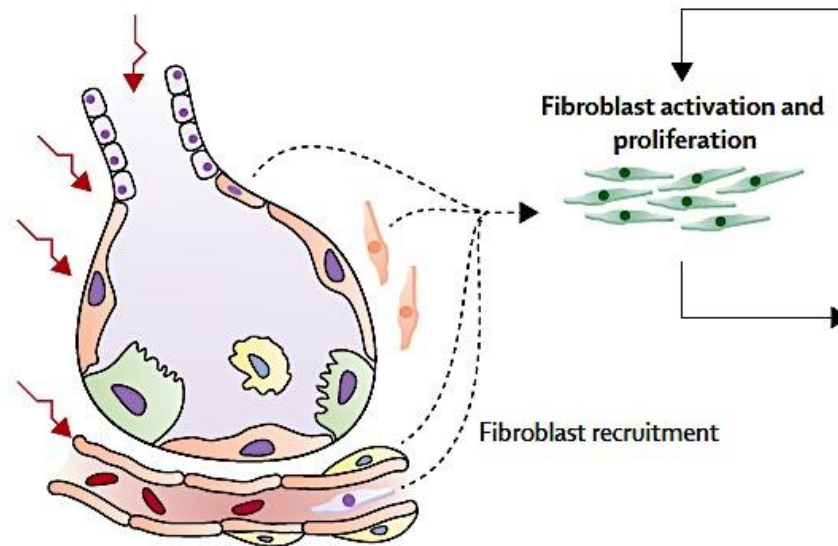


- Epithelial cell apoptosis and senescence

Fibrosis

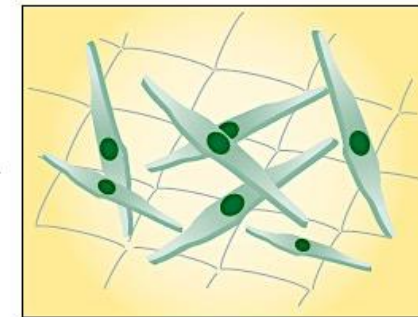


- Extracellular matrix expansion
- Altered extracellular matrix composition
- Altered extracellular matrix biomechanics
- Deficient fibroblast apoptosis
- Alveolar collapse

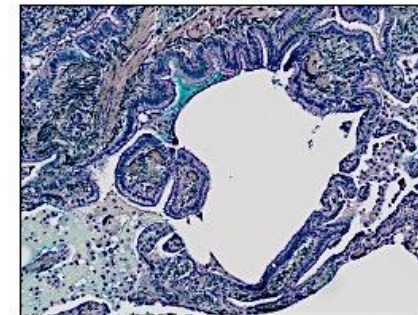


- Activation of epithelial cells
- Basement membrane disruption
- Dysregulated signalling
- Immune activation

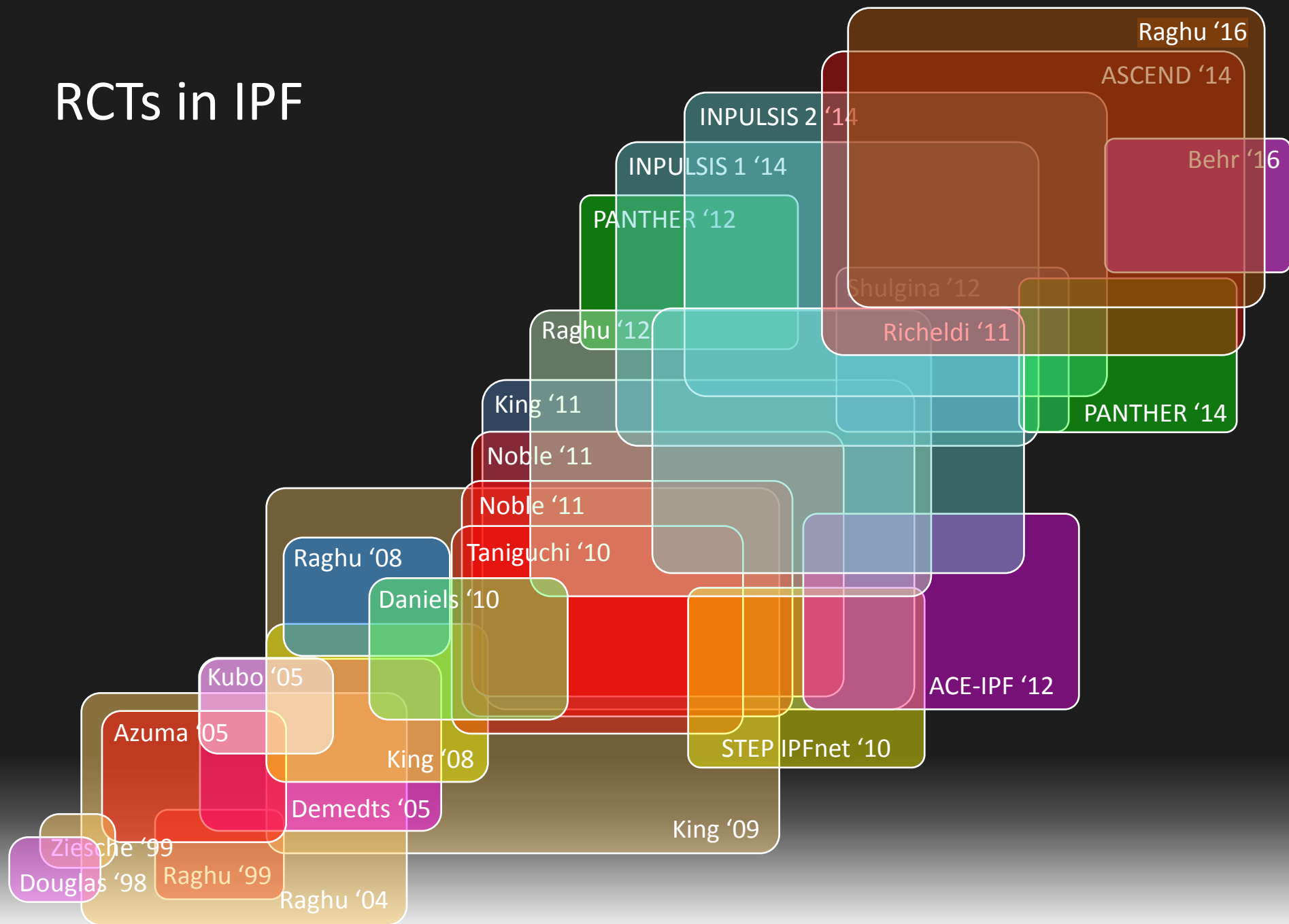
- Alveolar stem-cell exhaustion
- Basal cell dysfunction
- Abnormal extracellular matrix remodelling
- Bronchiolisation
- Honeycomb cyst formation



Aberrant remodelling



RCTs in IPF



Panel: Therapies identified in clinical trials as harmful, ineffective, or effective in the treatment of idiopathic pulmonary fibrosis

