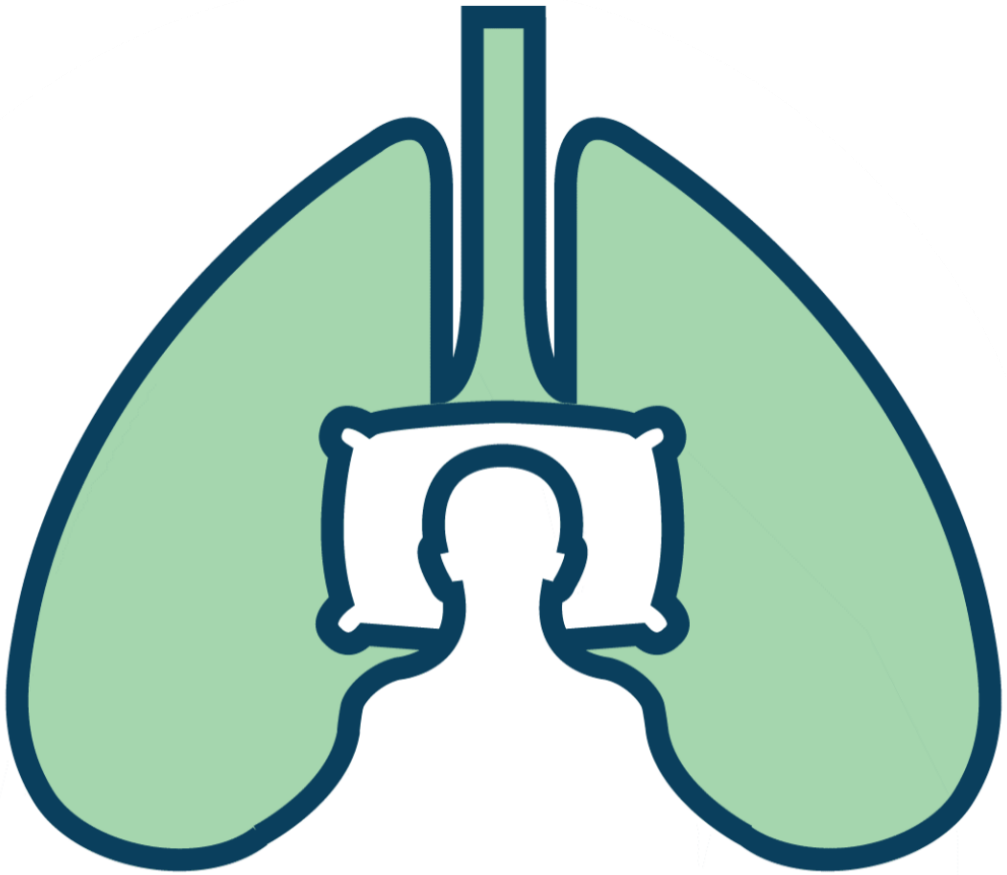
RSDC

Respiratory Sleep Disorder

Ali Aminazad MD FRACP FCCP MClinResMeth

ERS meeting Paris September 2018



RSDC

Respiratory Sleep Disorder

Pulmonary Vascular Disease

Asthma

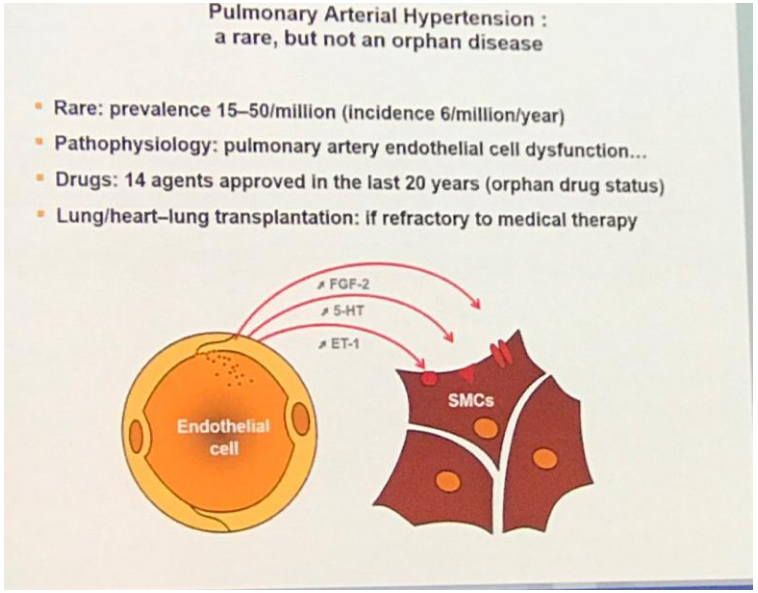
State of the art session

Pulmonary Vascular Disease

PAH

CTEPH

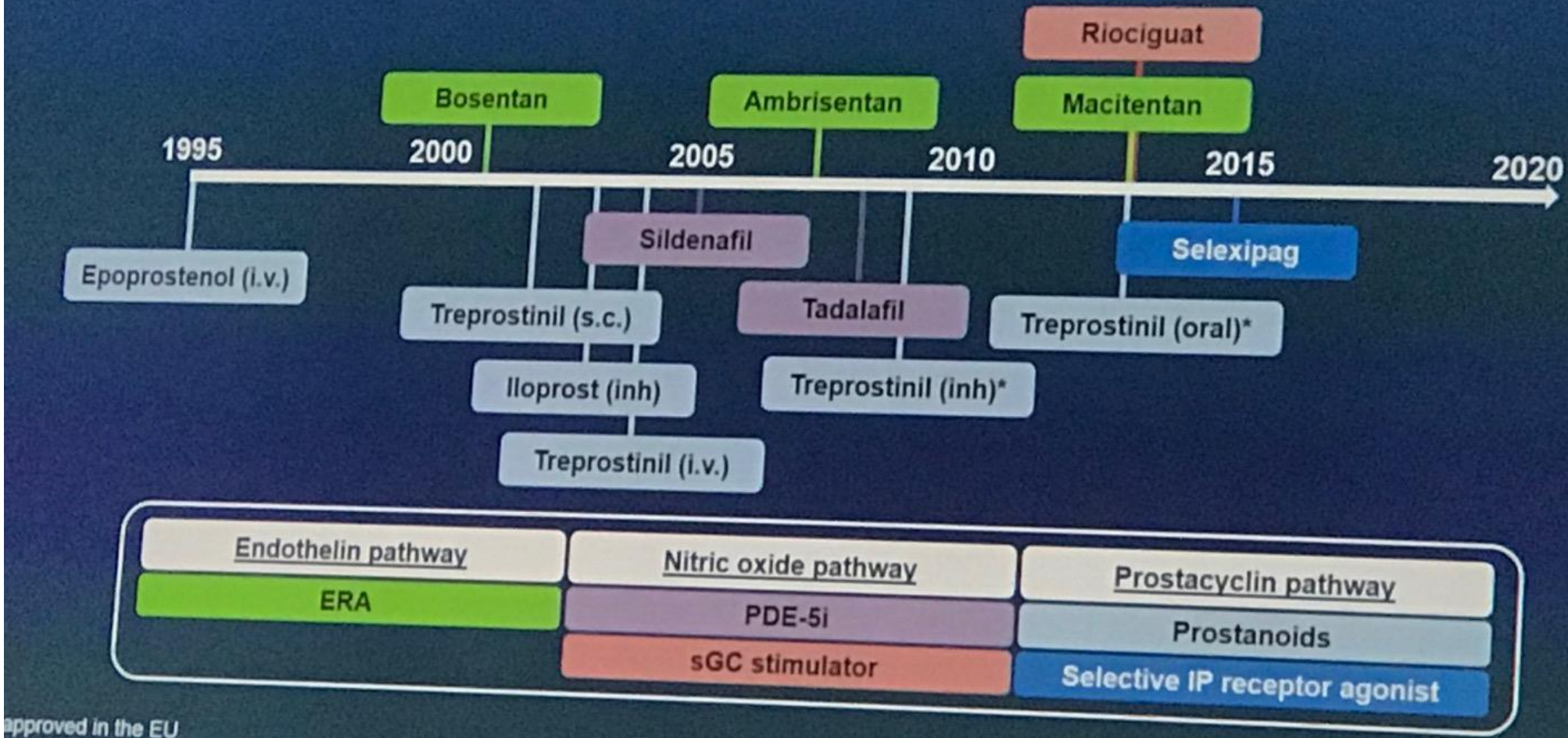
RSDC
Respiratory Sleep Disorder Centre



PAH group 1

- Chronic precapillary PH, PCWP<15
- 6 per million per year incidence
- 15-50 / million
- 14 drugs are approved
- Lung and heart Tx still very relevant

The PAH treatment armamentarium has expanded, providing more options targeting the three well-established disease pathways in PAH

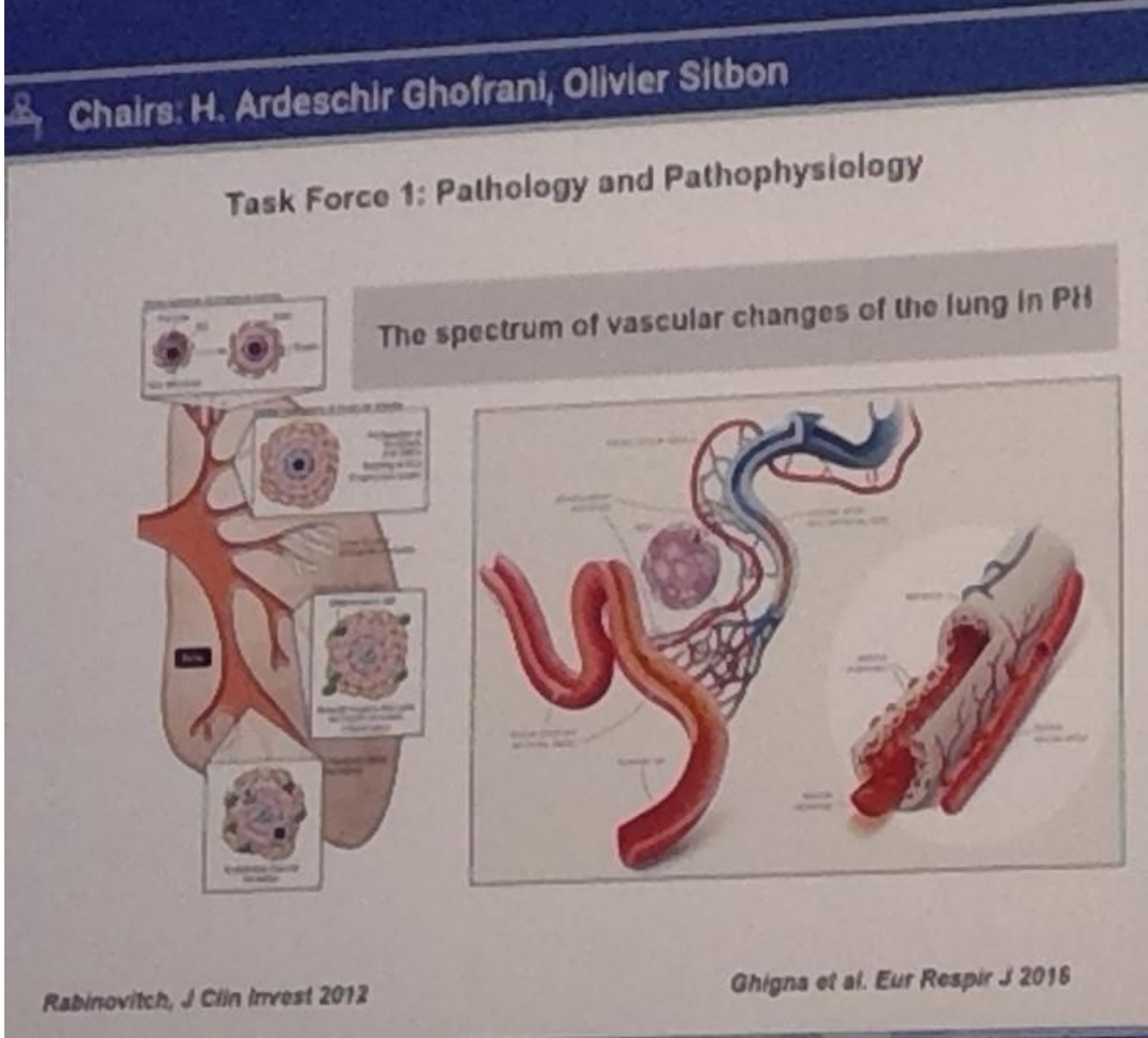


approved in the EU
pies that are approved in the USA and/or European Union are included

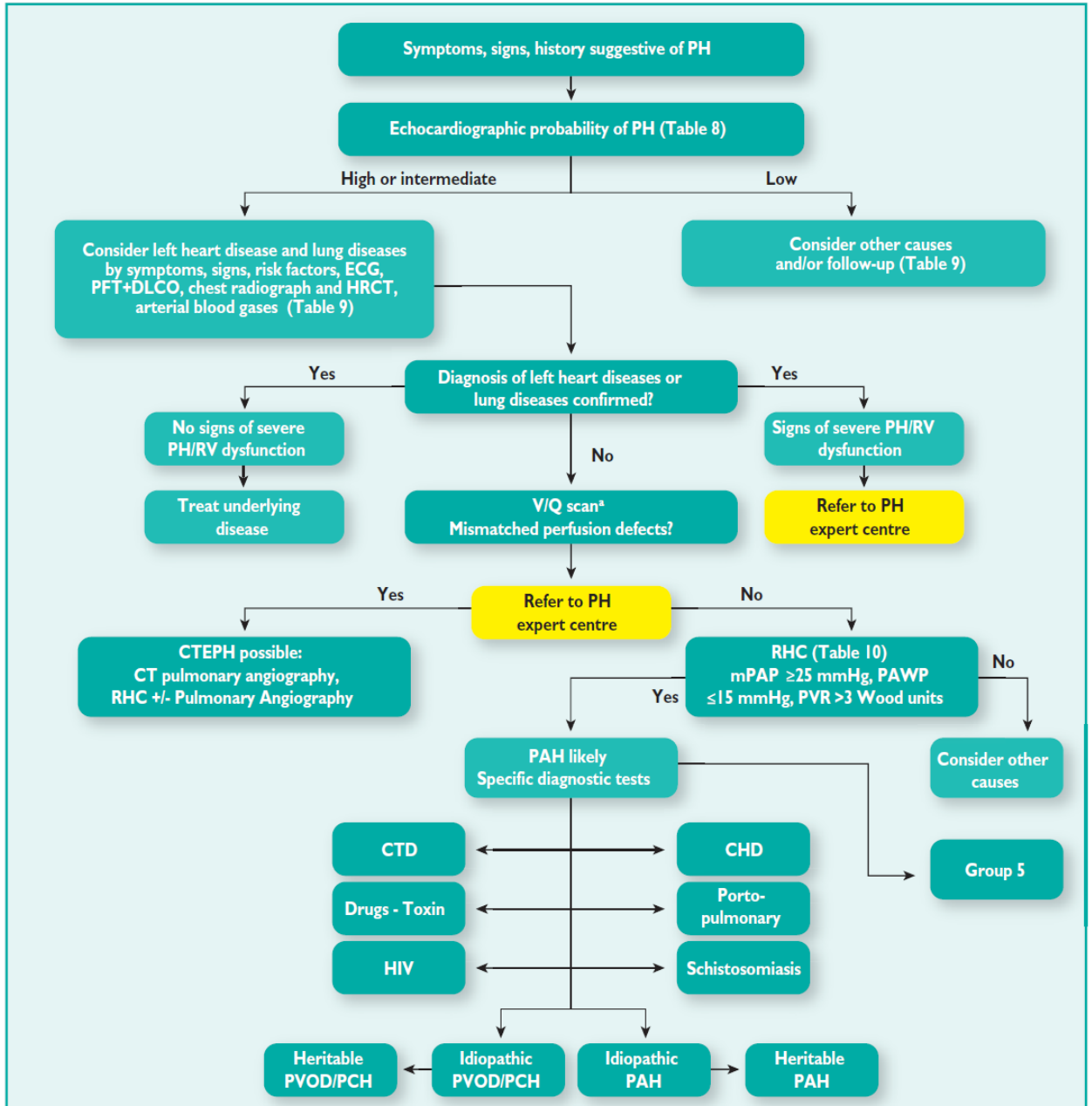
Gaine S and McLaughlin V. *Eur Respir Rev* 2017; 26:170095.

RSDC
Respiratory Sleep Disorder

- ERS guidelines 2015
- When the patient becomes symptomatic 70 % of the vessels already involved, so its important to find early



Diagnosis and Treatment



CHD = congenital heart diseases; CT = computed tomography; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = carbon monoxide diffusing capacity; ECG = electrocardiogram; HIV = Human immunodeficiency virus; HR-CT = high resolution CT; mPAP = mean pulmonary arterial pressure; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PFT = pulmonary function tests; PH = pulmonary hypertension; PVOD/PCH = pulmonary veno-occlusive disease or pulmonary capillary hemangiomathosis; PVR = pulmonary vascular resistance; RHC = right heart catheterisation; RV = right ventricular; V/Q = ventilation/perfusion.

[a]CT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension.

RSDC
Respiratory Sleep Disorder

- Diagnosis is often delayed
- 2.8 years average time between symptoms and diagnosis
- Majority of patients have FC III/IV at the time of diagnosis

Screening is efficacious especially in scleroderma

RSDC
Respiratory Sleep Disorder

Screening can assist in the early detection of high-risk patient populations

Echocardiographic evaluation for PAH is recommended in high-risk patients[1,2]:

Asymptomatic: SSc, liver transplantation candidates; BMPR2 mutation carriers and first degree relatives of HPAH patients; sickle cell disease

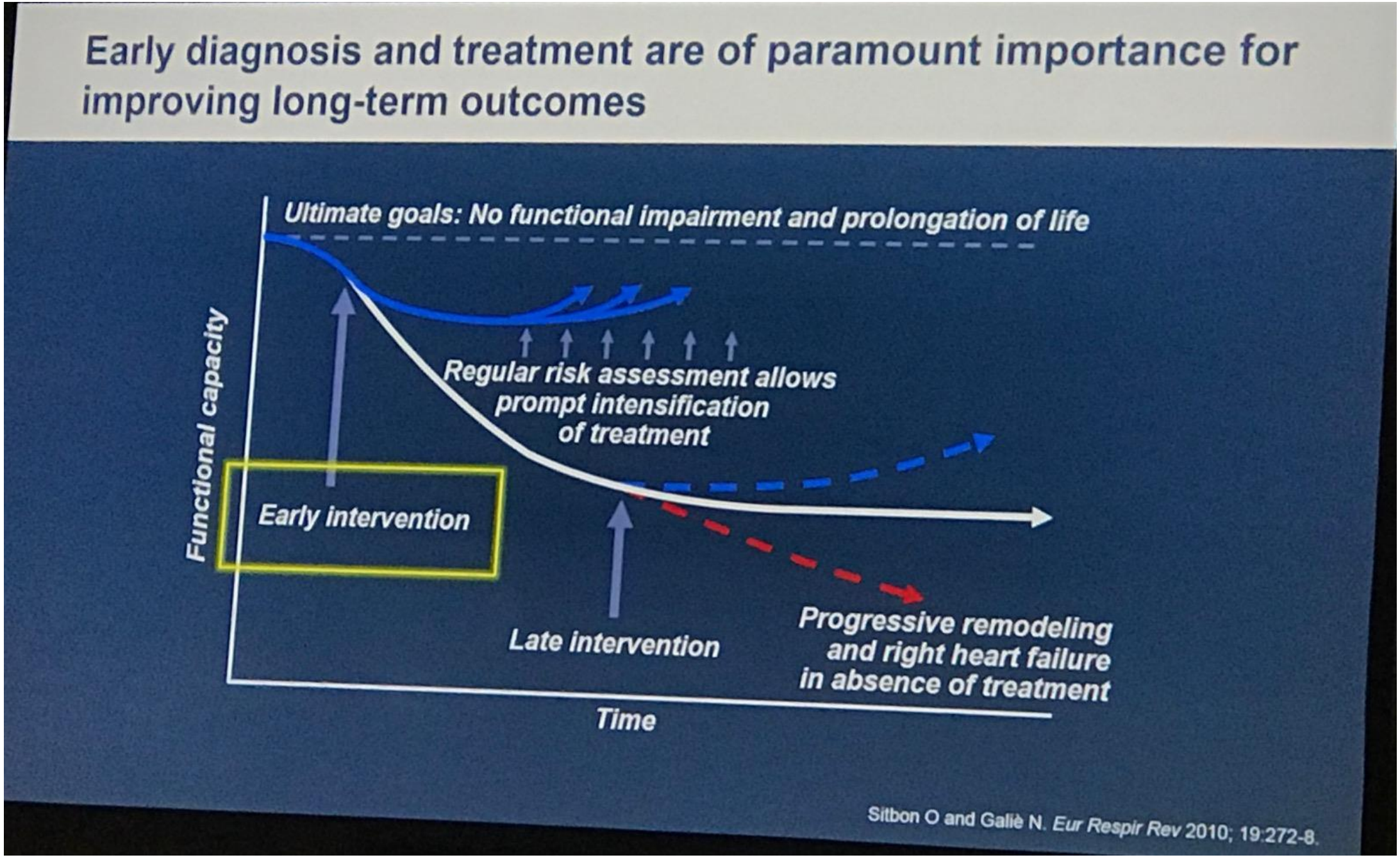
✓ Screening allows earlier detection and intervention of PAH-SSc thereby improving long-term outcomes[3]

Symptomatic: Portal hypertension, other connective tissue disease, HIV infection

1. Galiè N, *et al. Eur Respir J* 2015; 46:903-75;
2. Galiè N, *et al. Eur Heart J* 2016; 37:67-119.
3. Humbert M, *et al. Arthritis Rheum* 2011; 63:3522-30.