Potentially harmful therapies

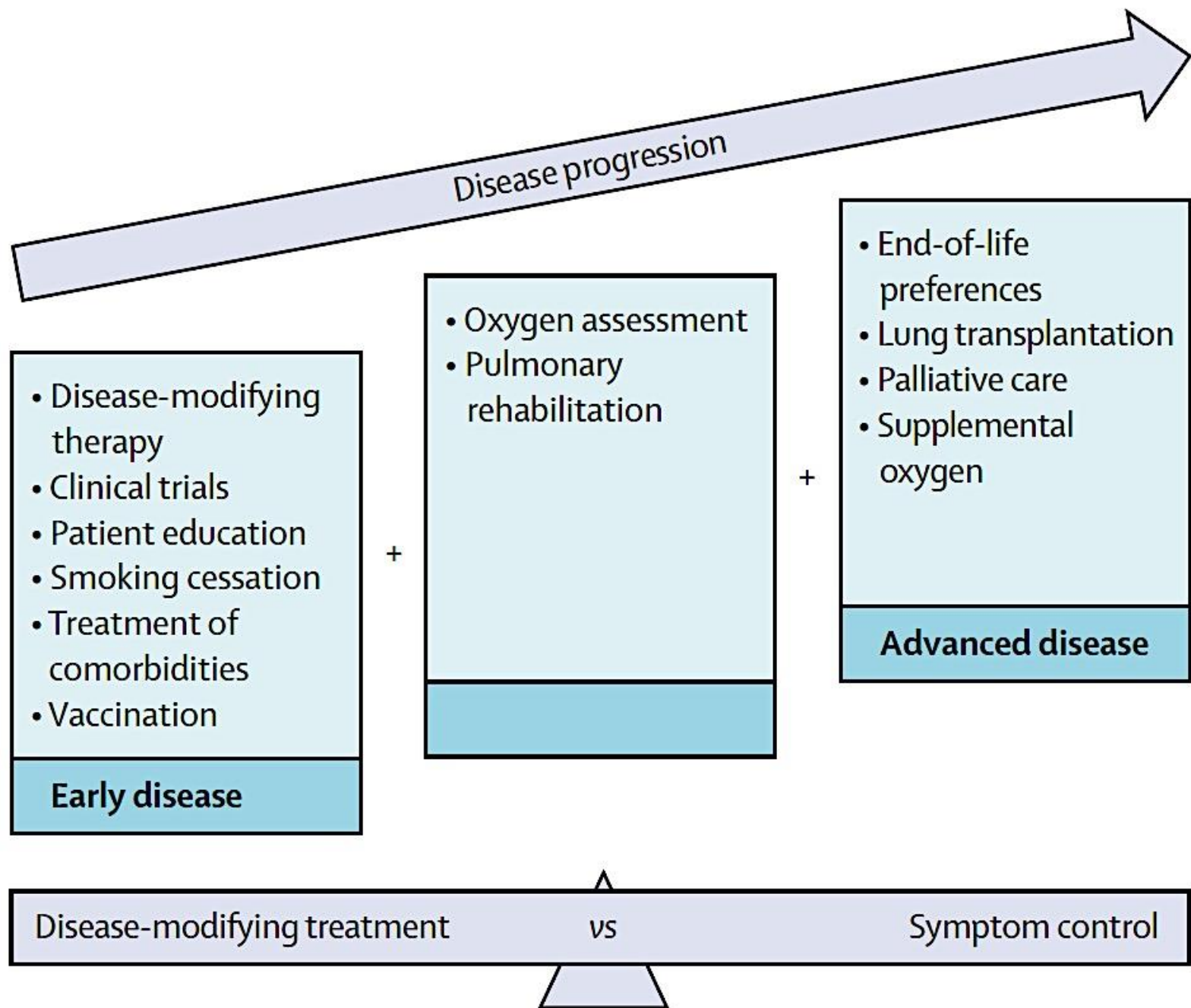
- Ambrisentan⁸¹
- Everolimus⁸²
- Prednisolone, azathioprine, acetylcysteine⁹
- Warfarin⁸³

Potentially ineffective therapies

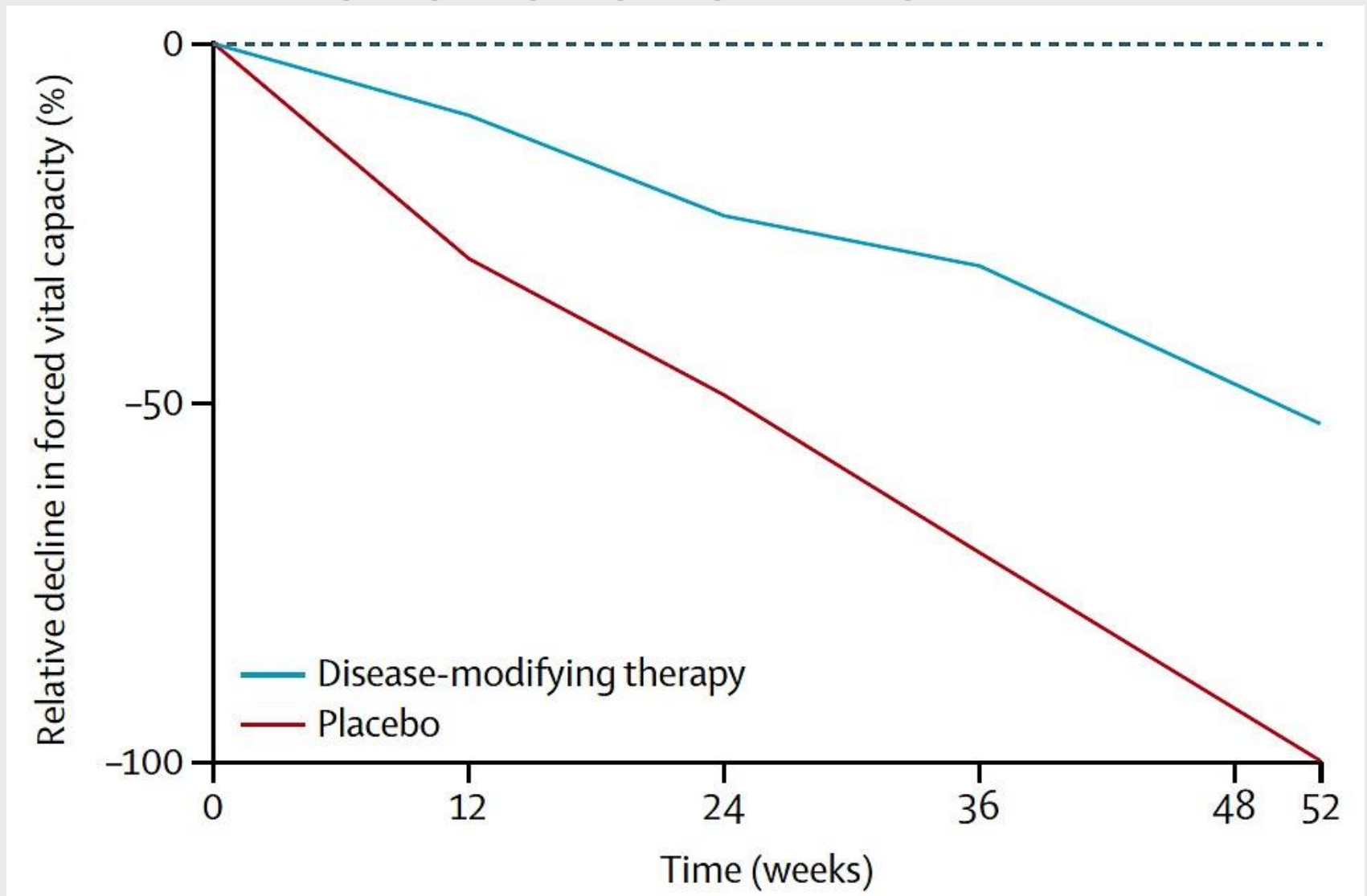
- Bosentan⁸⁴
- Imatinib⁸⁵
- Macitentan⁸⁶
- Acetylcysteine⁸⁷
- Sildenafil⁸⁸