RSDC
Respiratory Sleep Disorder

Early diagnosis and treatment are of paramount importance for improving long-term outcomes



Sitbon O and Galiè N. *Eur Respir Rev* 2010; 19:272-8.

RSDC
Respiratory Sleep Disorder

Assessment of risk allows the treatment strategy to be tailored to the individual patient

Guidelines recommend regular multi-parameter risk assessment both at diagnosis and follow ups

RSDC
Respiratory Sleep Disorder

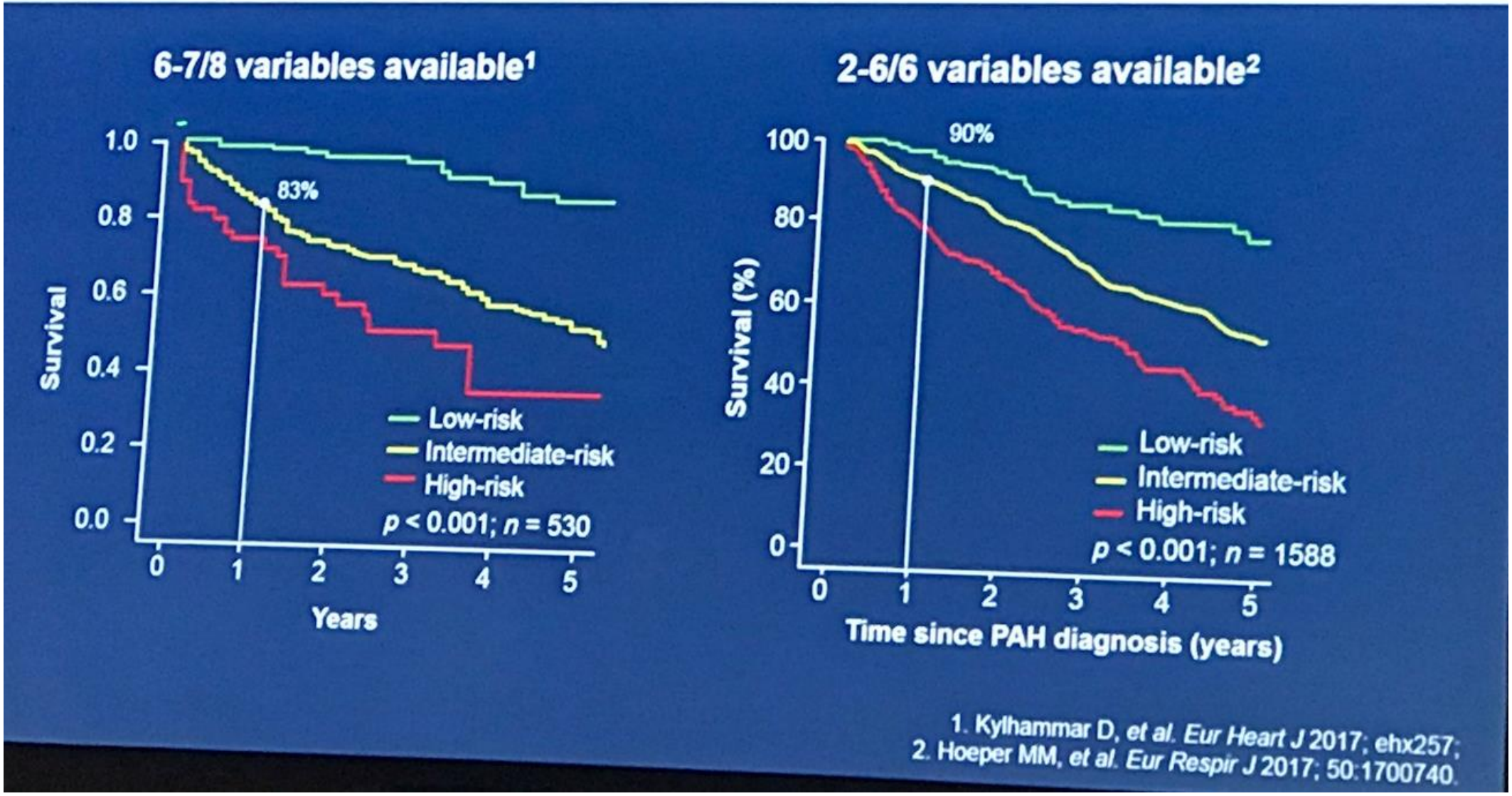
- Eur Resp J 2015; 46:903-75;Eur Heart J 2016;37:67-119

Table 13 **Risk assessment in pulmonary arterial hypertension**

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

RSDC
Respiratory Sleep Disorder

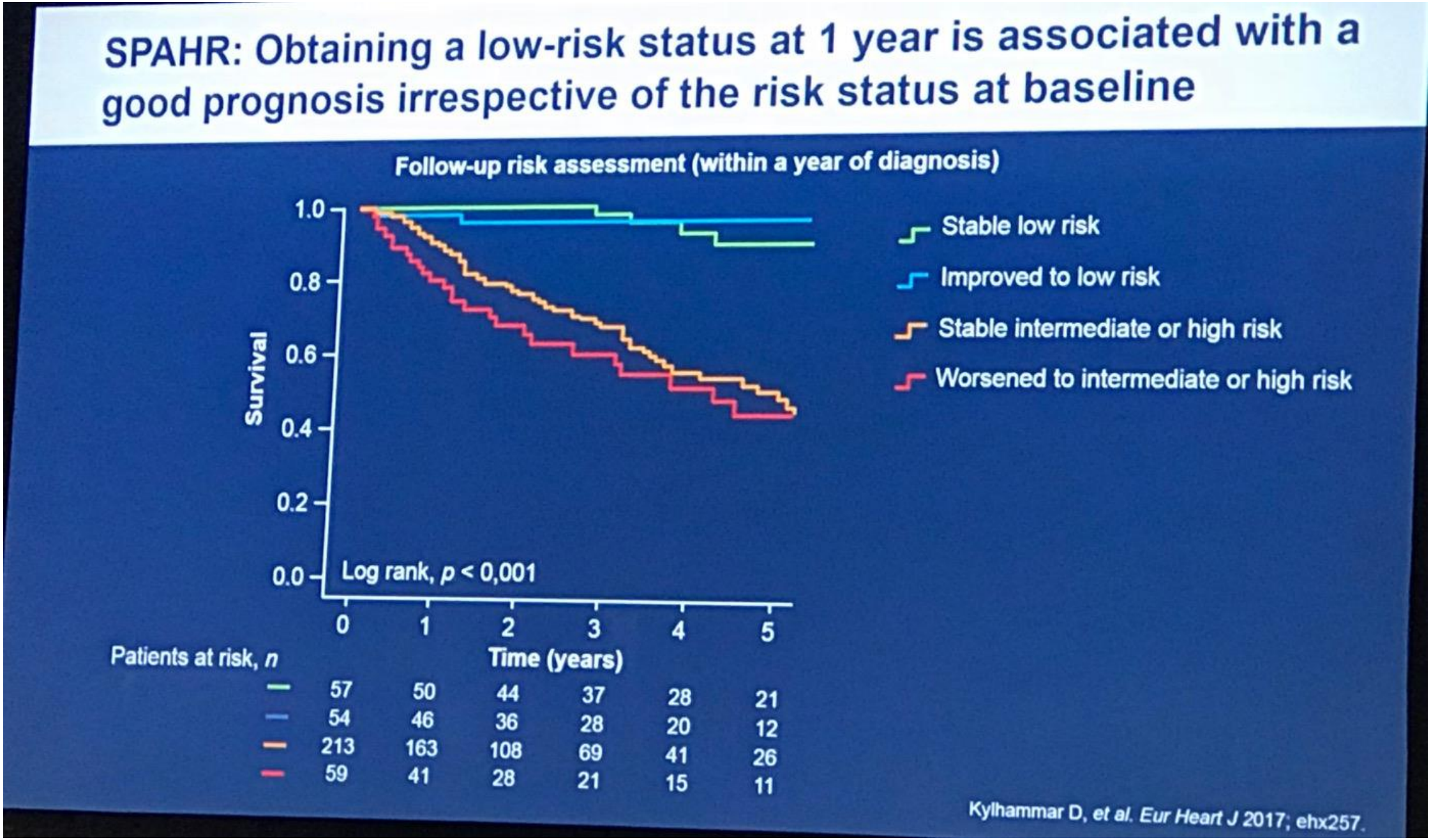
One-year survival from diagnosis



1. Kylhammar D, *et al. Eur Heart J* 2017; ehx257;
2. Hoeper MM, *et al. Eur Respir J* 2017; 50:1700740.

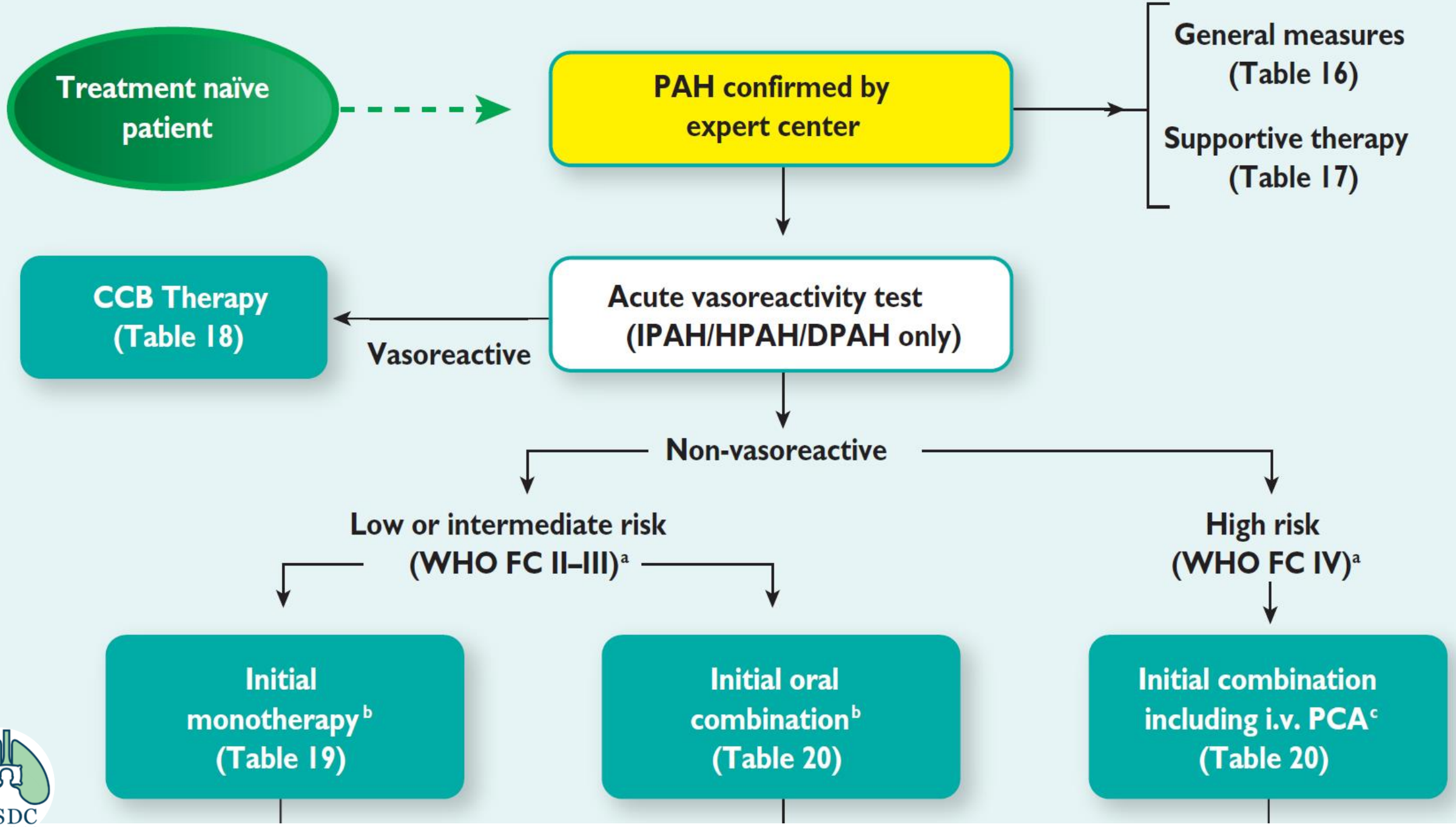
RSDC
Respiratory Sleep Disorder

SPAHR: Obtaining a low-risk status at 1 year is associated with a good prognosis irrespective of the risk status at baseline

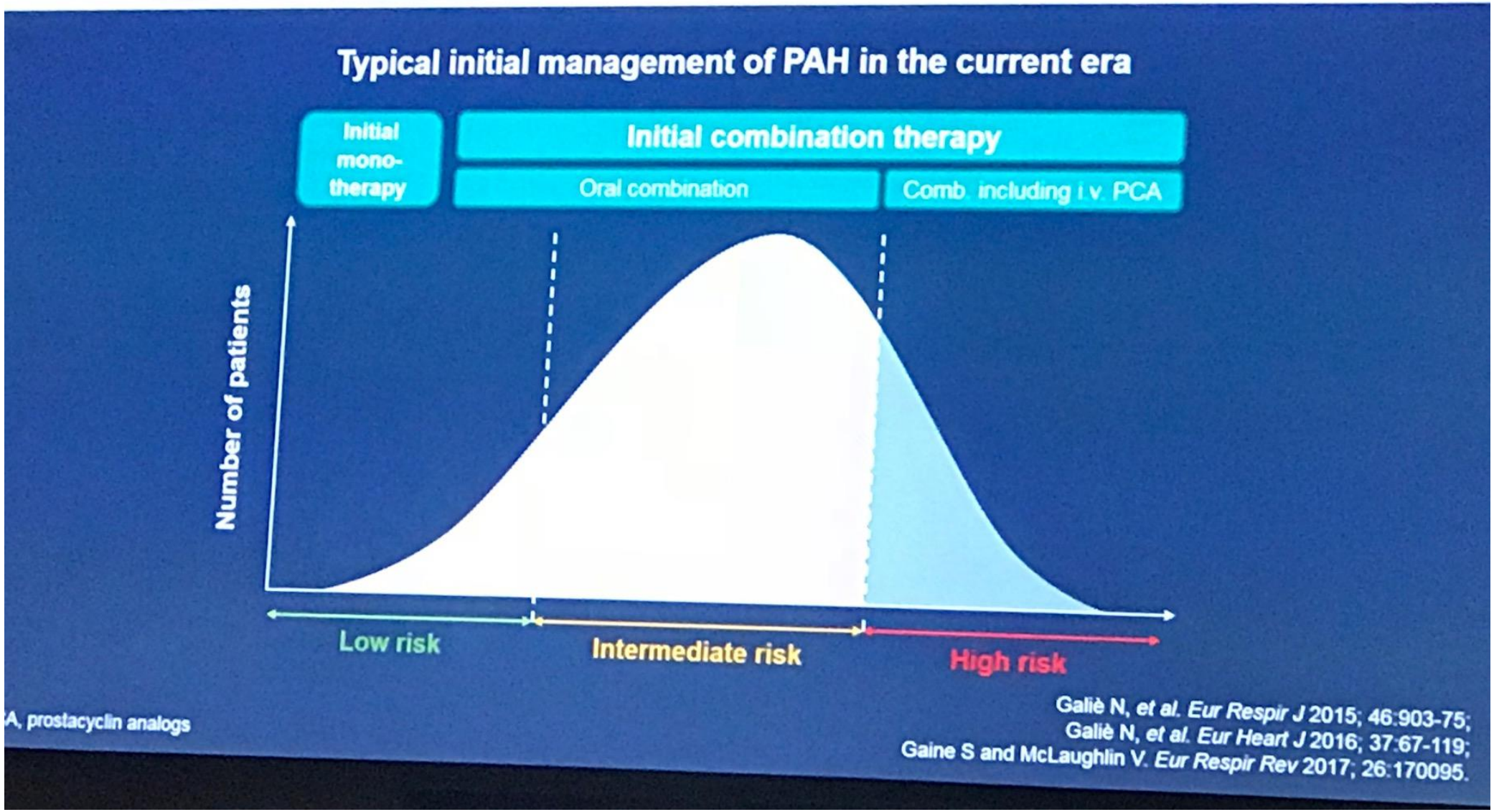


Kylhammar D, *et al. Eur Heart J* 2017; ehx257.

RSDC
Respiratory Sleep Disorder

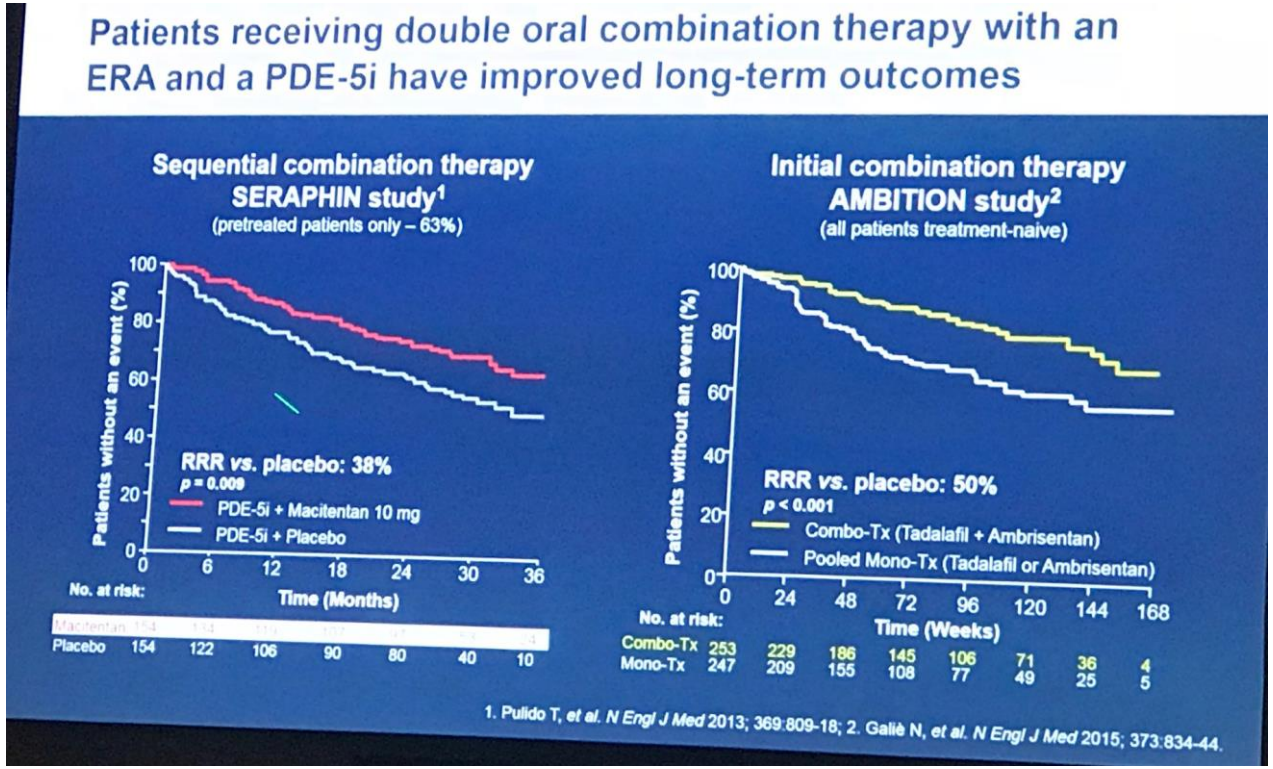

Treatment naïve patient
PAH confirmed by expert center
General measures (Table 16)
Supportive therapy (Table 17)
CCB Therapy (Table 18)
Vasoreactive
Acute vasoreactivity test (IPAH/HPAH/DPAH only)
Non-vasoreactive
Low or intermediate risk (WHO FC II–III)a
High risk (WHO FC IV)a
Initial monotherapyb (Table 19)
Initial oral combinationb (Table 20)
Initial combination including i.v. PCAc (Table 20)

Combination therapy is now the standard of care in the majority of PAH patients



RSDC
Respiratory Sleep Disorder

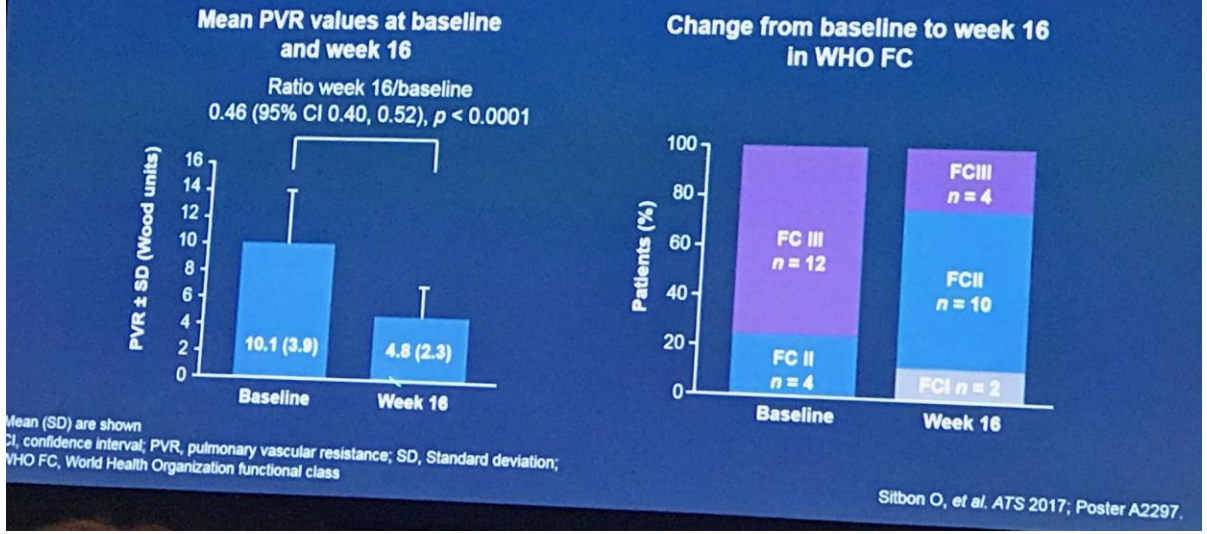
Patients receiving double oral combination therapy with an ERA and a PDE-5i have improved long-term outcomes



1. Pulido T, *et al. N Engl J Med* 2013; 369:809-18; 2. Galiè N, *et al. N Engl J Med* 2015; 373:834-44.

OPTIMA: Combination therapy with macitentan and tadalafil led to improvements in cardiopulmonary hemodynamics and WHO FC

OPTIMA (NCT02968901) is an ongoing study evaluating the efficacy, safety and tolerability of initial combination therapy with macitentan and tadalafil in newly diagnosed patients with PAH



Mean (SD) are shown
CI, confidence interval; PVR, pulmonary vascular resistance; SD, Standard deviation; WHO FC, World Health Organization functional class

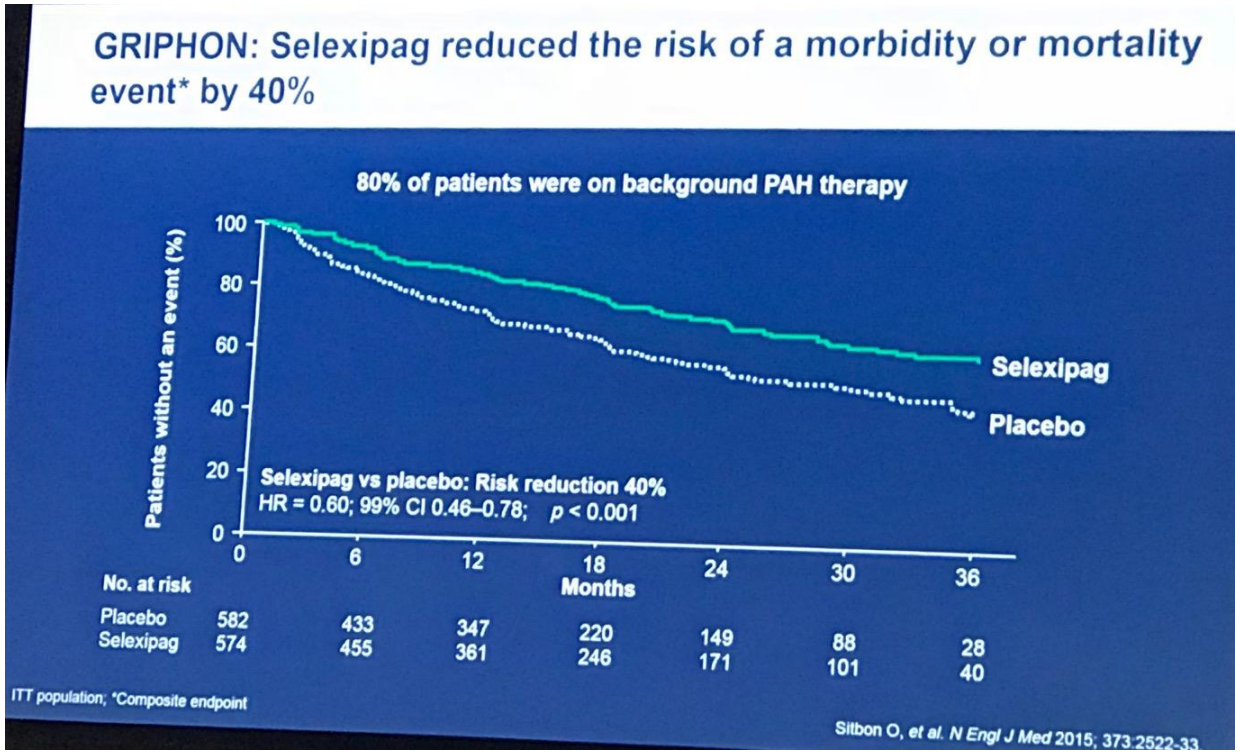
Sitbon O, *et al. ATS* 2017; Poster A2297.

RSDC
Respiratory Sleep Disorder

- Irrespective of what combination used the effect is similar in combination therapy
- Triple therapy tried in severe patients the impressive result was on haemodynamics which persisted over a long time
- Triton is a study to compare triple vs dual therapy in treatment naïve patients

RSDC
Respiratory Sleep Disorder

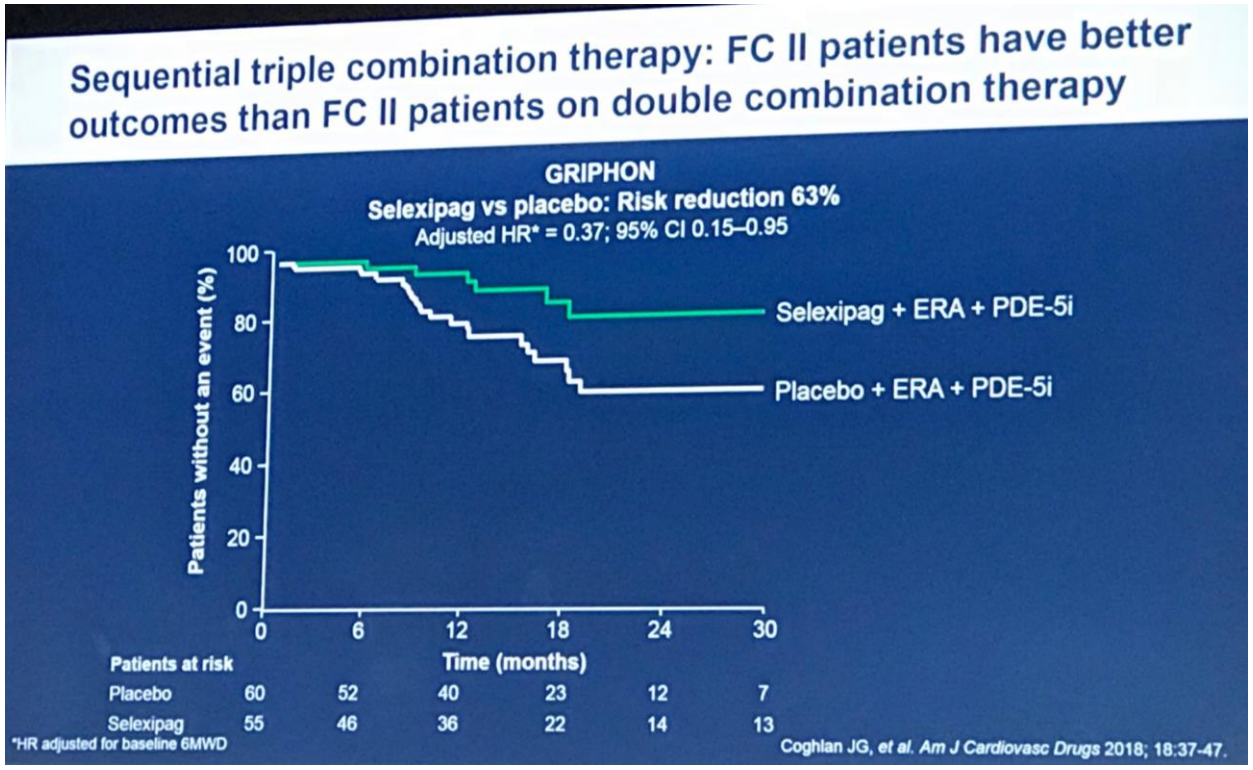
GRIPHON: Selexipag reduced the risk of a morbidity or mortality event* by 40%



ITT population; *Composite endpoint

Sitbon O, *et al. N Engl J Med* 2015; 373:2522-33.

Sequential triple combination therapy: FC II patients have better outcomes than FC II patients on double combination therapy



*HR adjusted for baseline 6MWD

Coghlan JG, *et al. Am J Cardiovasc Drugs* 2018; 18:37-47.

RSDC
Respiratory Sleep Disorder

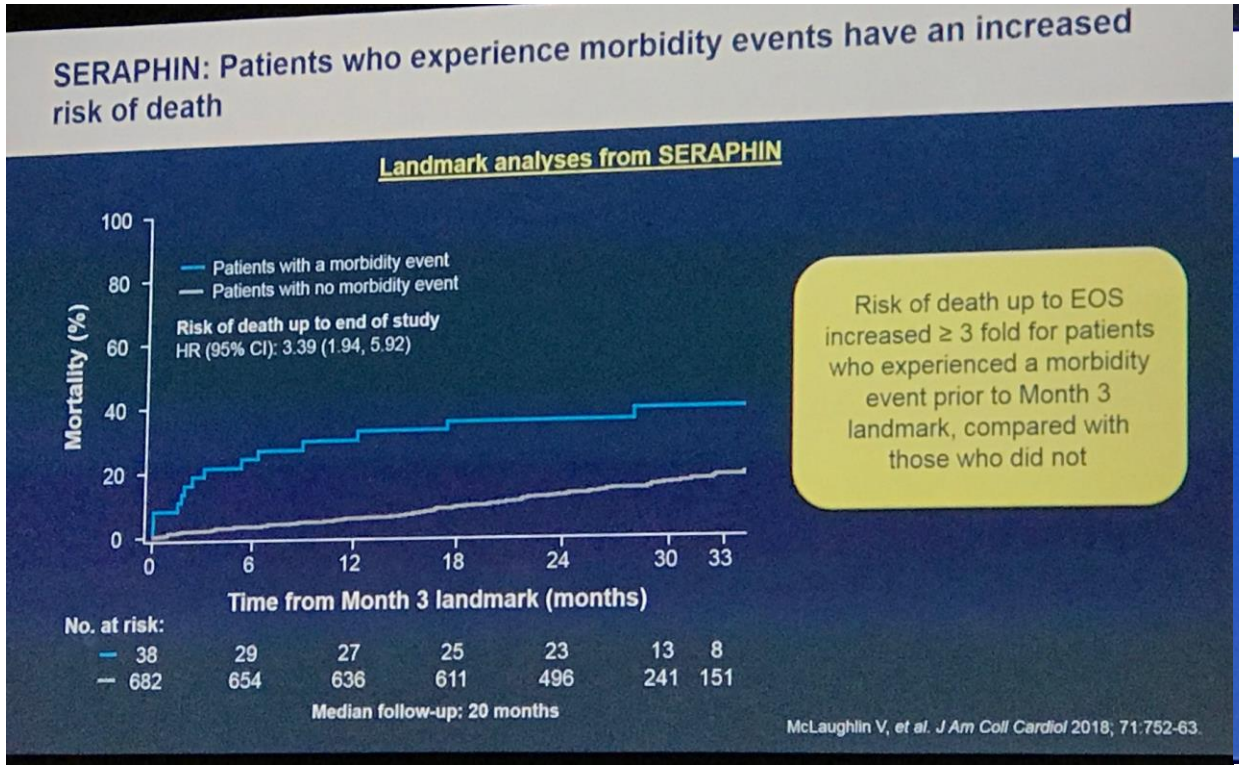
What is the impact of clinical worsening for patients?
Evidence from SERAPHIN and GRIPHON

- The two pivotal trials, SERAPHIN with macitentan (*n* = 742) and GRIPHON with selexipag (*n* = 1156), are the largest randomized controlled trials in PAH[1,2]
- The primary endpoint in each study was a composite of first morbidity or mortality event, occurring on the assigned treatment
- In both trials, all patients were followed for all-cause mortality up to the end of the study
- The landmark method[3,4] was utilized to evaluate the association between morbidity events and long-term mortality

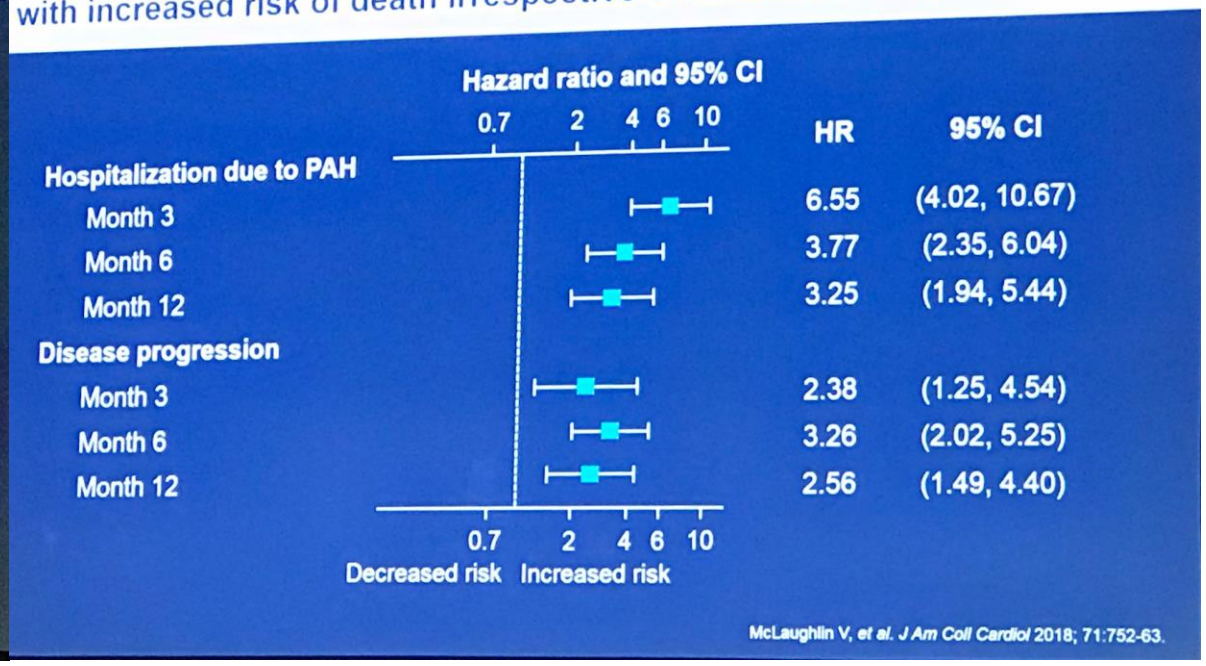
1. Pulido T, *et al. N Engl J Med* 2013; 369:809-18;
2. Sitbon O, *et al. N Engl J Med* 2015; 373:2522-33;
3. Dafni U. *Circ Cardiovasc Qual Outcomes* 2011; 4:363-71;
4. Anderson JR, *et al. J Clin Oncol* 1983; 1:710-9.

RSDC
Respiratory Sleep Disorder

SERAPHIN: Patients who experience morbidity events have an increased risk of death



GRIPHON: Hospitalization and disease progression were associated with increased risk of death irrespective of landmark timepoint



RSDC
Respiratory Sleep Disorder

Summary

- A wealth of data on effective management and treatment strategies for PAH is available
- Aiming to achieve and maintain a low-risk profile is a key treatment goal in PAH
- It is essential to perform repeated multi-parameter risk assessments in patients at baseline and follow-up
- Morbidity events are associated with an increased risk of death, therefore treatment strategies that delay disease progression are essential
- GRIPHON is the first long-term RCT to provide evidence that the addition of a third drug is both efficacious and safe

RSDC
Respiratory Sleep Disorder

Beyond double combination therapy in PAH: Initial triple combination therapy - A single center experience

- **Initial** triple combination therapy:
  i.v. epoprostenol + bosentan + sildenafil
- 19 treatment-naïve incident patients with idiopathic (*n* = 9) or heritable (*n* = 10) PAH
- Mean age 39 ± 14 years (18 – 63)
- NYHA FC III (*n* = 8) or IV (*n* = 11)
- Severe hemodynamics: CI < 2.0 L/min/m^2 or PVR > 1000 dyn·s·cm^{-5}

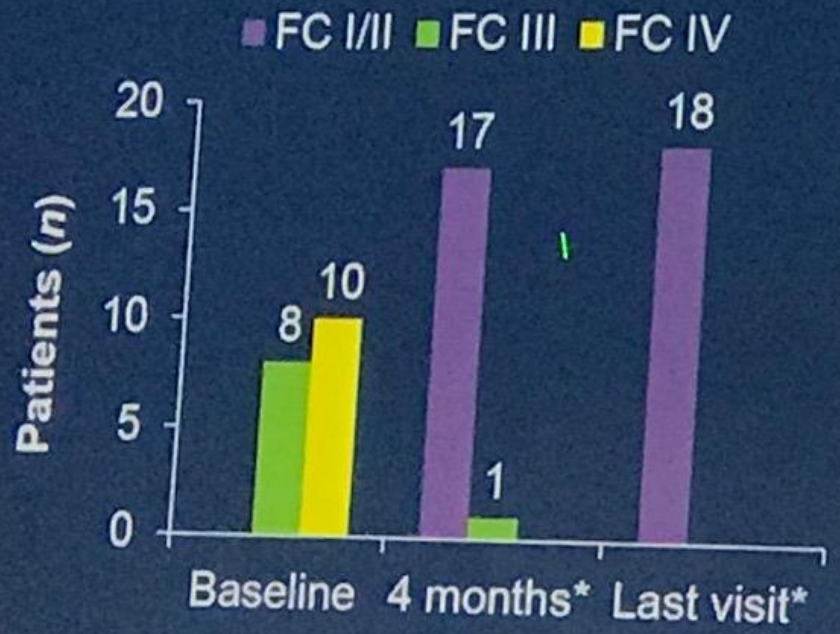
One patient was not included in the month 4 assessment due to an emergency lung transplant in month 3

Sitbon O, *et al. Eur Respir J* 2014; 43:1691-7.