Effective **disease-modifying therapies**

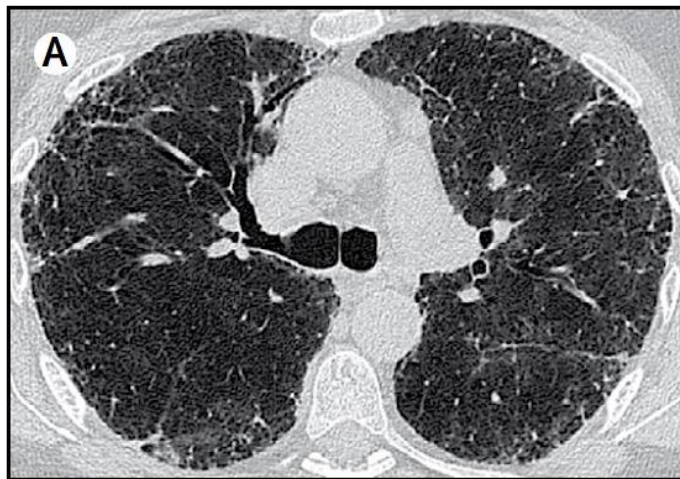
- Nintedanib⁸⁹
- Pirfenidone^{90,91}



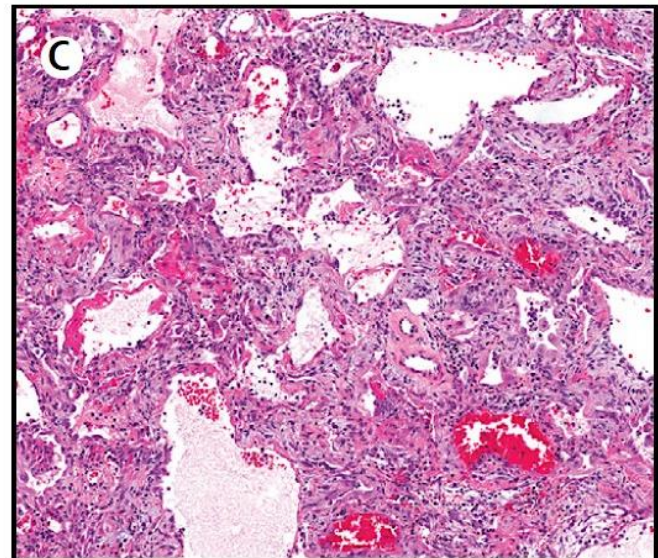
EFFECT OF DISEASE-MODIFYING THERAPY ON LUNG FUNCTION DECLINE



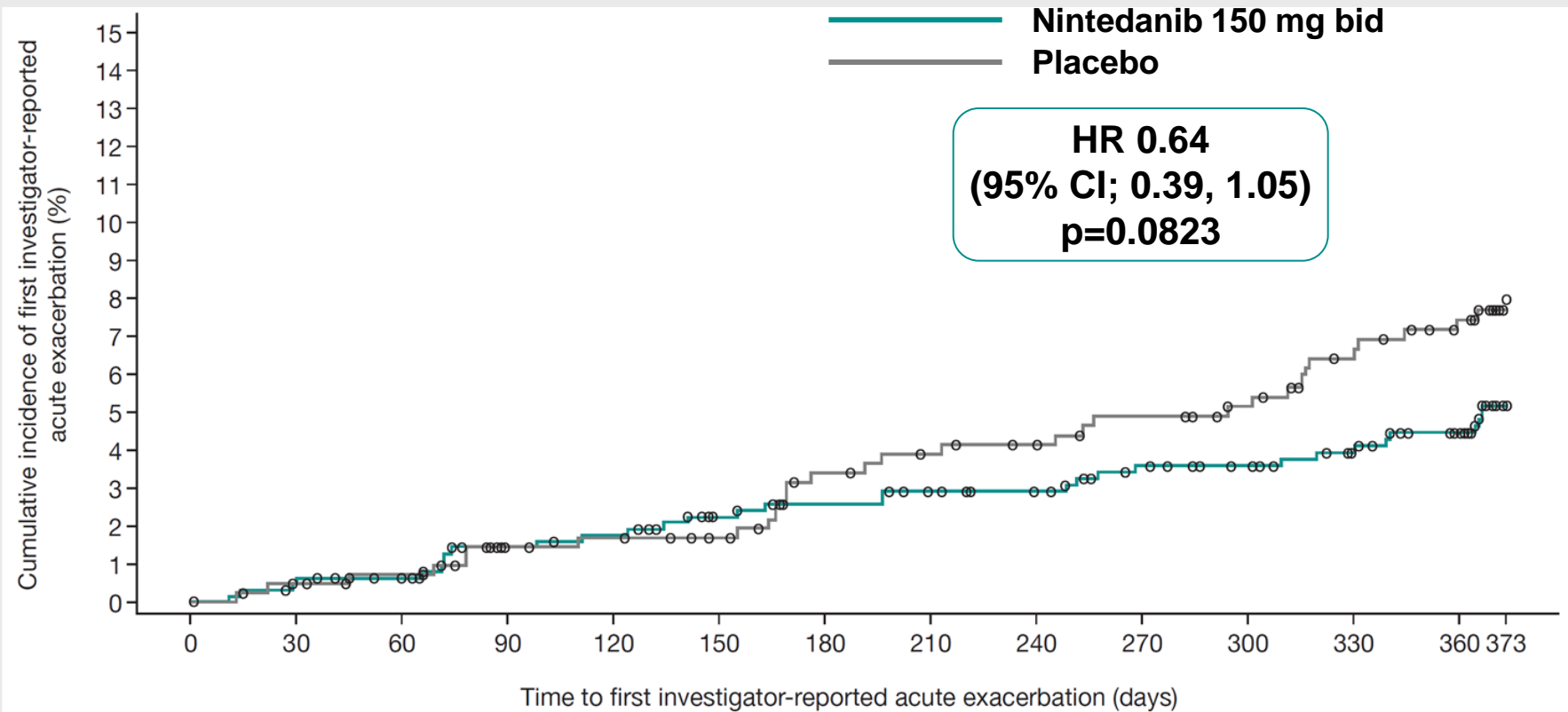
RADIOLOGICAL AND HISTOPATHOLOGICAL CHANGES THAT OCCUR DURING AN ACUTE EXACERBATION OF IPF



⚡
→
Acute
clinical
deterioration



TIME TO FIRST ACUTE EXACERBATION (INVESTIGATOR-REPORTED) IN POOLED DATA

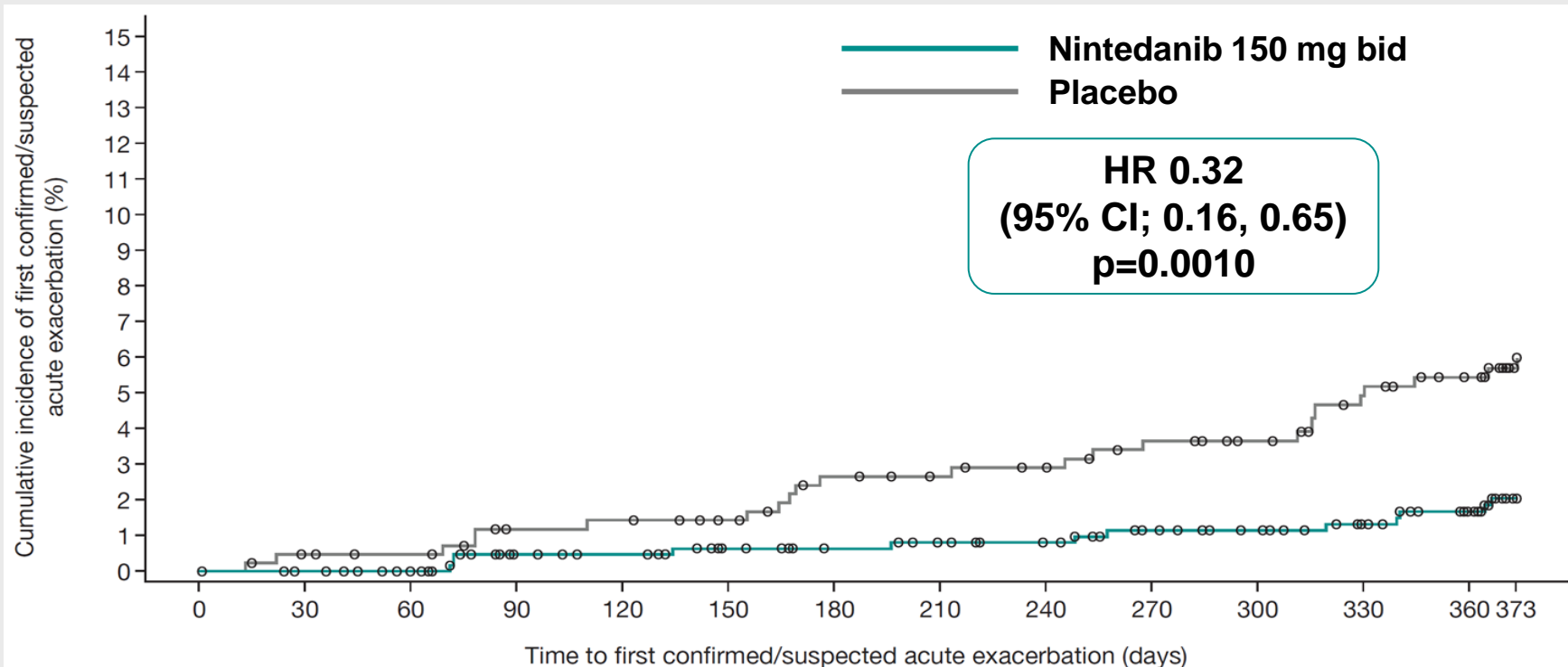


No. of patients

	638	632	627	609	605	595	589	584	580	570	562	553	537	492
Nintedanib														
Placebo														