RSDC
Respiratory Sleep Disorder

Initial triple combination therapy in severe PAH: Treatment benefit on FC and hemodynamics

Prospective, observational analysis of idiopathic or heritable PAH patients (*n* = 18) treated with triple initial combination therapy (epoprostenol, bosentan and sildenafil)[1,†]

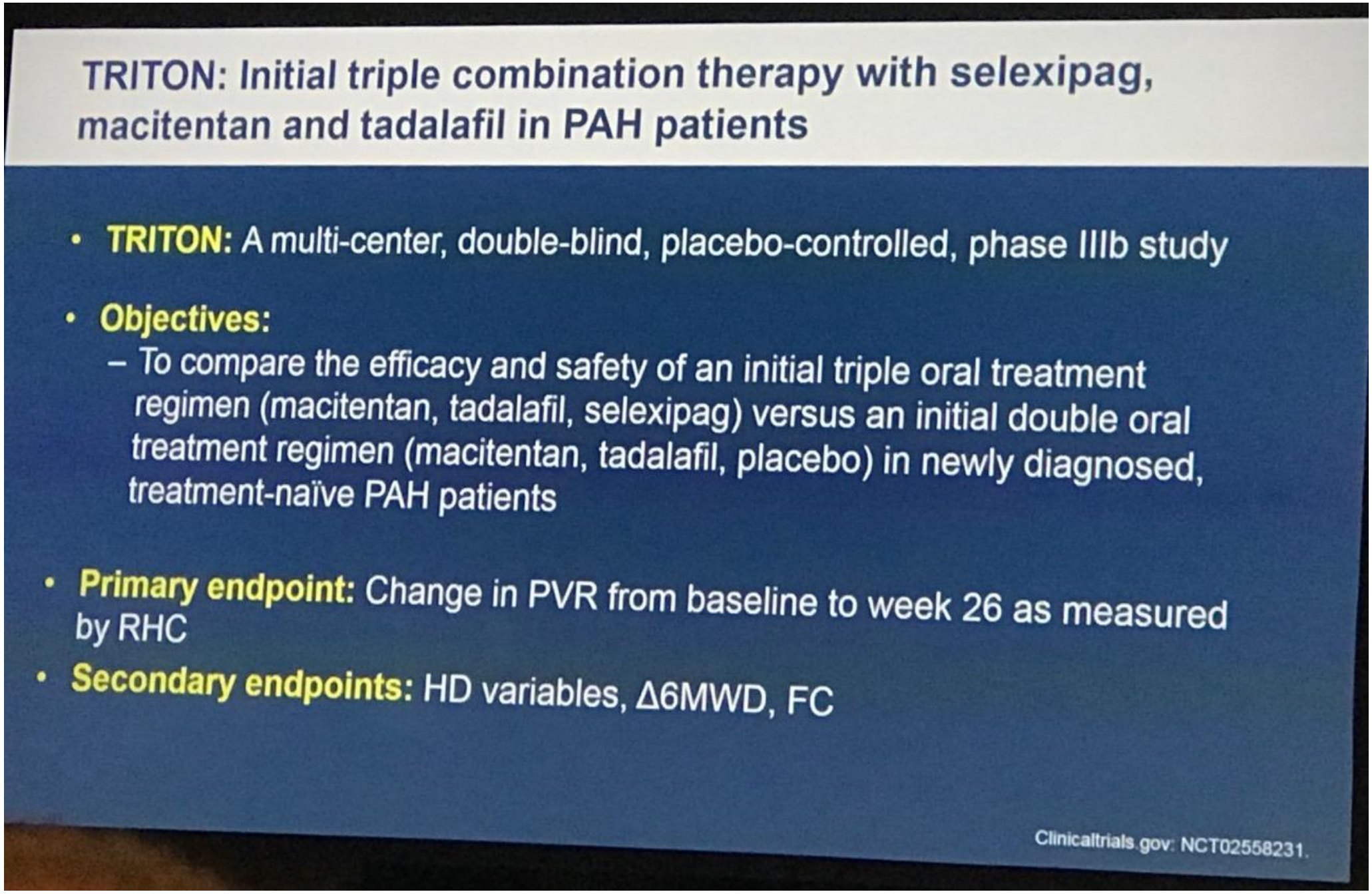


	Baseline	4 months	Last visit (32 ± 19 months)
RAP (mmHg)	11.9 ± 5.2	4.9 ± 4.9*	5.2 ± 3.5*
mPAP (mmHg)	65.8 ± 13.7	45.7 ± 14.0*	44.4 ± 13.4*
CI (l/min/m^2)	1.66 ± 0.35	3.49 ± 0.69*	3.64 ± 0.65*
PVR (d.s.cm^{-5})	1718 ± 627	564 ± 260*	492 ± 209*
SvO_2 (%)	51.0 ± 8.5	69.7 ± 5.2*	72.2 ± 4.0*

*$p < 0.01$ versus baseline; †Current guidelines state that this initial drug combination should be considered in patients with PAH in FC III-IV[2,3]. For specific product-related information please consult your local summary of product characteristics.

1. Sitbon O, *et al. Eur Respir J* 2014; 43:1691-7;
2. Galiè N, *et al. Eur Respir J* 2015; 46:903-75;
3. Galiè N, *et al. Eur Heart J* 2016; 37:67-119

RSDC
Respiratory Sleep Disorder

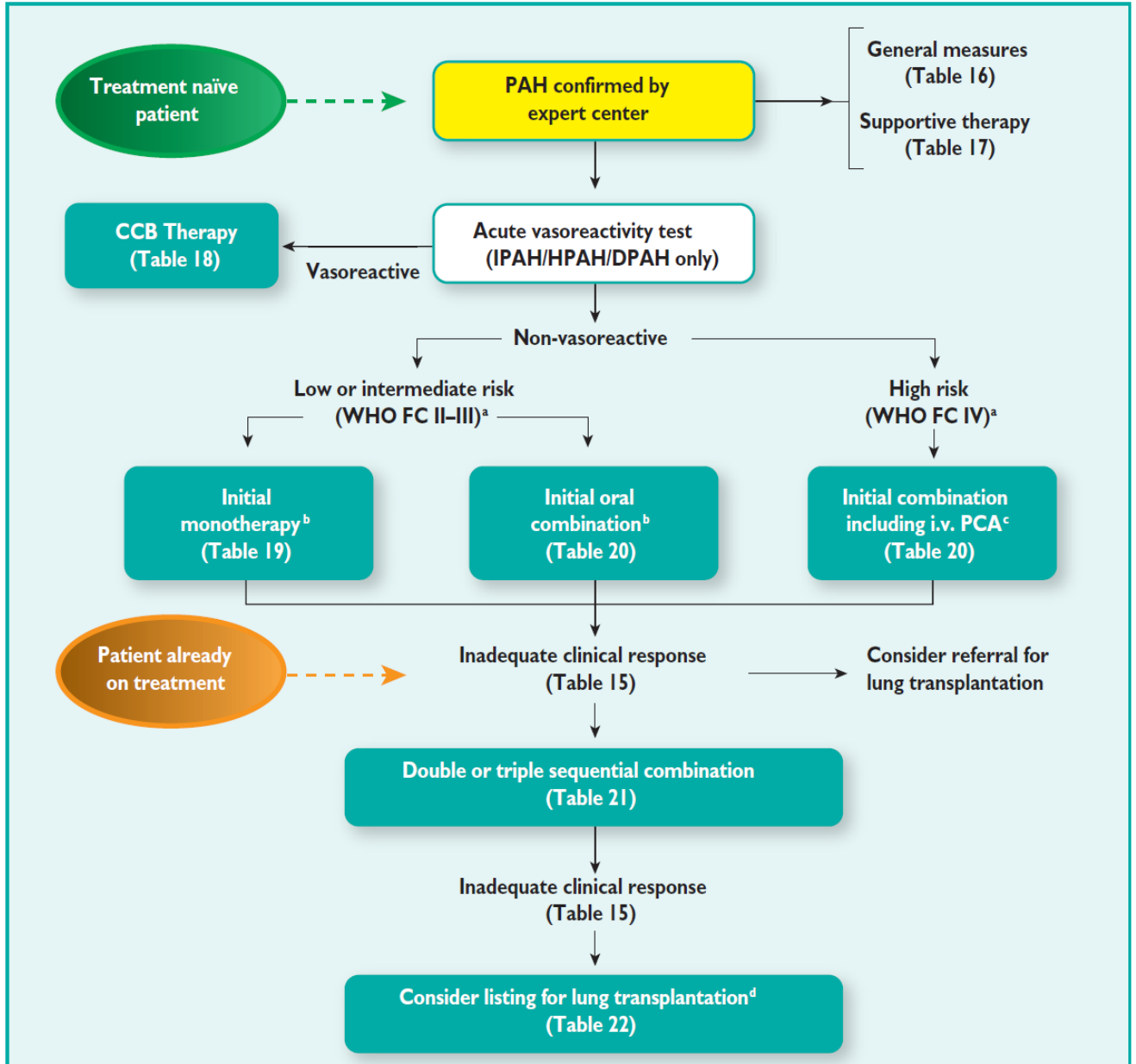


RSDC
Respiratory Sleep Disorder

Conclusions

- Early diagnosis and detection of worsening are key for the initiation of early treatment and timely intensification of therapy
- Risk assessment at diagnosis (and follow-up) is essential to determine treatment strategy
- Initial double combination therapy may not be sufficient in controlling disease progression, and initial or sequential triple therapy may be required
- TRITON is underway to determine the efficacy and safety of initial triple oral combination therapy in treatment naïve patients
- By working together, patients and physicians can ensure that they achieve the best outcomes

RSDC
Respiratory Sleep Disorder



CCB = calcium channel blockers; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; i.v. = intravenous; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues; WHO-FC = World Health Organization functional class.

[a]Some WHO-FC III patients may be considered high risk (see Table 13).

[b]Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure.

[c]Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy.

[d]Consider also balloon atrial septostomy.

RSDC
Respiratory Sleep Disorder

CTEPH

Chronic Thromboembolic Pulmonary Hypertension

CTEPH diagnosis

- mPAP > 25
- PCWP<15
- VQ positive with any burden disease
- Treated with anticoagulant for >3 months
- The issue is that they can be diagnosed as acute PE
- The incidence after acute PE is: 3%, is rare but under diagnosed
- New or worsened dyspnoea after PE

RSDC
Respiratory Sleep Disorder

Predictors of CTEPH after acute PE

At the time of index PE:

Massive and Recurrent PE
Unprovoked PE
Symptoms present > 2 weeks before presentation

In the follow up of acute PE:

New or worsened dyspnoea
Splenectomy
Chronic inflammatory disorder
Non-O blood group

RSDC
Respiratory Sleep Disorder

Operability assessment by a multidisciplinary CTEPH team

Technically operable

Technically non-operable

Acceptable risk/benefit ratio

Non-acceptable risk/benefit ratio[a]

Pulmonary endarterectomy

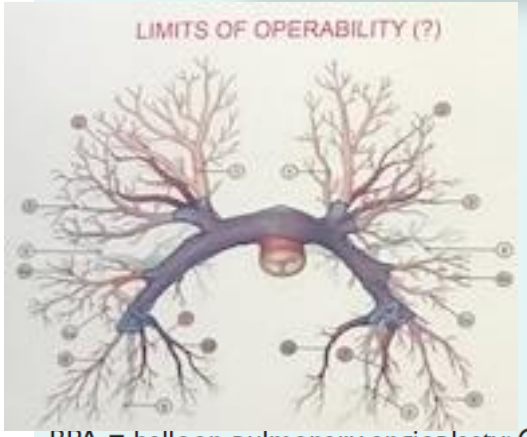
Persistent symptomatic PH

Targeted medical therapy

Consider BPA in expert center[b]

Consider lung transplantation

Persistent severe symptomatic PH



BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension.

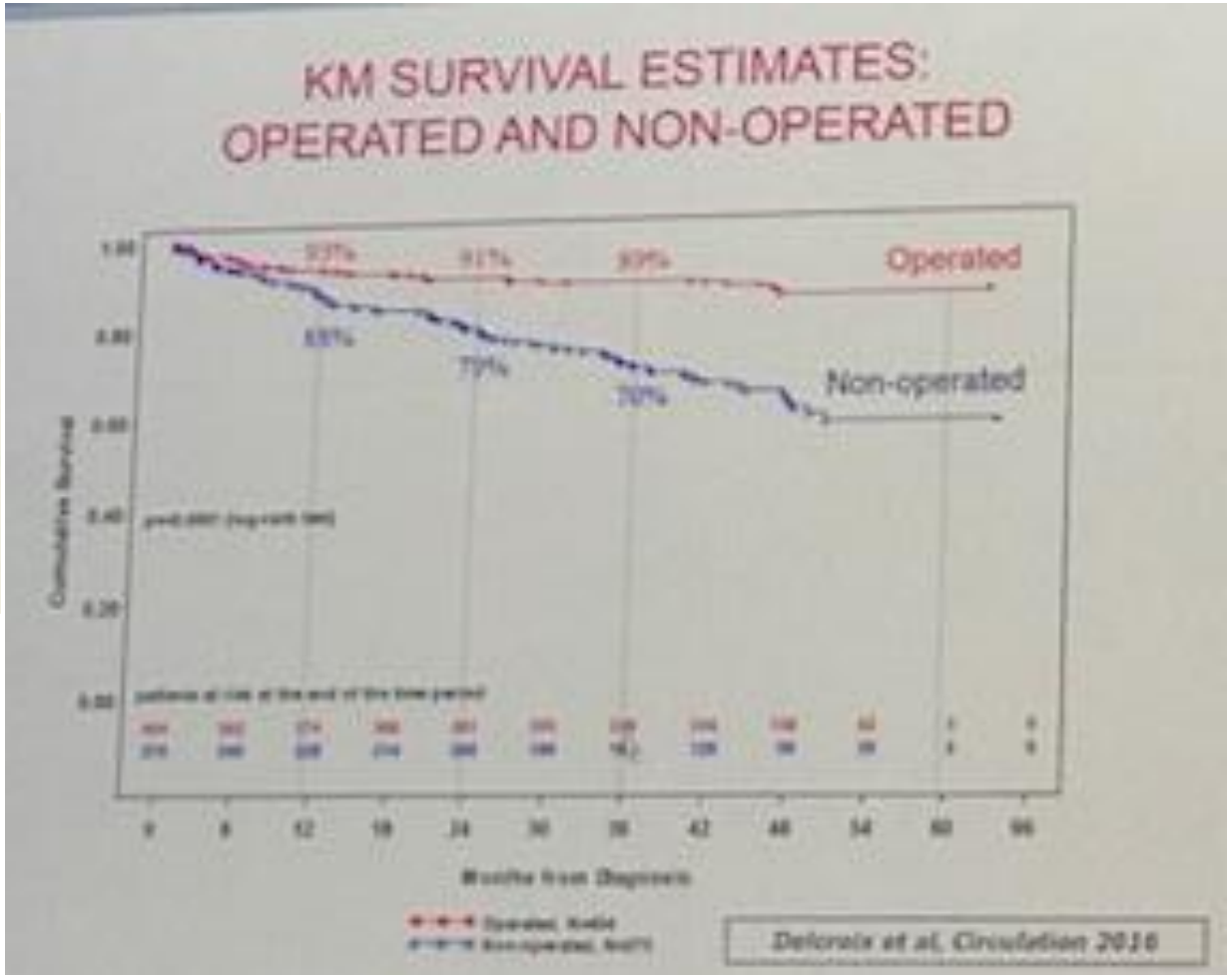
[a]Technically operable patients with non-acceptable risk/benefit ratio can be considered also for BPA.

[b]In some centers medical therapy and BPA are initiated concurrently.

RSDC
Respiratory Sleep Disorder

PEA INHOSPITAL MORTALITY

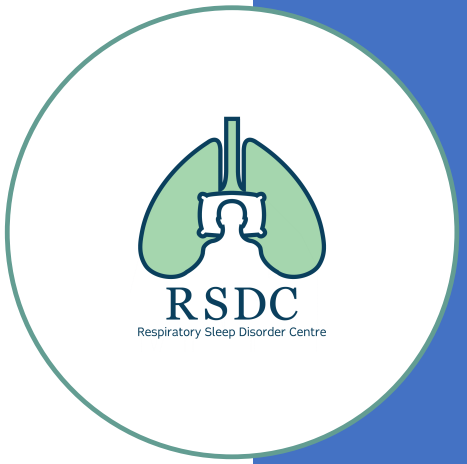
- PEACOG study, 74 patients — 1.4%
  - Vuylsteke et al Lancet 2011;378:1379
- UCSD, last 500 patients — 2.2%
  - Madani et al Ann Thor Surg 2012;94:97
- European prospective registry — 4.7%
  - Mayer et al J Thorac Cardiovasc Res 2011;141:702



- We can find 3 times cases than what we already now
- We have more haemoptysis is CTEPH than IPH
- 60% reduction in PVR after endarterectomy
- Surgery increase survival
- Macitentan and Riociguat improved 6MWD

RSDC
Respiratory Sleep Disorder

Asthma



What is the most important cell in Asthma?

Epithelial barrier is defective in asthma

The role of Tight Junctions (TJ)

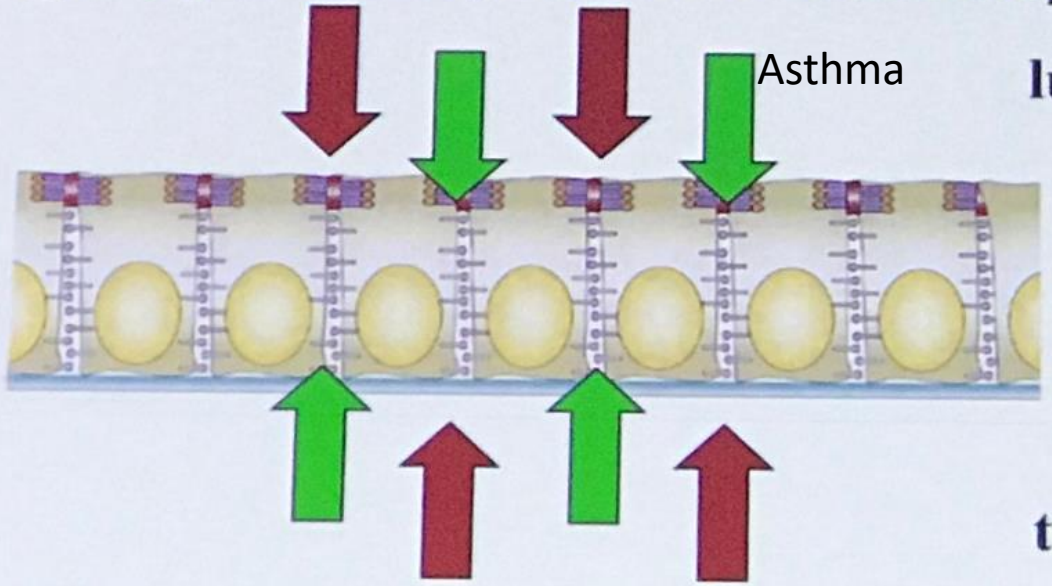
Asthma

RSDC
Respiratory Sleep Disorder

Functions

- Closed tight junctions: preventive and protective against environment

- Open tight junctions: to drain inflammation, but allow allergen, pollutant, toxin accessibility



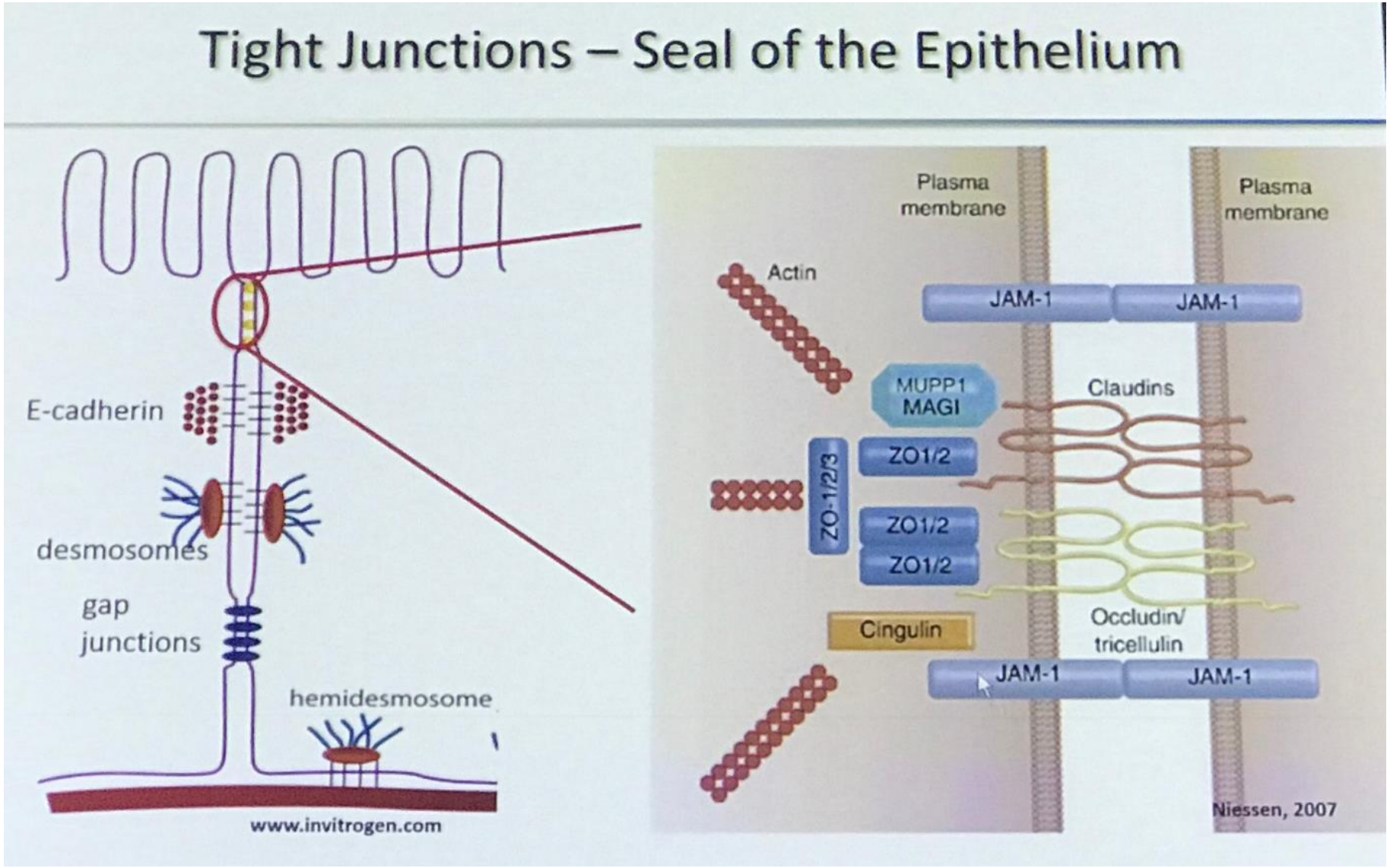
TJs PROTEINS:

3-membrane domains
- occludin
- claudins (24 proteins)
- tricellulin (novel - between 3 neihbouring cells)

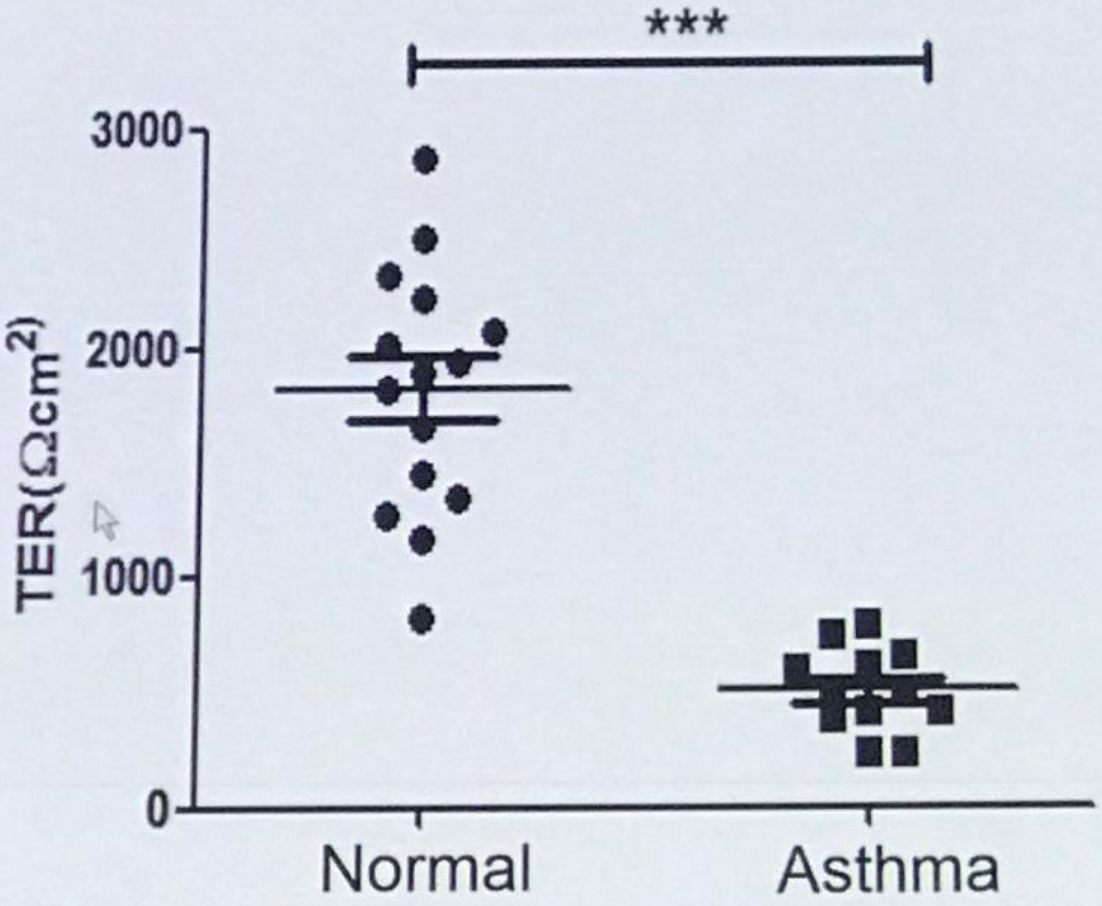
1-membrane domain
- JAMs – junction adherent proteins

RSDC
Respiratory Sleep Disorder

Tight Junctions – Seal of the Epithelium



Bronchial Epithelial Leakiness in Asthma

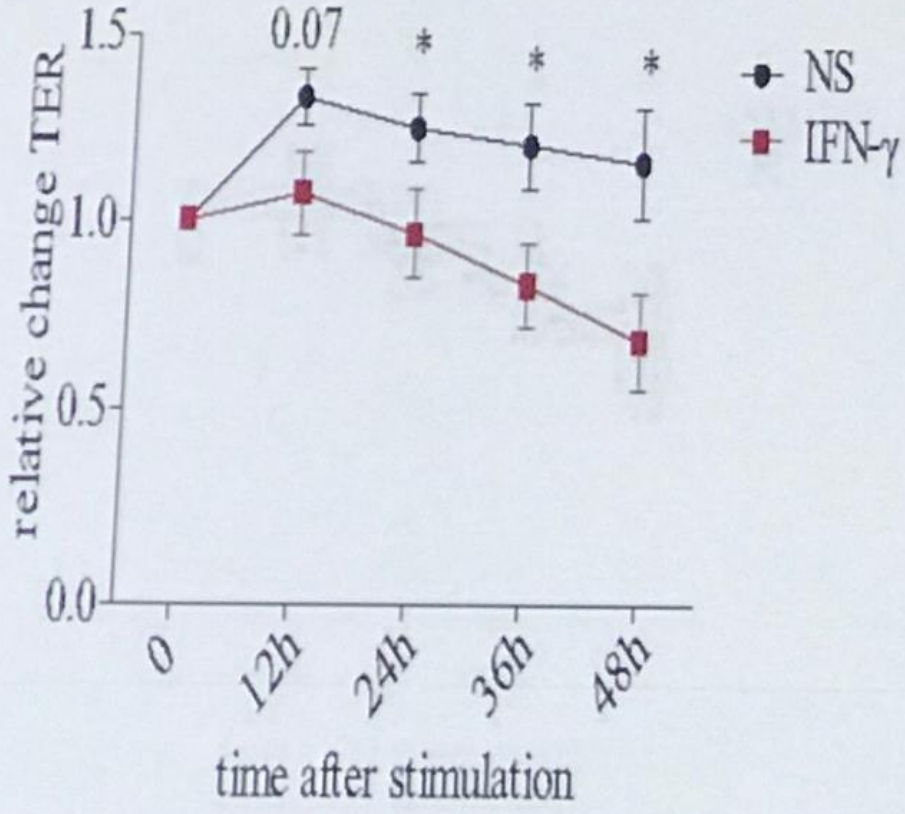


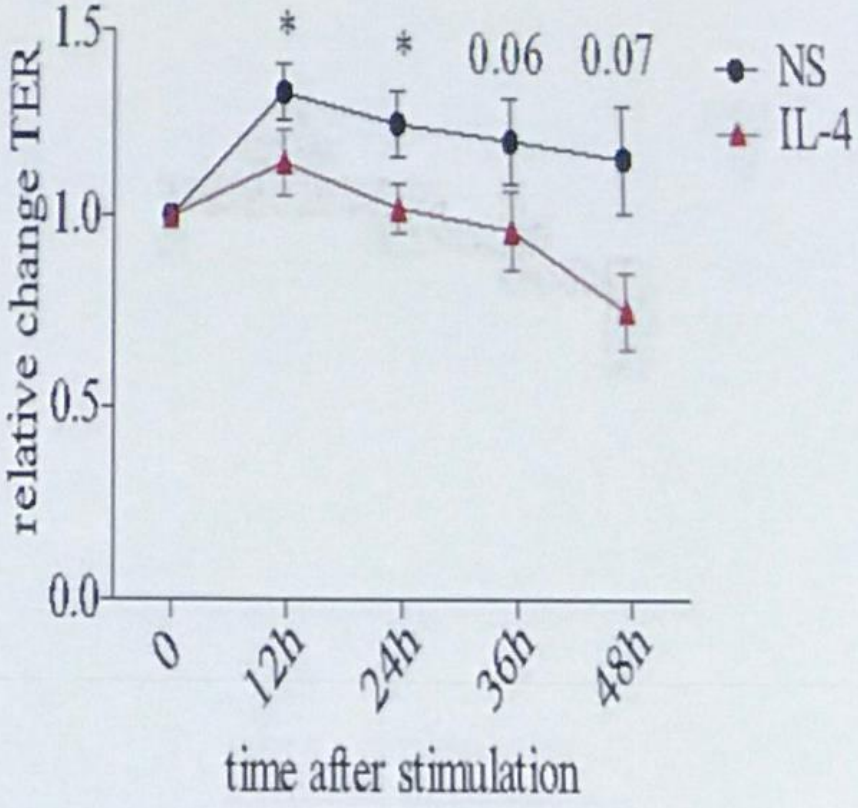
Leaky asthmatic epithelial barrier even after 3 passages

Wawrzyniak et al. 2017

RSDC
Respiratory Sleep Disorder

A IL-4 and IFN-γ open TJs

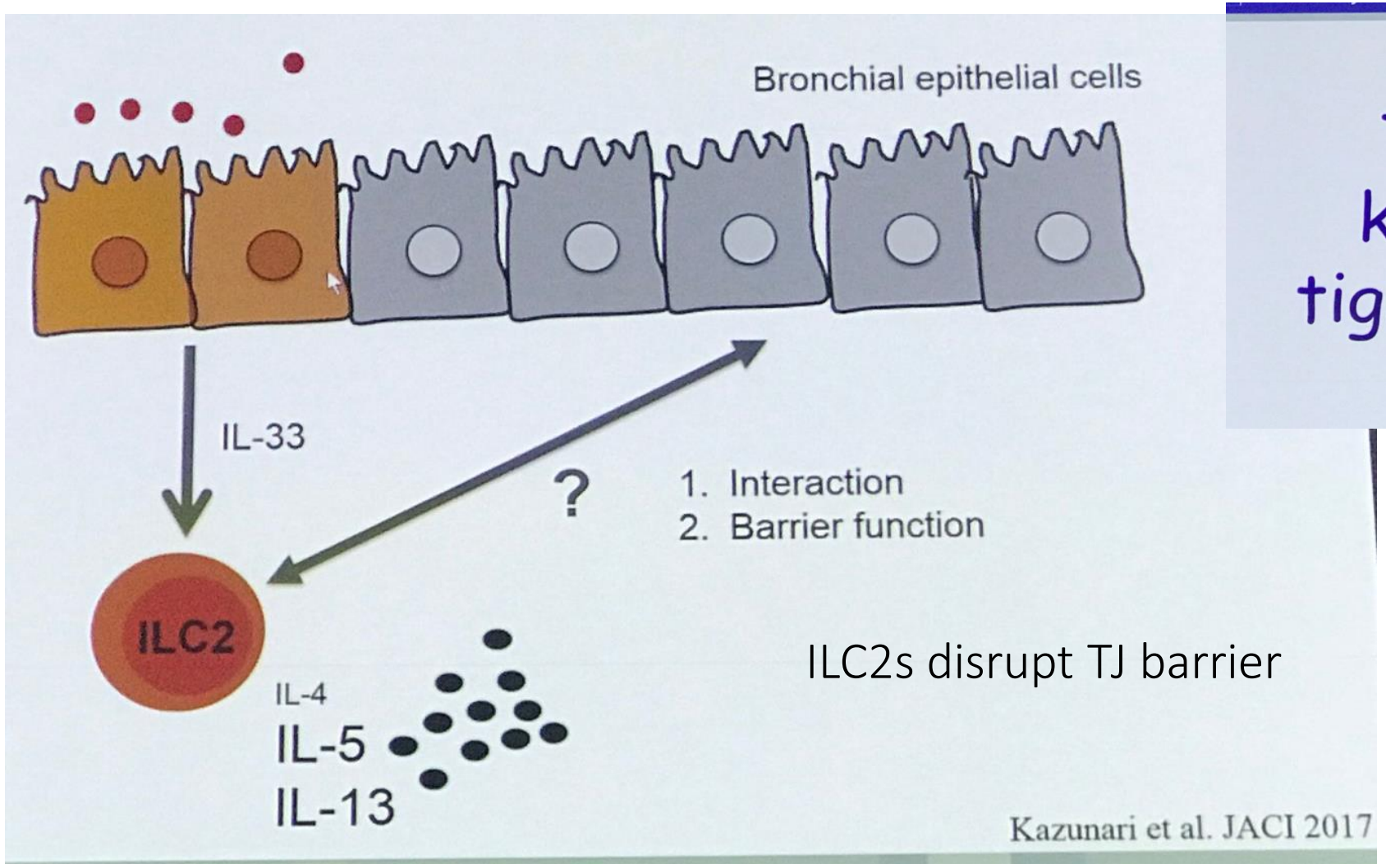




Soyka et al 2012

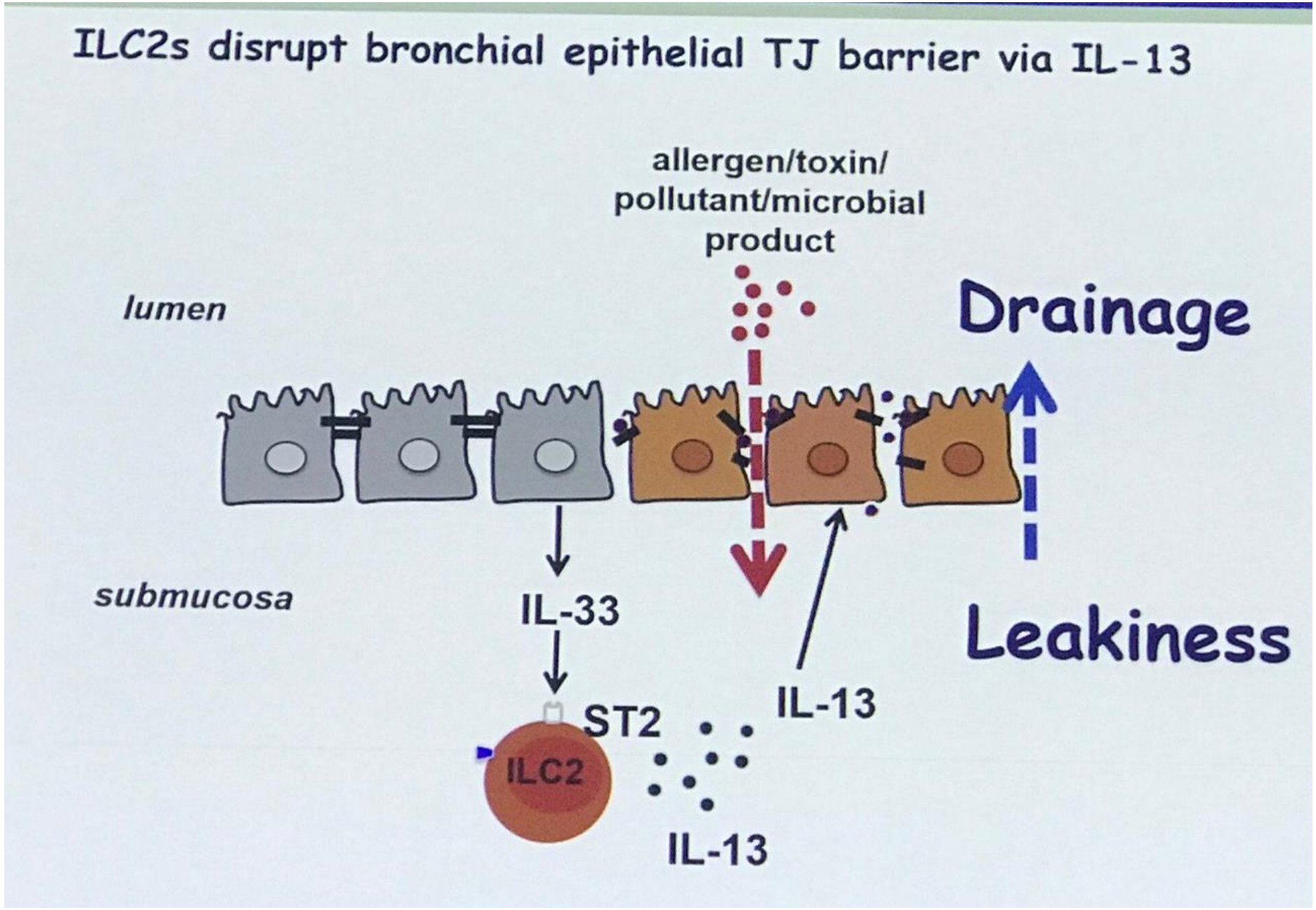
RSDC
Respiratory Sleep Disorder

ILC2 and IL-13 in bronchial epithelial tight junction barrier leakiness

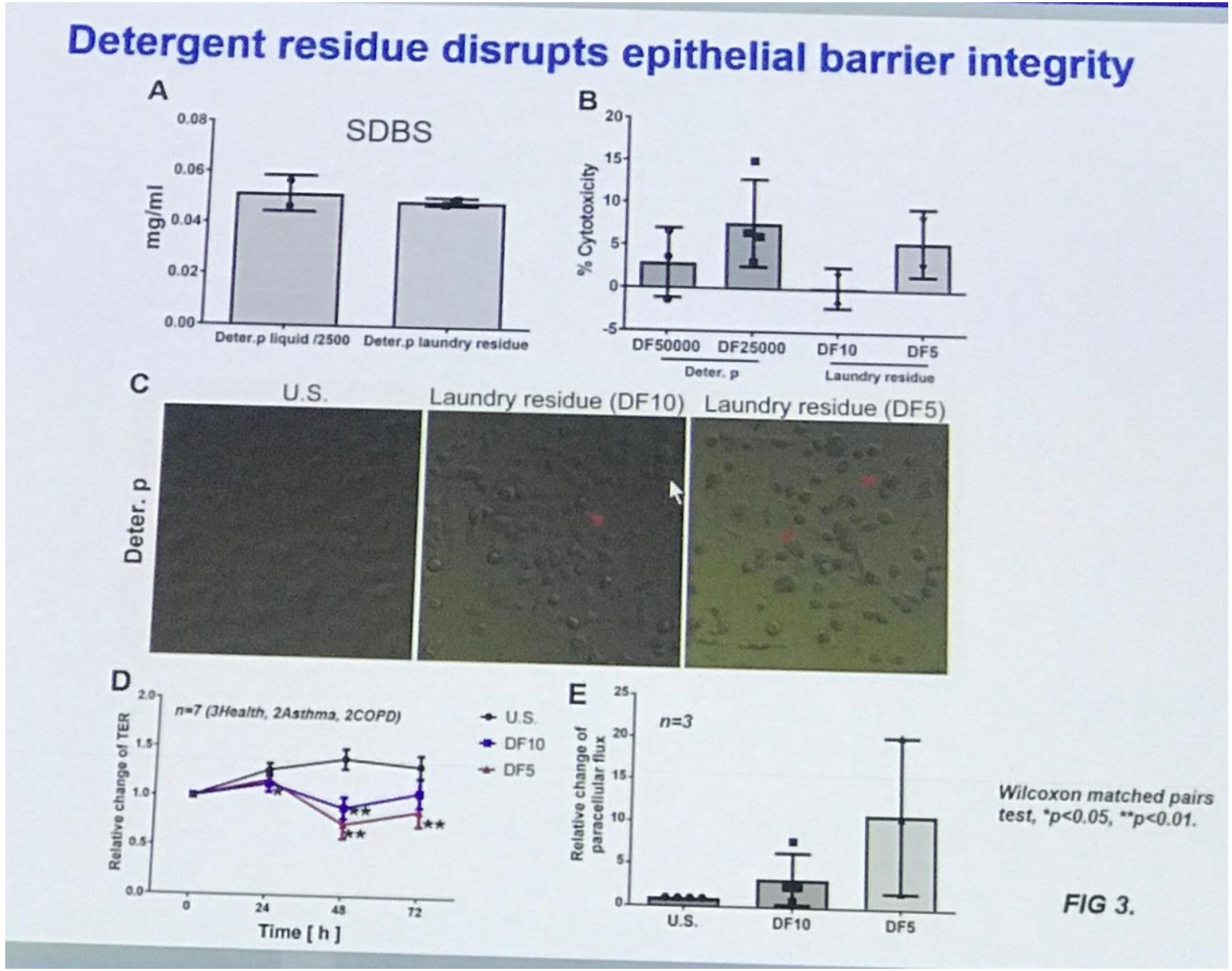


Treg cells kindly open tight junctions

ILC2s disrupt TJ barrier


ILC2s disrupt bronchial epithelial TJ barrier via IL-13
allergen/toxin/
pollutant/microbial
product
lumen
Drainage
submucosa
IL-33
Leakiness
IL-13
ST2
ILC2
IL-13

Detergent residue disrupts epithelial barrier integrity



*Wilcoxon matched pairs test, *p<0.05, **p<0.01.*

FIG 3.