	Nintedanib 150 mg bid (n=638)		Placebo (n=423)	
Patients with ≥ 1 acute exacerbation, n (%)	31 (4.9)		32 (7.6)	

TIME TO FIRST CONFIRMED OR SUSPECTED ACUTE EXACERBATION PER ADJUDICATION (PRESPECIFIED SENSITIVITY ANALYSIS OF POOLED DATA)

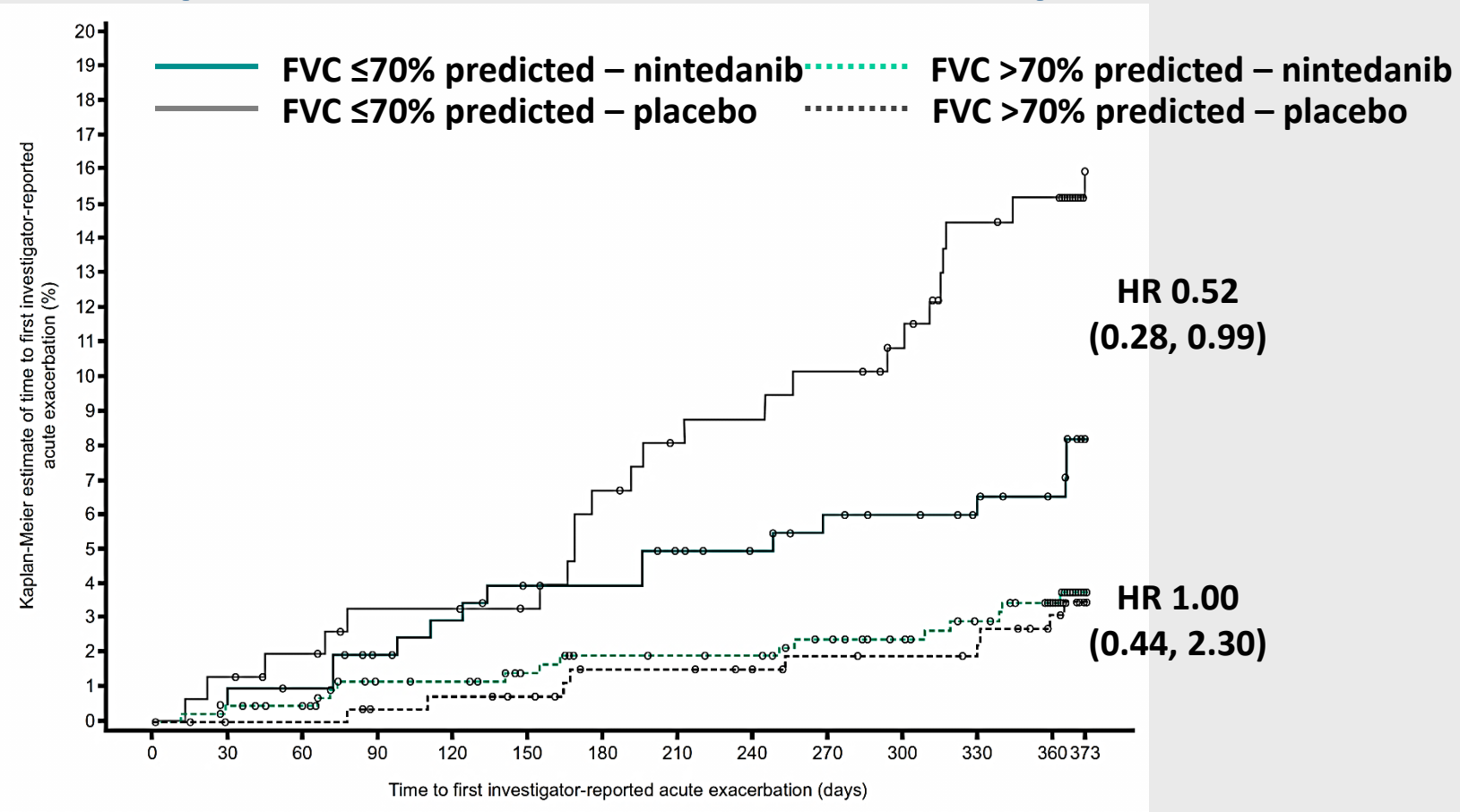


No. of patients

Nintedanib	638	634	629	613	610	602	597	593	589	580	572	563	548	503
Placebo	423	419	416	409	408	404	396	393	390	384	380	371	363	345

	Nintedanib 150 mg bid (n=638)	Placebo (n=423)
Patients with ≥ 1 acute exacerbation, n (%)	12 (1.9)	24 (5.7)

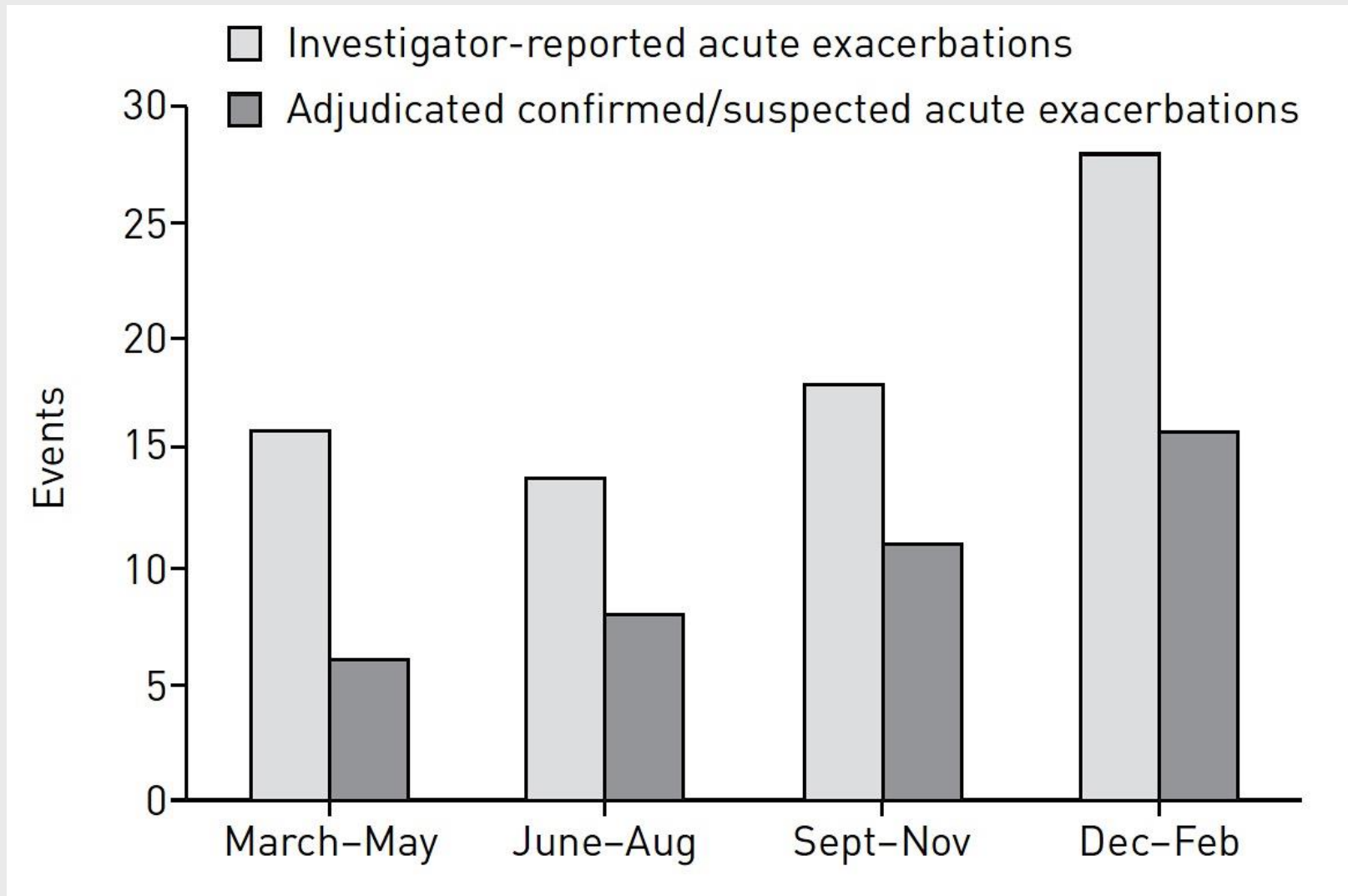
TIME TO FIRST ACUTE EXACERBATION (INVESTIGATOR-REPORTED)



No. of patients

FVC ≤70% predicted – nintedanib	207	205	203	198	195	191	190	186	183	179	177	174	169	160
FVC >70% predicted – nintedanib	431	427	424	411	410	404	399	398	397	391	385	379	368	332
FVC ≤70% predicted – placebo	154	152	148	144	144	142	137	133	132	130	126	118	116	106
FVC >70% predicted – placebo	269	267	267	264	263	261	256	256	254	251	250	249	243	235

SEASONALITY OF IPF ACUTE EXACERBATIONS



RISK OF IPF ACUTE EXACERBATIONS

- Patients with more severe lung function impairment
- During the winter season
- Up to 15-20% per year risk without background therapy
- Vaccination

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis

An Update of the 2011 Clinical Practice Guideline

Ganesh Raghu, Bram Rochwerg, Yuan Zhang, Carlos A. Cuello Garcia, Arata Azuma, Juergen Behr, Jan L. Brozek, Harold R. Collard, William Cunningham*, Sakae Homma, Takeshi Johkoh, Fernando J. Martinez, Jeffrey Myers, Shandra L. Protzko, Luca Richeldi, David Rind, Moisés Selman, Arthur Theodore, Athol U. Wells, Henk Hoogsteden, and Holger J. Schünemann; on behalf of the ATS, ERS, JRS, and ALAT

This guideline is dedicated to the memory of Mr. William Cunningham (June 7, 1935–October 23, 2014)

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS, MAY 2015, THE EUROPEAN RESPIRATORY SOCIETY (ERS), APRIL 2015, THE JAPANESE RESPIRATORY SOCIETY (JRS), APRIL 2015, AND THE LATIN AMERICAN THORACIC ASSOCIATION (ALAT), APRIL 2015