RSDC
Respiratory Sleep Disorder

Conclusions:

Detergents kill cells in 1:10'000 dilutions
and open TJ barrier in 1:100'000, 1:1000000 doses.

Rinse residue is still toxic at 1:10 or more dilutions.

RNAseq: In non cytotoxic concentrations: they directly attack epithelial barrier molecules
affect cell adhesion, lipid metabolism, oxidative stress and apoptosis

Methylome: Detergents are not too active in methlytion of genes in short time, long-term exposure should be studied

ATAC seq: increased TSS in open chromatin, to be analysed

RSDC
Respiratory Sleep Disorder

Mast Cells

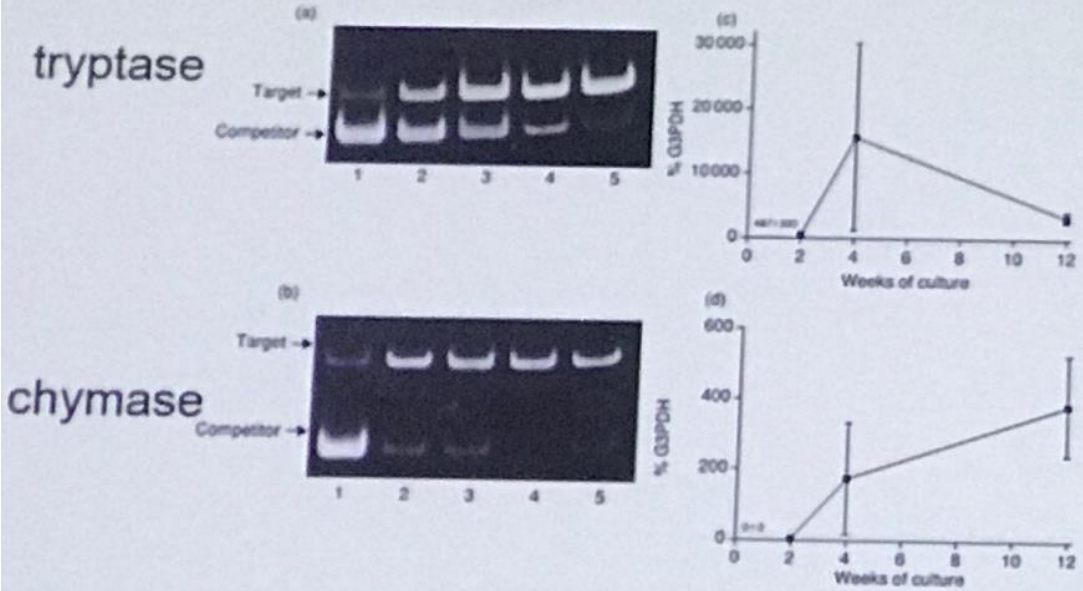
- There are different phenotypes of mast cells
- In the lung we have MCT

RSDC
Respiratory Sleep Disorder

AARHUS
UNIVERSITET

Characterization of 'adult-type' mast cells derived from human bone marrow CD34+ cells cultured in the presence of stem cell factor and interleukin-6. Interleukin-4 is not required for constitutive expression of CD54, FcεRIα and chymase, and CD13 expression is reduced during differentiation

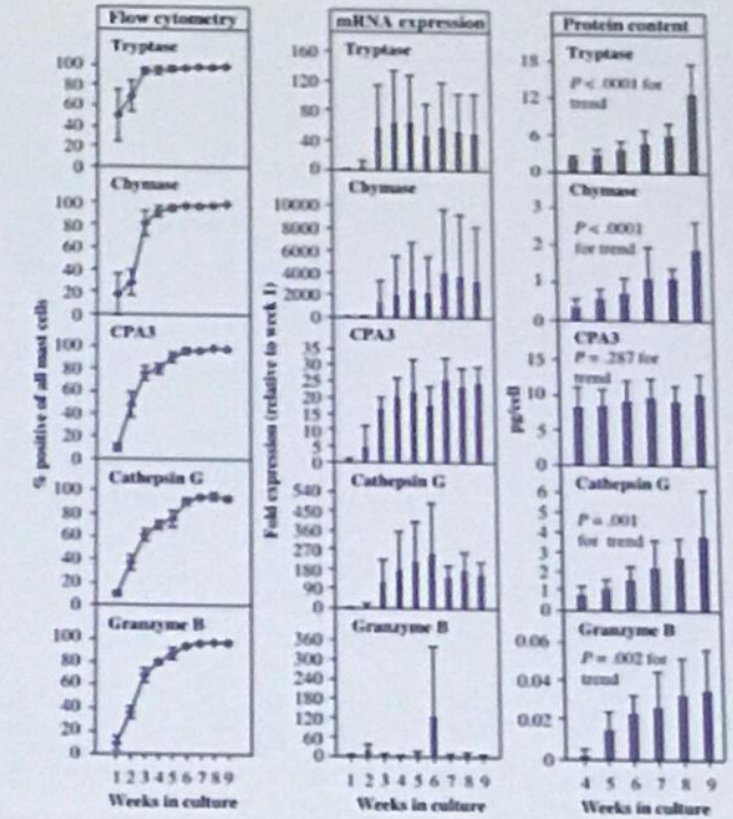
Y. Shimizu, K. Sakai*, T. Miura†, T. Narita‡, H. Tsukagoshi, Y. Satohǁ, S. Ishikawaǁ, Y. Morishitaǁ, S. Takai¶, M. Miyazaki¶, M. Mori, H. Saito**, H. Xia†† and L. B. Schwartz††



Shimizu Y et al (2002), CEA v32, p872

Human mast cells arise from a common circulating progenitor

Katariina Maaninka, BSc, Jani Lappalainen, MSc, and Petri T. Kovanen, MD, PhD *Helsinki, Finland*



Maaninka K et al (2013); JACI v132:p463-9

RSDC
Respiratory Sleep Disorder

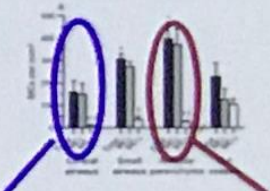
An alternative hypothesis to having local factors differentiate mast cells into either MC_T or MC_{TC} is that MC_T are younger than MC_{TC}
In other words,

In the lung we predominantly have MC_T because there is a high turnover of MC, that rarely live long enough to express appreciable amounts of Chymase

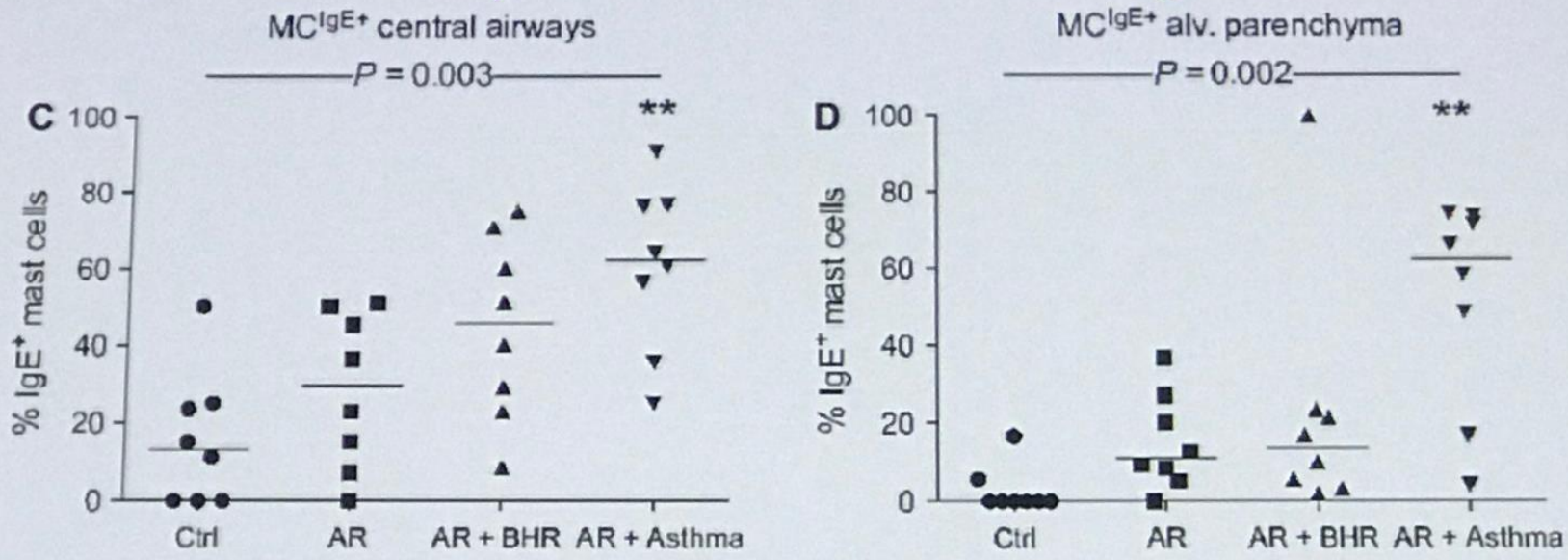
In connective tissue, we have predominantly MC_{TC} because there is a lower turnover of MC, that live long enough to express measureable amounts of Chymase

RSDC
Respiratory Sleep Disorder

AARHUS
UNIVERSITET

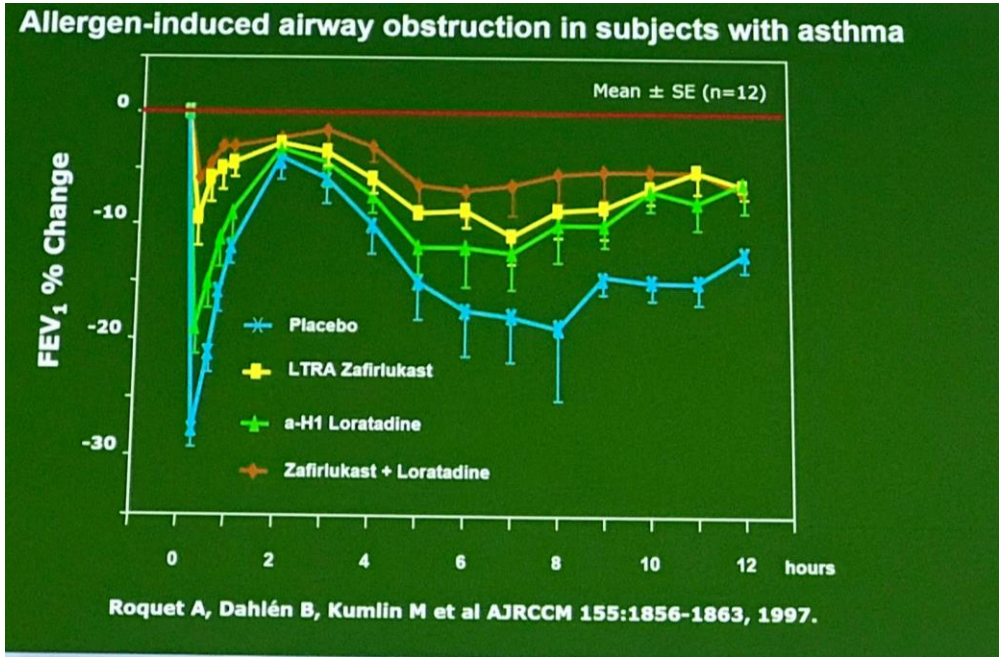


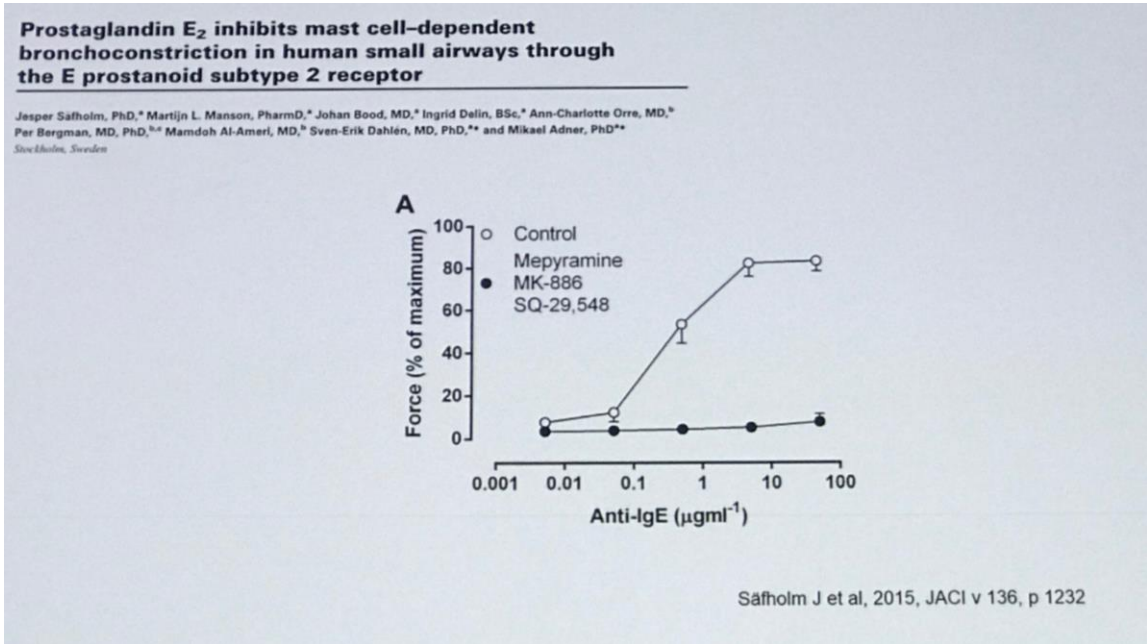
ASTHMATICS PATIENTS HAVE MORE IGE+ MAST CELLS THAN NORMAL SUBJECTS



Andersson et al, Allergy 2011;61; 1590

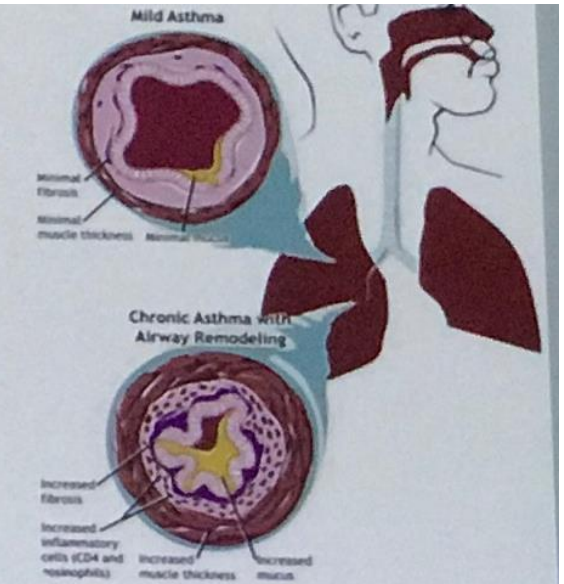
RSDC
Respiratory Sleep Disorder





RSDC
Respiratory Sleep Disorder

CONCLUSIONS



- Mast cells play a pivotal role in asthma and bronchconstriction
- MC histamine and lipid mediators (PGD2, Cys LT) are direct inducers of brochhoconstriction
- IgE mediated activation induces synthesis of these mediators
- The composition of IgE defines the response of the mast cell;
  - Absolute and specific concentration of IgE determine reactivity and senstivity
  - Compexity of IgE increases reactivity
  - IgE affinity shapes the immediate and the late response of human mast cells

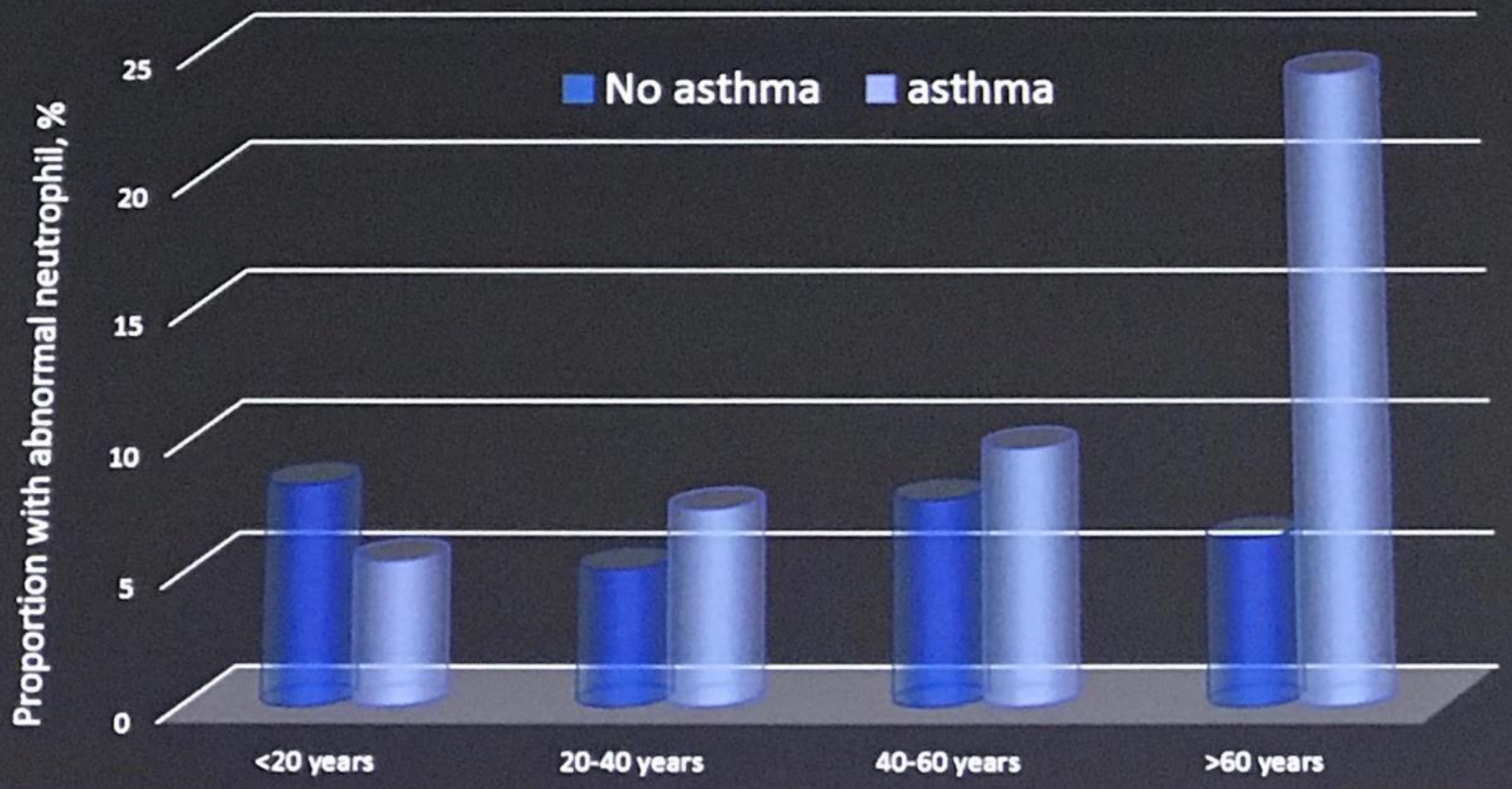
RSDC
Respiratory Sleep Disorder

Asthma and Neutrophils

Most abundant WBC in mammals- essential to life

RSDC
Respiratory Sleep Disorder

What is the impact of age?....



Brooks CR *et al* Respirology. 2013 Jul;18(5):857-65

RSDC
Respiratory Sleep Disorder

Neutrophilic Asthma

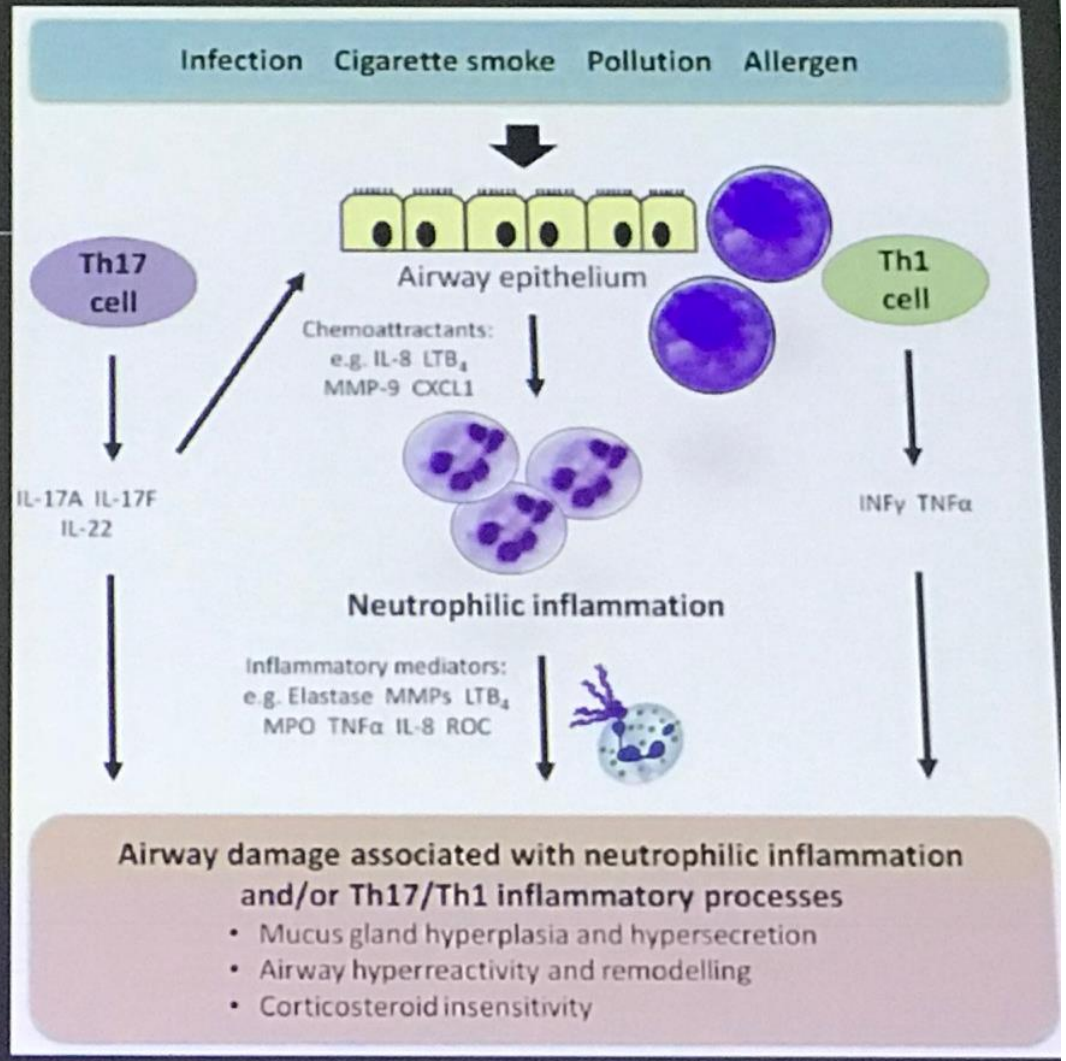
- 15-20% of stable asthma
- Older, AHR – but less severe
- Higher rates of rhinosinusitis and reflux

Increased

- IL-8, NE , 8-isoprostane, IL-1β
- TLR2/4, eDNA
- Colonisation (most often *H.Influenzae*)+ endotoxin

Reduced

- Macrophage efferocytosis
- Microbial diversity
- Galectin-3



from NC Thomson Ther Adv Respir Dis. 2016 Jun;10(3):211-34

RSDC
Respiratory Sleep Disorder

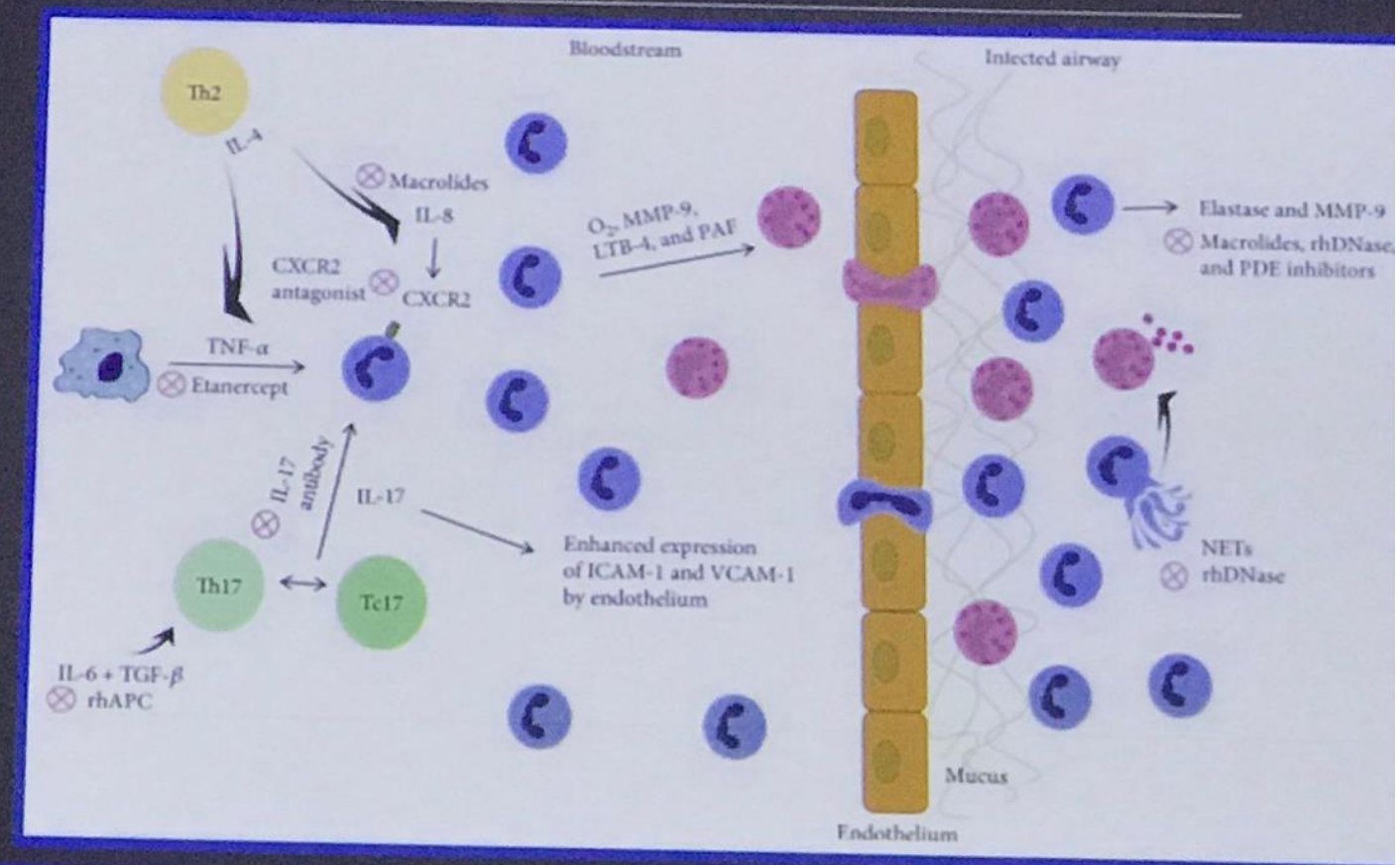
Therapeutic targets

What do we want to target?

- Neutrophil function
- Neutrophil activation
- Neutrophil migration

Where should we target?

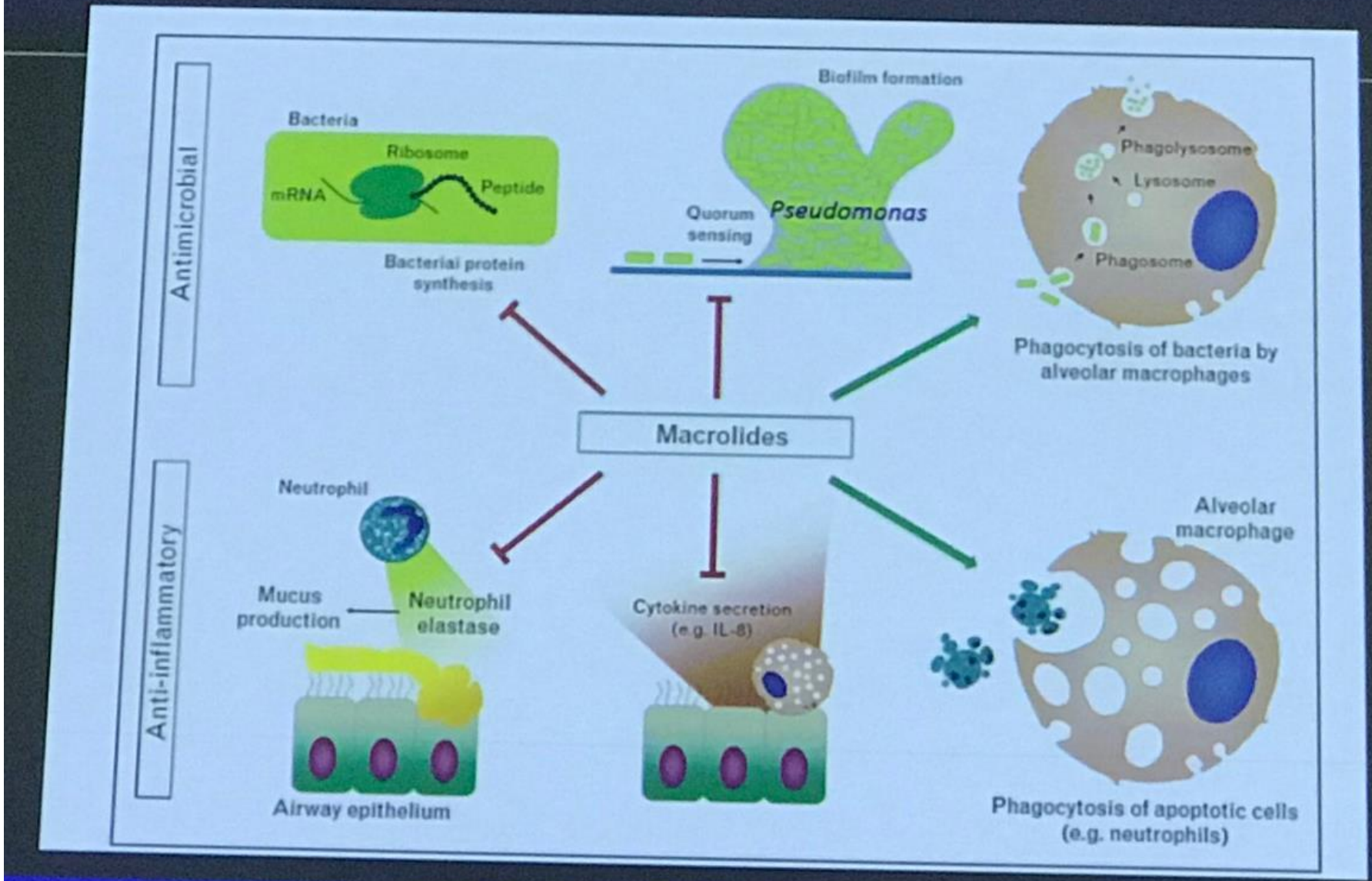
- Circulation
- Airways



Han Gao *et al.* J Immunol Res. 2017;2017:3743048. doi: 10.1155/2017/3743048.

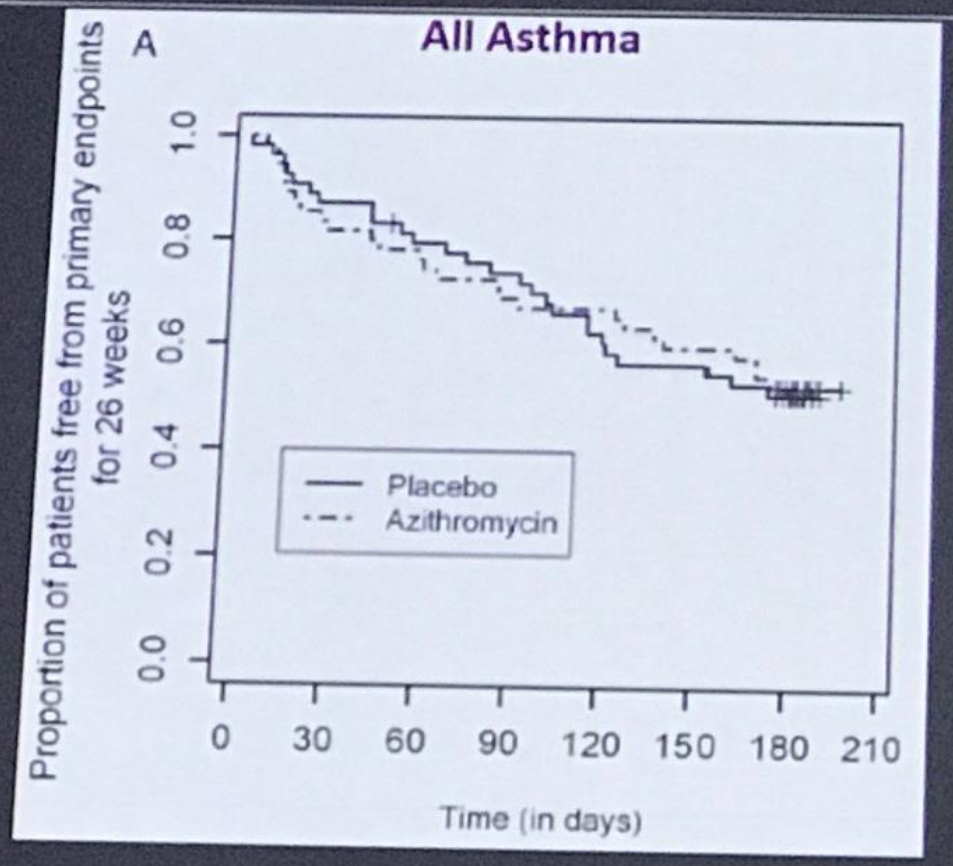
RSDC
Respiratory Sleep Disorder

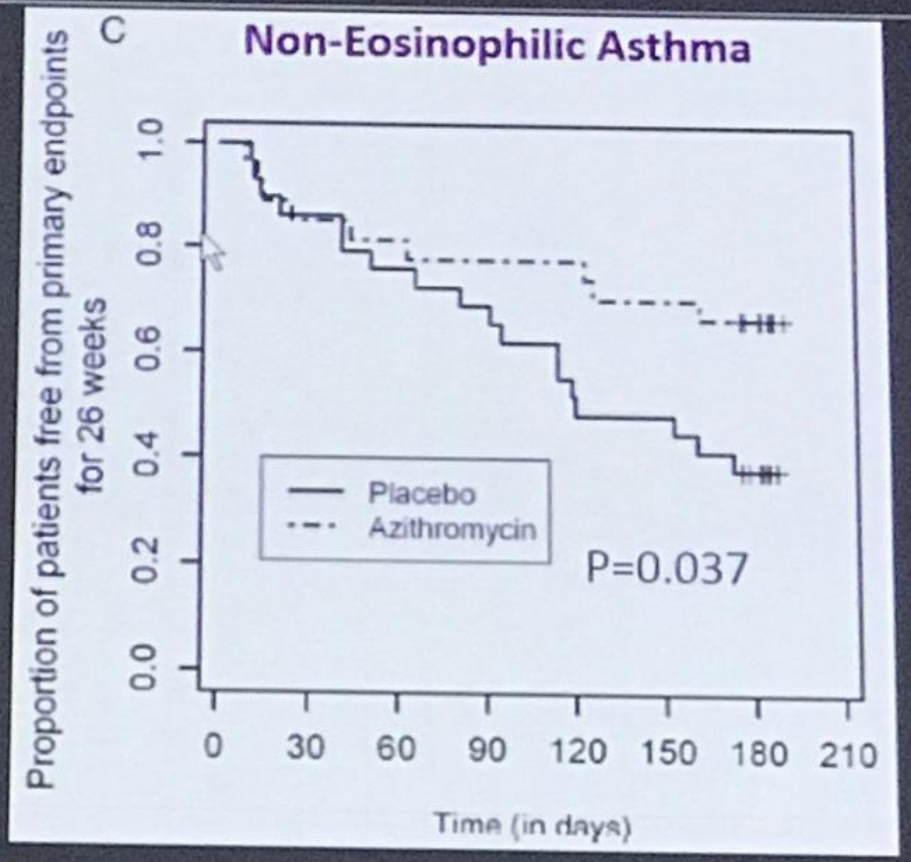
Effects of Macrolide Antibiotics



RSDC
Respiratory Sleep Disorder

AZISAST: Add-on Azithromycin

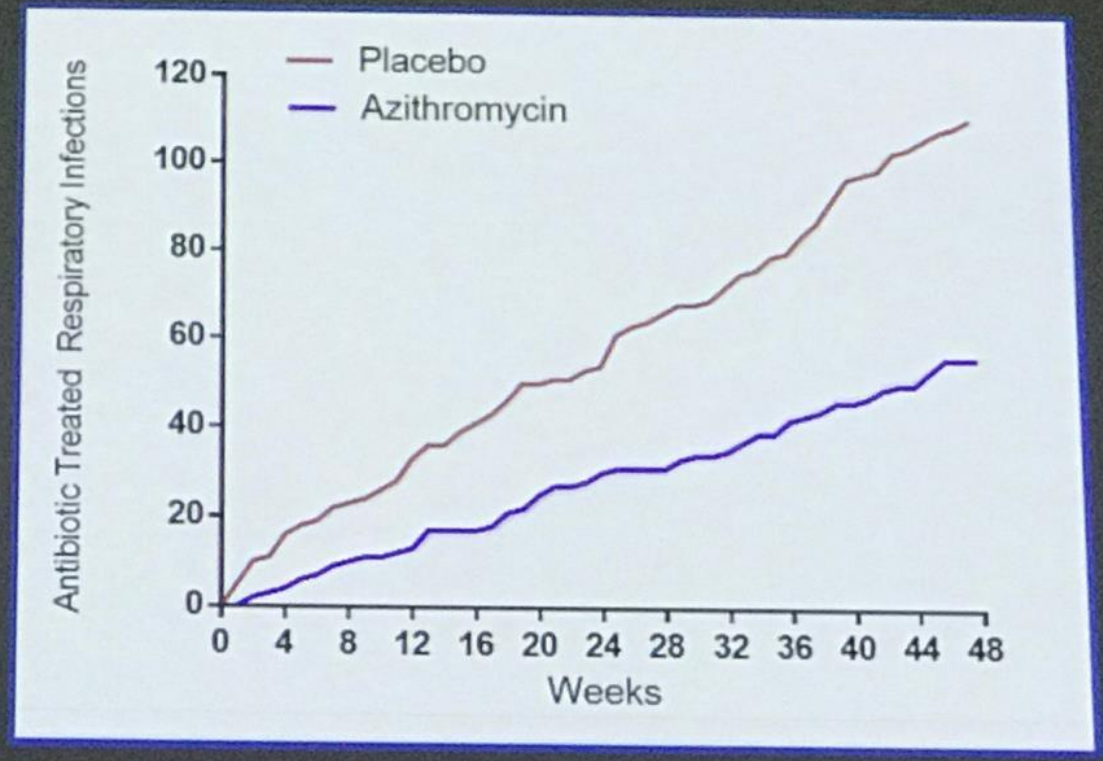




Brusselle *et al.* Thorax. 2013

RSDC
Respiratory Sleep Disorder

Azithromycin Treatment Reduces Asthma Attacks



RSDC
Respiratory Sleep Disorder

Summary

Neutrophils are essential defenders of the airways

In asthma they are increased in a sub-group of adults with stable asthma and also during asthma attacks