AGAINST

FOR

STRENGTH

STRONG

CONDITIONAL

STRONG

CONDITIONAL

EVIDENCE

L/VL

M/H

L/VL

M/H

L/VL

M/H

L/VL

M/H

**Anticoagulants
(warfarin)**

Imatinib

**Prednisone + AZA +
NAC**

Ambrisentan

Nintedanib

Pirfenidone


Antiacid medication

Sildenafil

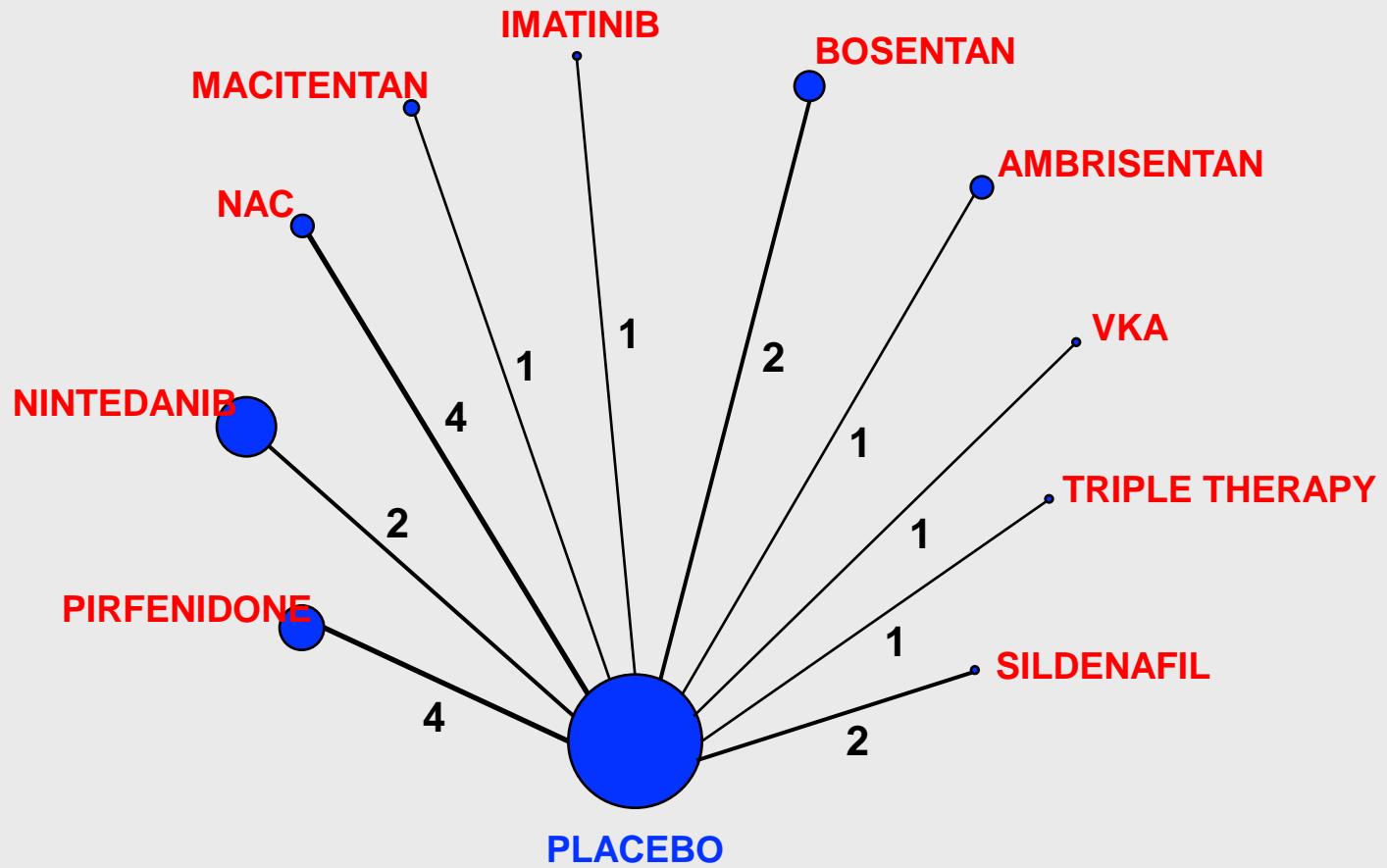
**Bosentan or
Macitentan**

NAC monotherapy

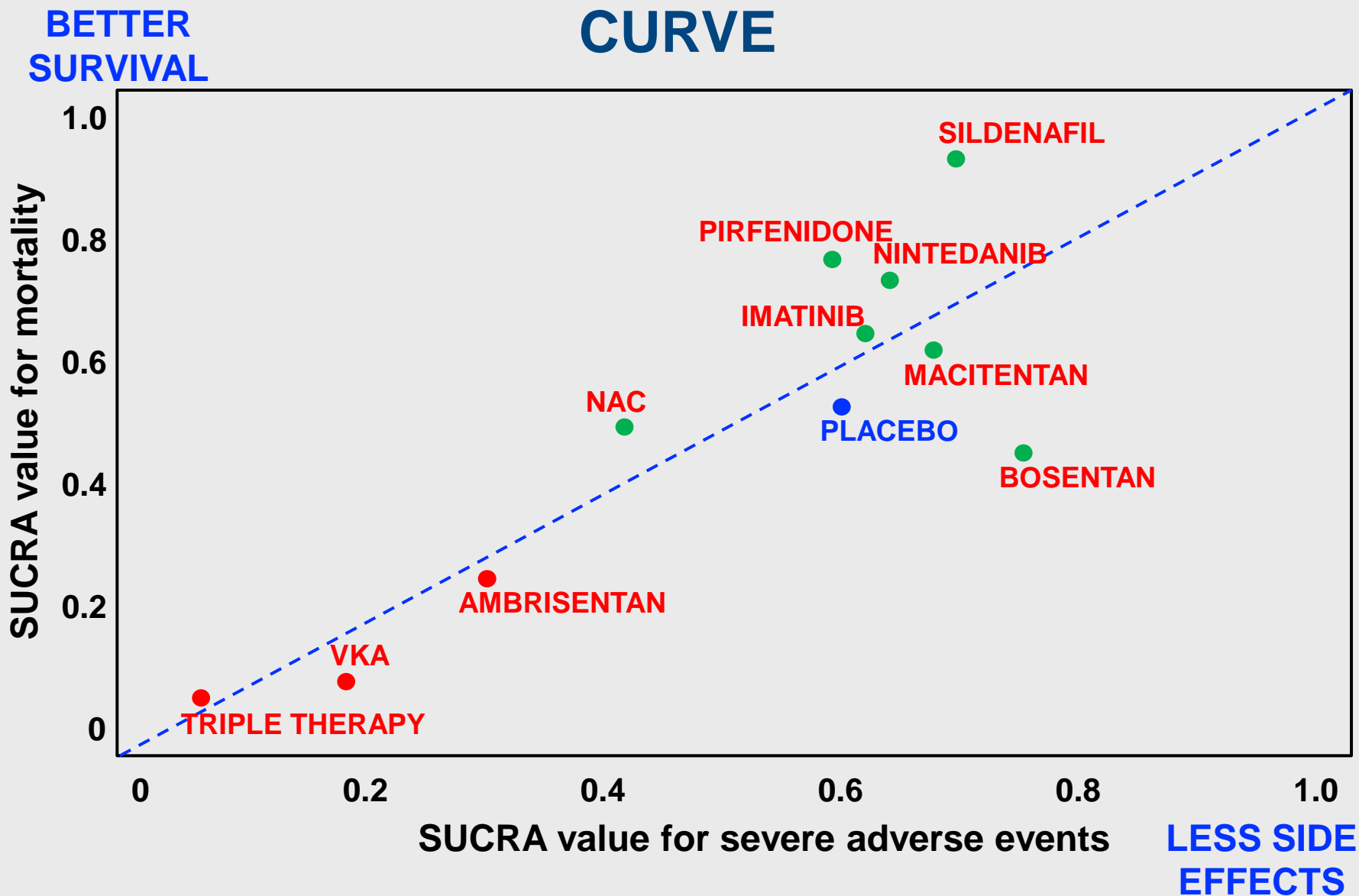
Treatment of idiopathic pulmonary fibrosis: a network meta-analysis

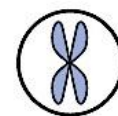
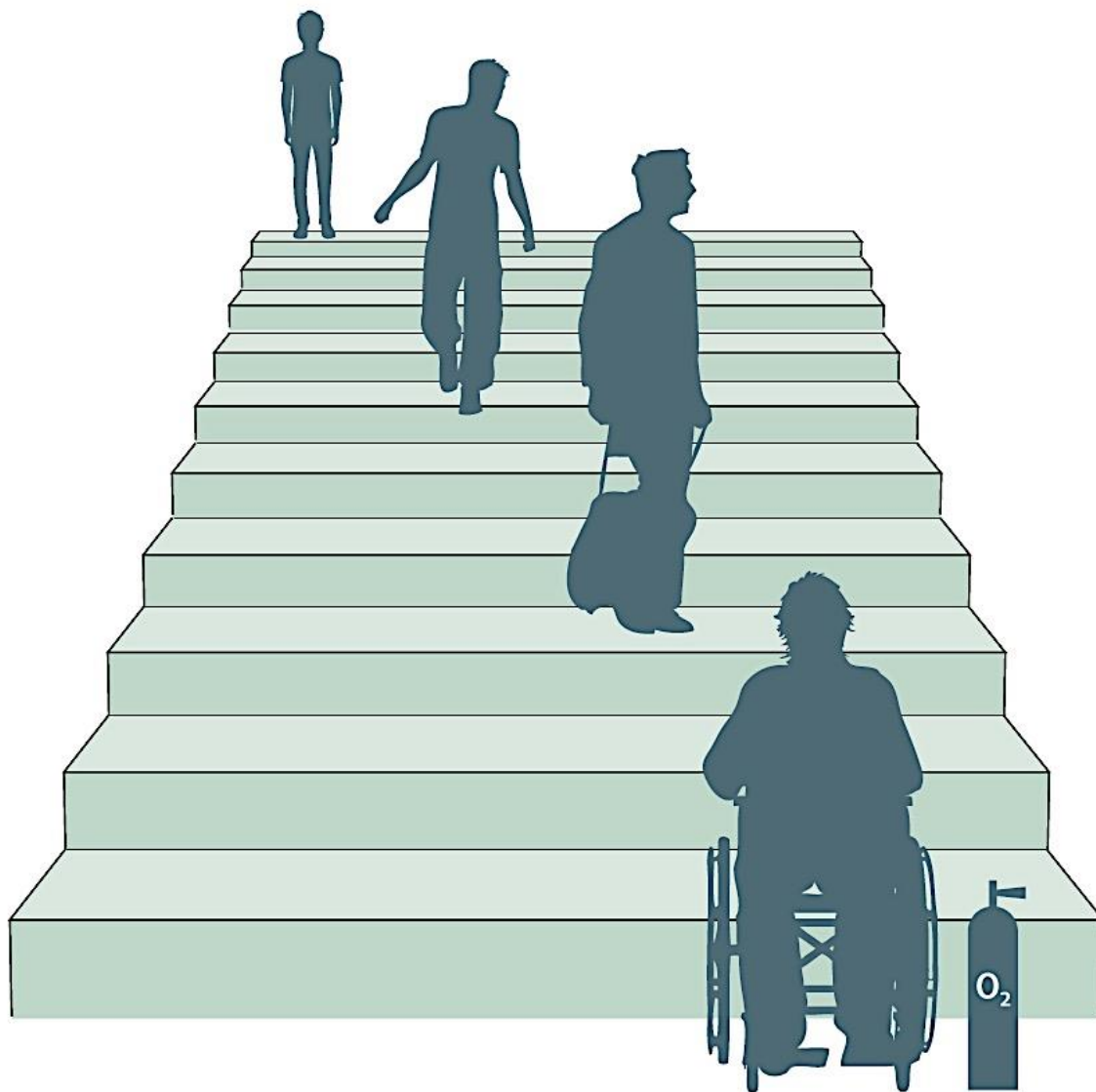
Bram Rochwerg^{1,2,3*} , Binod Neupane², Yuan Zhang^{2,3}, Carlos Cuello Garcia^{2,3,4}, Ganesh Raghu⁵, Luca Richeldi⁶, Jan Brozek^{2,3}, Joseph Beyene² and Holger Schünemann^{1,2,3}

Evidence network for mortality



SURFACE UNDER CUMULATIVE RANKING CURVE





Genetic predisposition



Smoking, occupational dust exposure, and other risk factors



Subclinical disease
(Velcro-type crackles)



Onset of symptoms



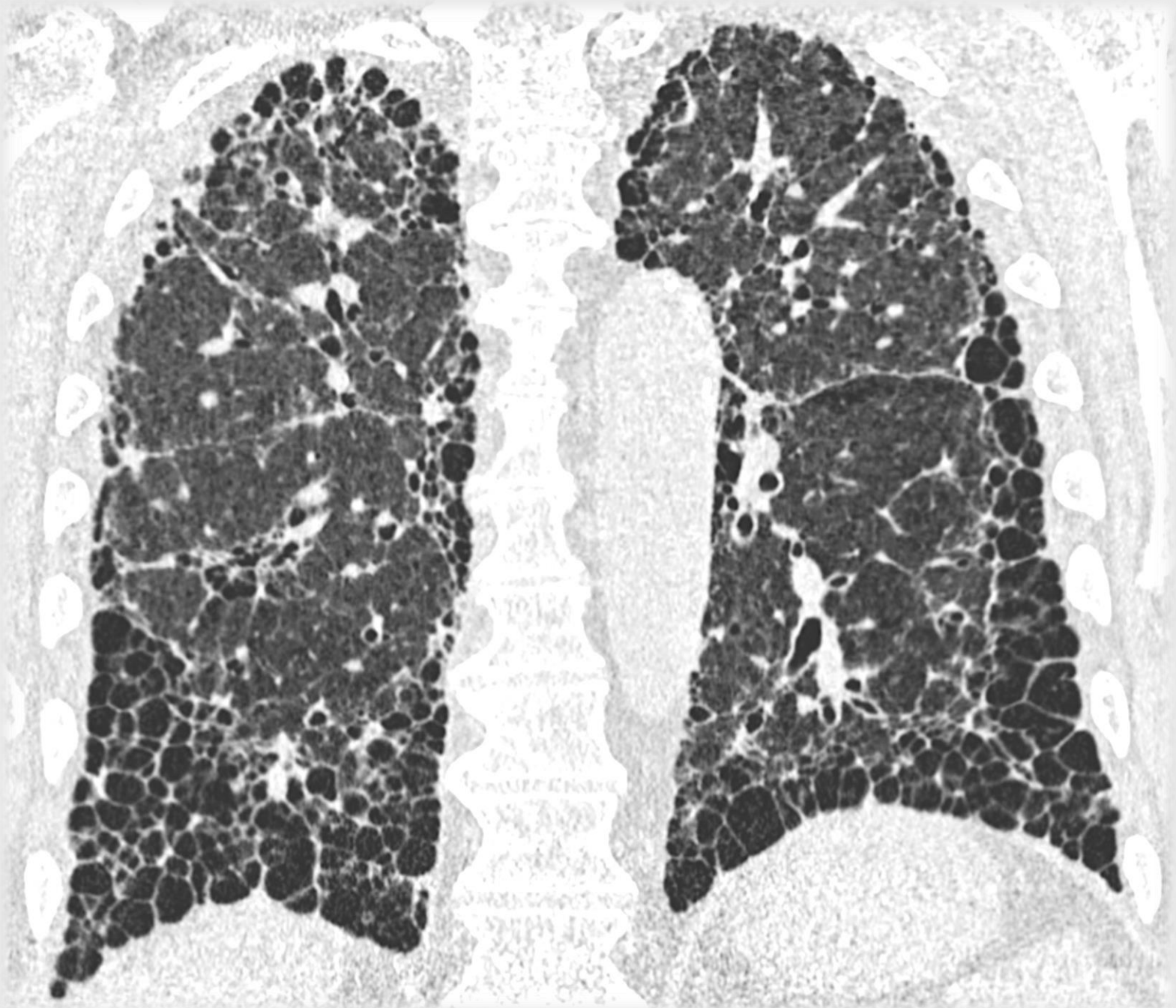
Diagnosis (typically age 60–70 years)



Disease-modifying therapy



Comprehensive management

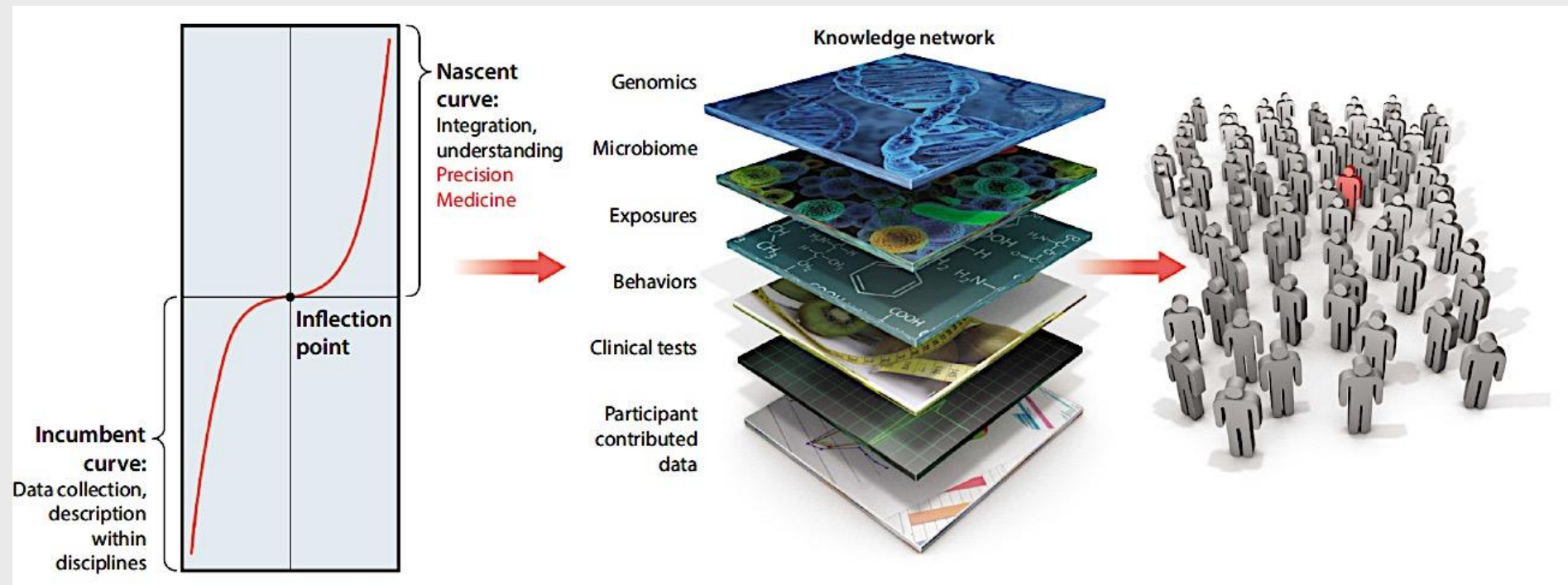


PERSPECTIVE

HUMAN HEALTH

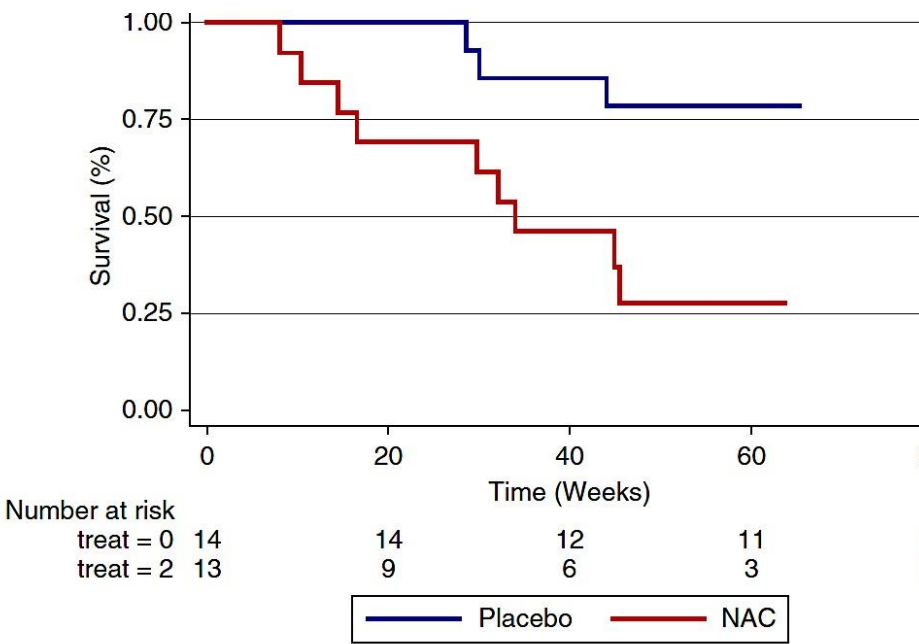
Precision medicine: Beyond the inflection point

**Sam Hawgood,¹ India G. Hook-Barnard,¹ Theresa C. O'Brien,¹
Keith R. Yamamoto^{1,2*}**



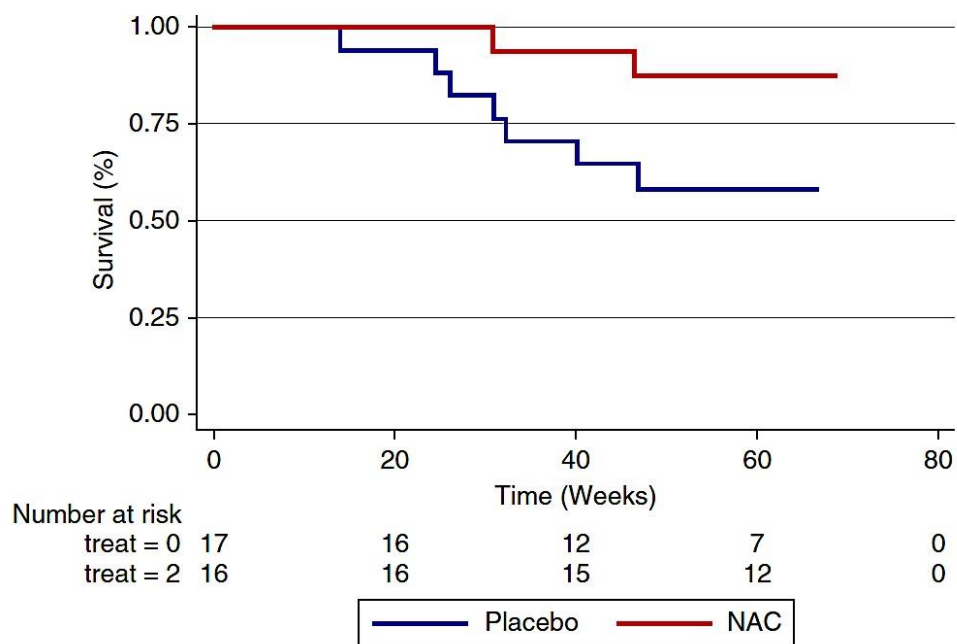
STRATIFICATION BY TOLLIP GENOTYPE

CC GENOTYPE



HR 3.23
95% CI 0.79-13.16
P=0.10

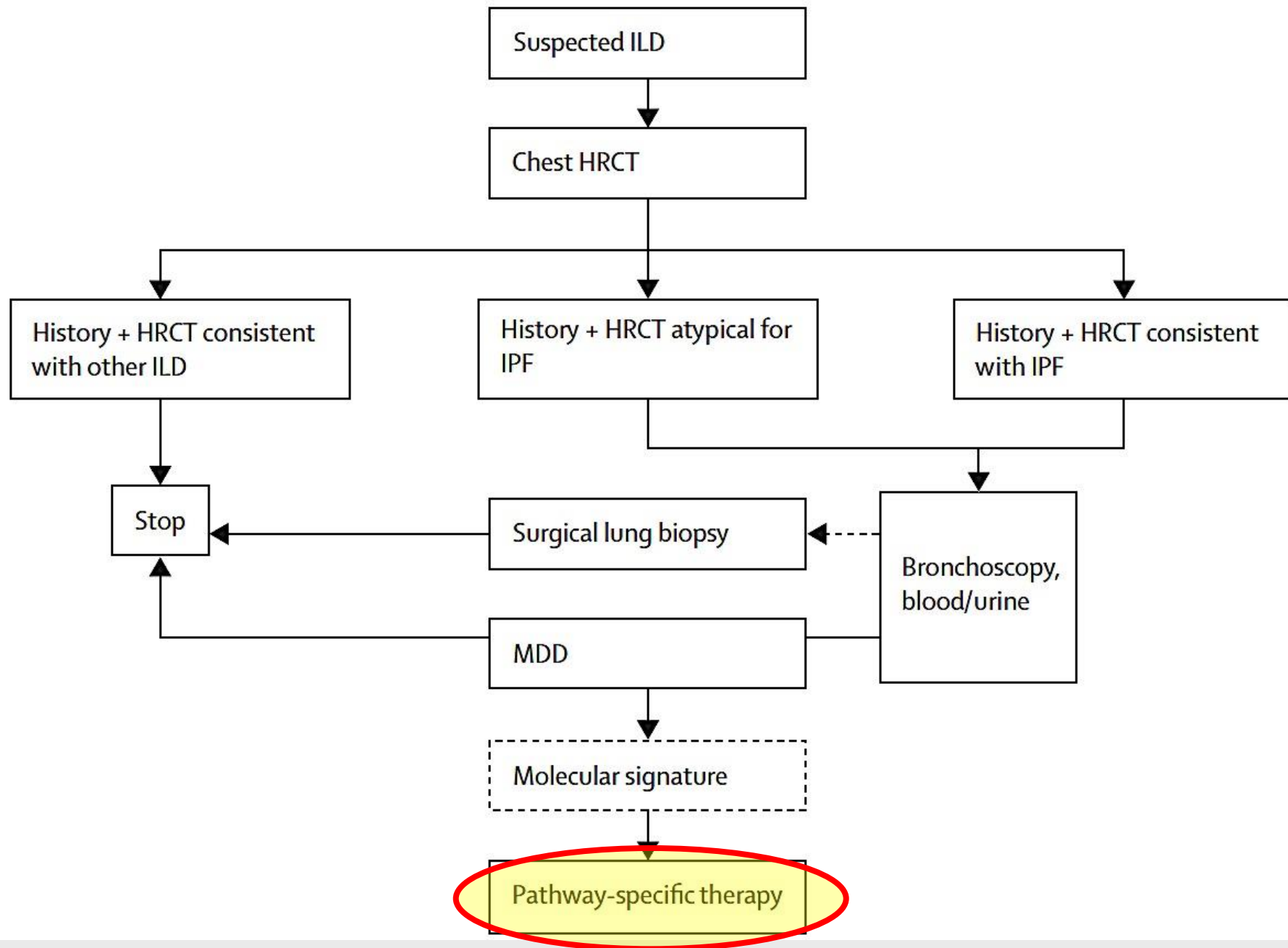
TT GENOTYPE



HR 0.14
95% CI 0.02-0.83
P=0.03

The diagnosis of idiopathic pulmonary fibrosis: current and future approaches

Fernando J Martinez, Alison Chisholm, Harold R Collard, Kevin R Flaherty, Jeffrey Myers, Ganesh Raghu, Simon L F Walsh, Eric S White, Luca Richeldi



List of References

1. <https://www.blf.org.uk/support-for-you/idiopathic-pulmonary-fibrosis-ipf/statistics>
2. Richeldi L et al, Lancet 2017; 389: 1941-1952
3. Lancet 2017 Mar 30 doi: 10.1016/S0140-6736(17)30866-8 [Epub ahead of print]
4. Richeldi L et al, NEJM 2014; 370: 2071-82
5. Collard HR et al, Am J Respir Crit Care Med 2007; 176: 636-643
6. Costabel U, et al. Am J Respir Crit Care Med 2015
7. Richeldi L et al, Respir Med 2016;113:74-79
8. Am J Respir Crit Care Med Vol 192, Iss 2, pp e3–e19, Jul 15, 2015
9. Rochwerg B et al, BMC Medicine 2016; 14: 18
10. Sam Hawgood et al, Science Transl Med 2015 Aug 12; 7(300): 300ps17
11. Oldham JM et al, AJRCCM 2015; 192: 1475
12. Martinez Fernando J et al, Lancet Resp Med 2017; 5: 61-71