No current treatments that target neutrophilic inflammation specifically

- Due to our poor understanding of neutrophil function in asthma
- Treatments that eliminate neutrophils are not the answer
- Need to understand neutrophils and their functional role in the airways further

RSDC
Respiratory Sleep Disorder

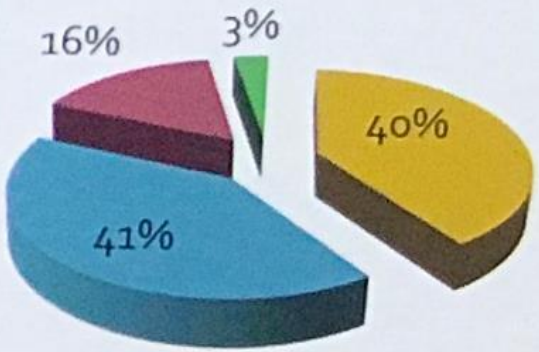
Eosinophilic phenotype

- Is the most common phenotype
- Day to day control
- Exacerbations
- Lung function decline

RSDC
Respiratory Sleep Disorder

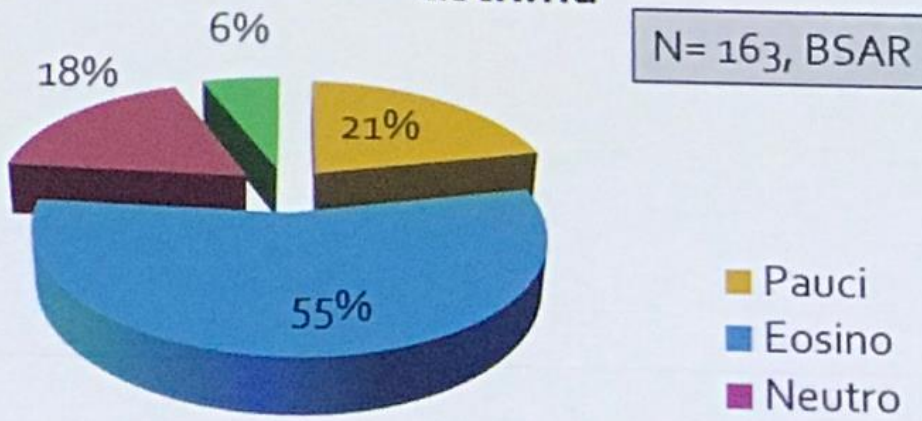
Eosinophilic asthma phenotype : the most frequent

Inflammatory phenotype **in an unselected population of asthmatics**



Inflammatory phenotype **in severe asthma**

N= 163, BSAR

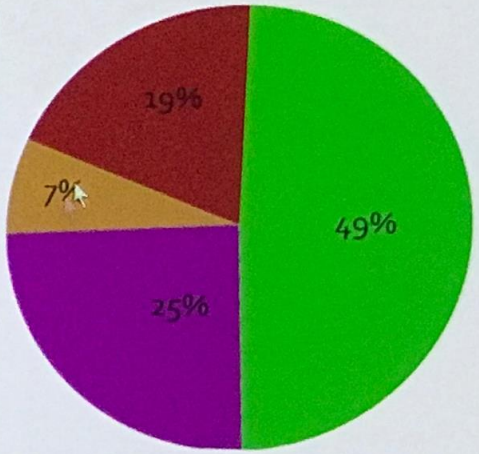


Schleich, Respir Med 2014
Schleich F, BMC Pulm Med 2013

RSDC
Respiratory Sleep Disorder

A new classification of asthma eosinophilic inflammatory phenotype

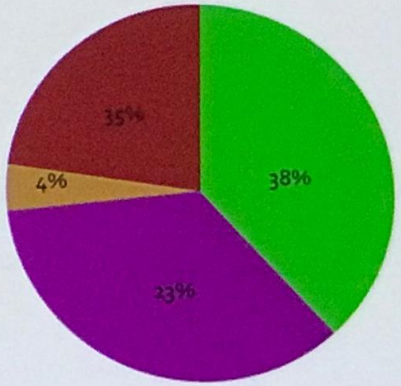
Distribution of Eosinophilic Trait in Asthma (N=508)
Blood (B) vs Sputum (S)



Unselected population
N=508

Low B Low S
Low B High S
High B Low S
High B High S

Blood Threshold 400/µl
Sputum Threshold 3%

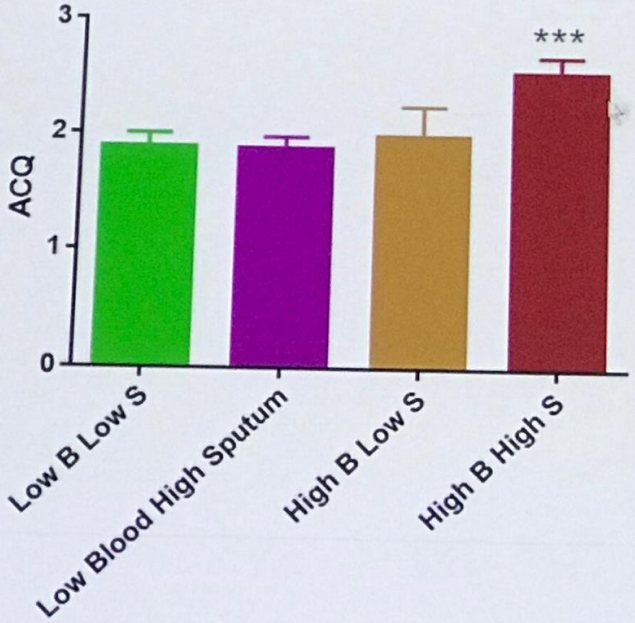


Severe asthma, BSAR
N= 83

Schleich F et al ERJ 2014, Schleich F Respir Med 2014

14

Eosinophilic inflammation and Asthma control (N=508)



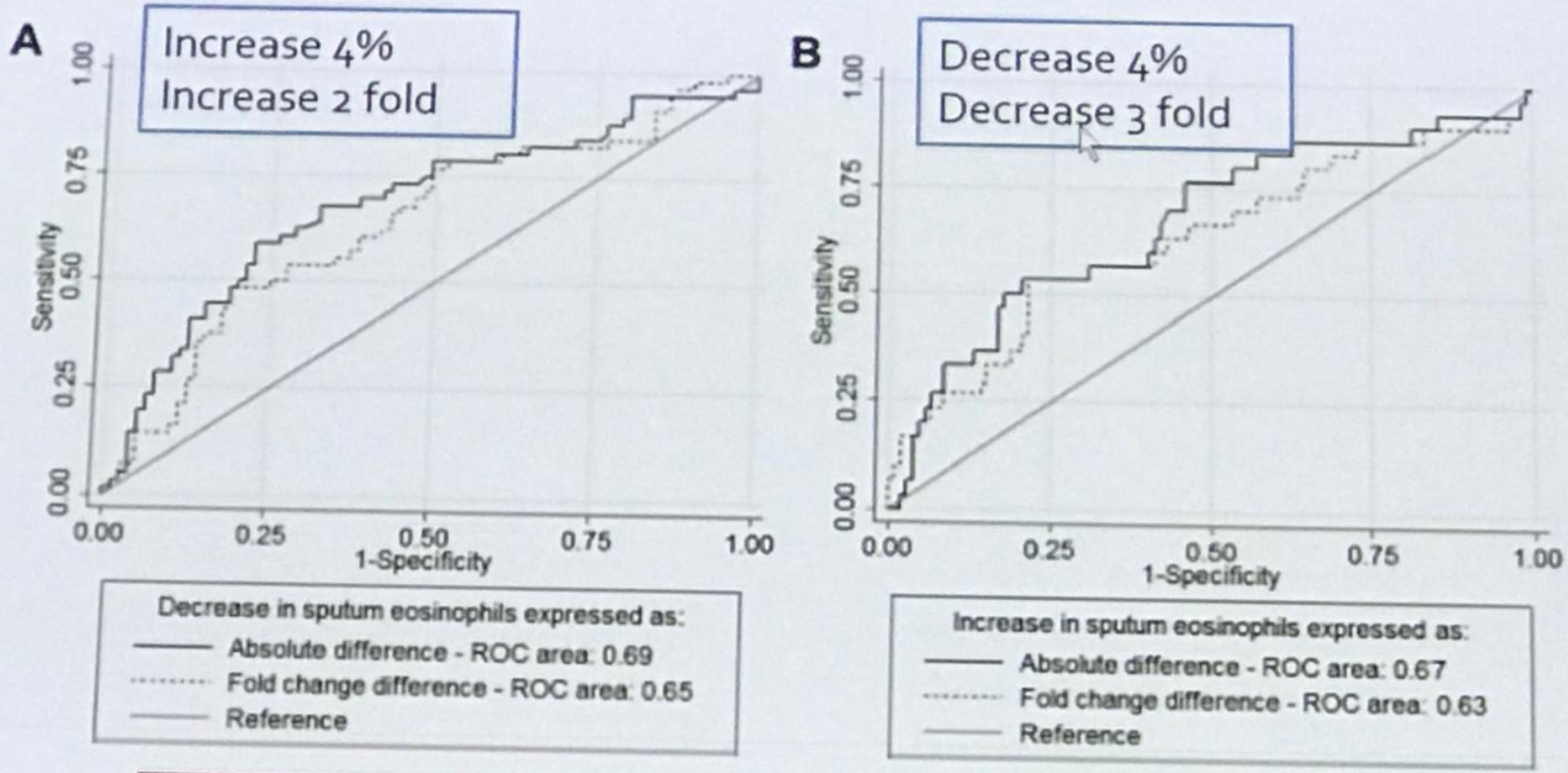
Low B Low S
Low Blood High Sputum
High B Low S
High B High S

* p< 0.05 Compared to Low Low

Schleich F et al ERJ 2014

RSDC
Respiratory Sleep Disorder

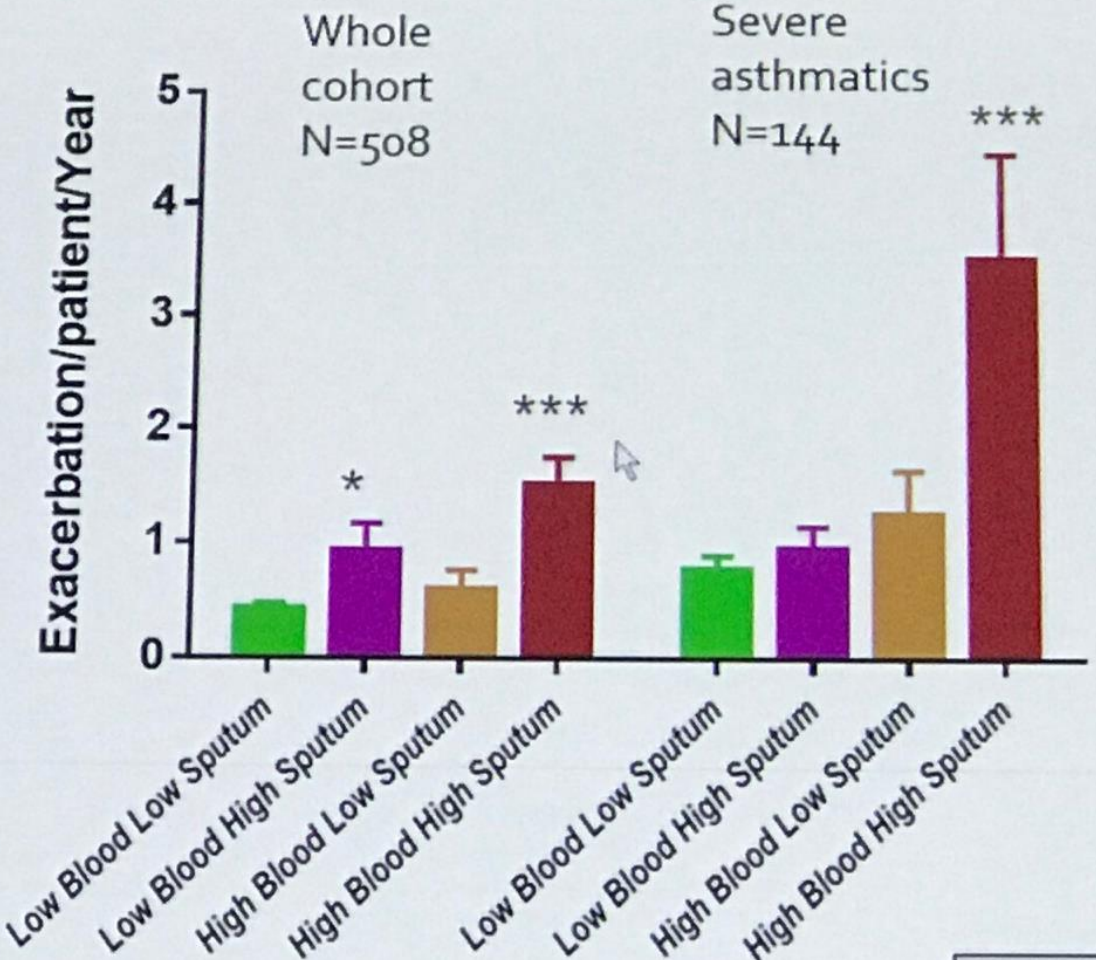
Fluctuation in sputum eosinophilia associates with significant change in asthma control



RSDC
Respiratory Sleep Disorder

Exacerbations

Eosinophilic inflammation and exacerbation rate



* p< 0.05 Compared to Low Low

Schleich F et al ERJ 2014

RSDC
Respiratory Sleep Disorder

Link between eosinophils and bronchial hyperresponsiveness

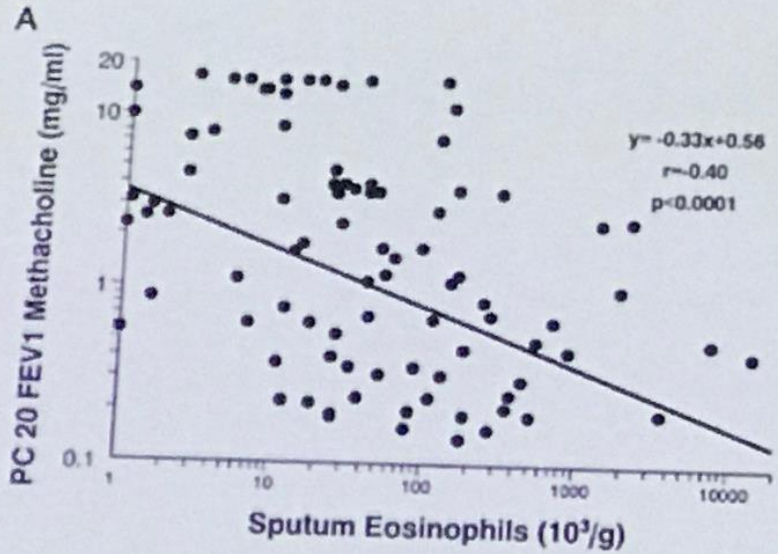


Table 3. Multiple regression analysis of the relationship between methacholine bronchial responsiveness and sputum cytology and baseline lung calibre in the asthma group

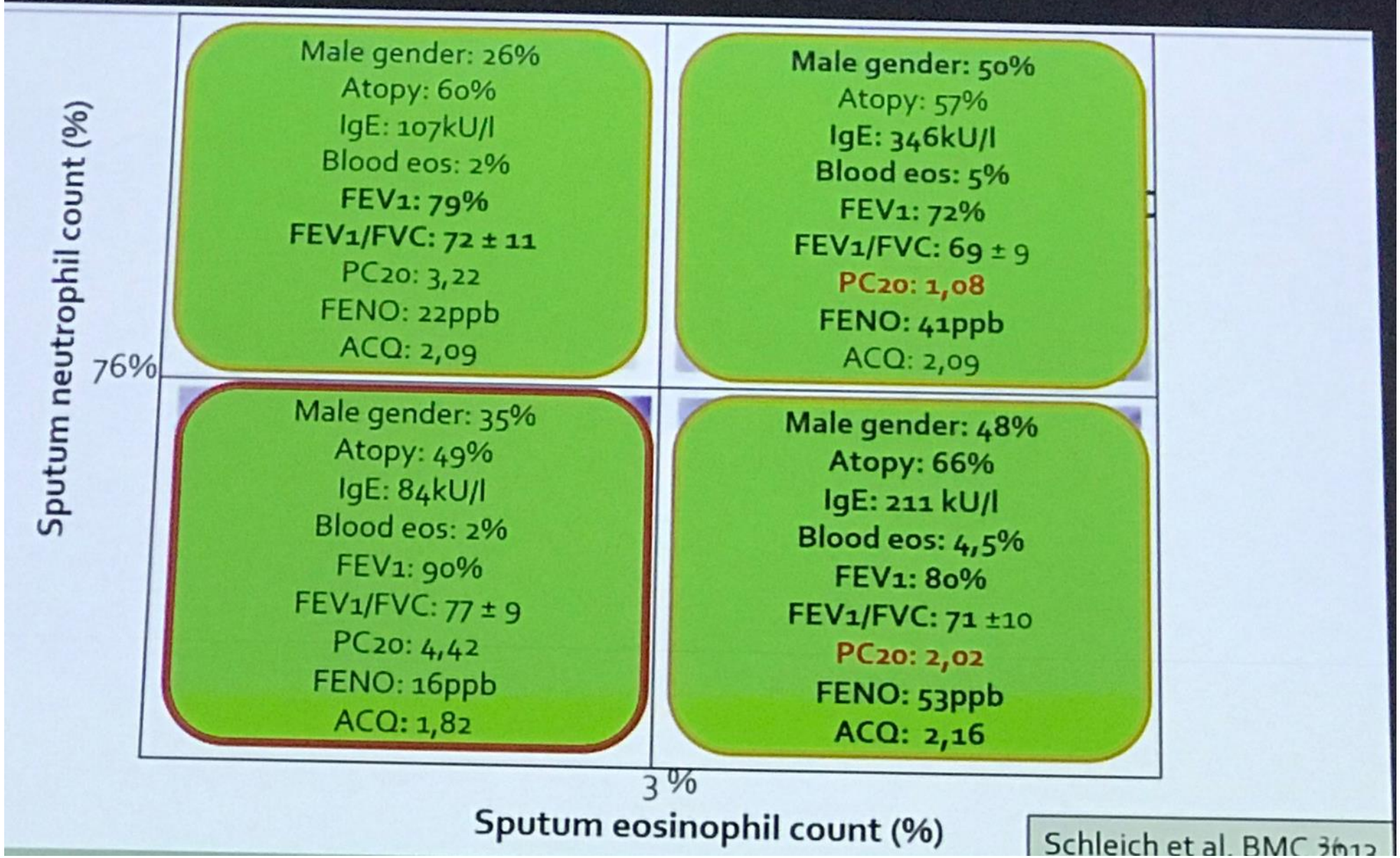
	PC_{20} methacholine		
	Global variance R^2	Partial regression coefficient β (SE)	*P* value
	0.29		0.0006
Macrophages		0.08 (0.14)	0.58
Lymphocytes		− 0.10 (0.08)	0.23
Neutrophils		0.28 (0.10)	0.006
Eosinophils		− 0.20 (0.06)	0.001
Epithelial cells		− 0.03 (0.09)	0.71
FEV_1		0.02 (0.008)	0.007

$PC_{20}M$ is the dependent variable. Cell absolute counts and FEV_1 % predicted are the independent variables.
SE, standard error.

Louis R, Allergy 2002

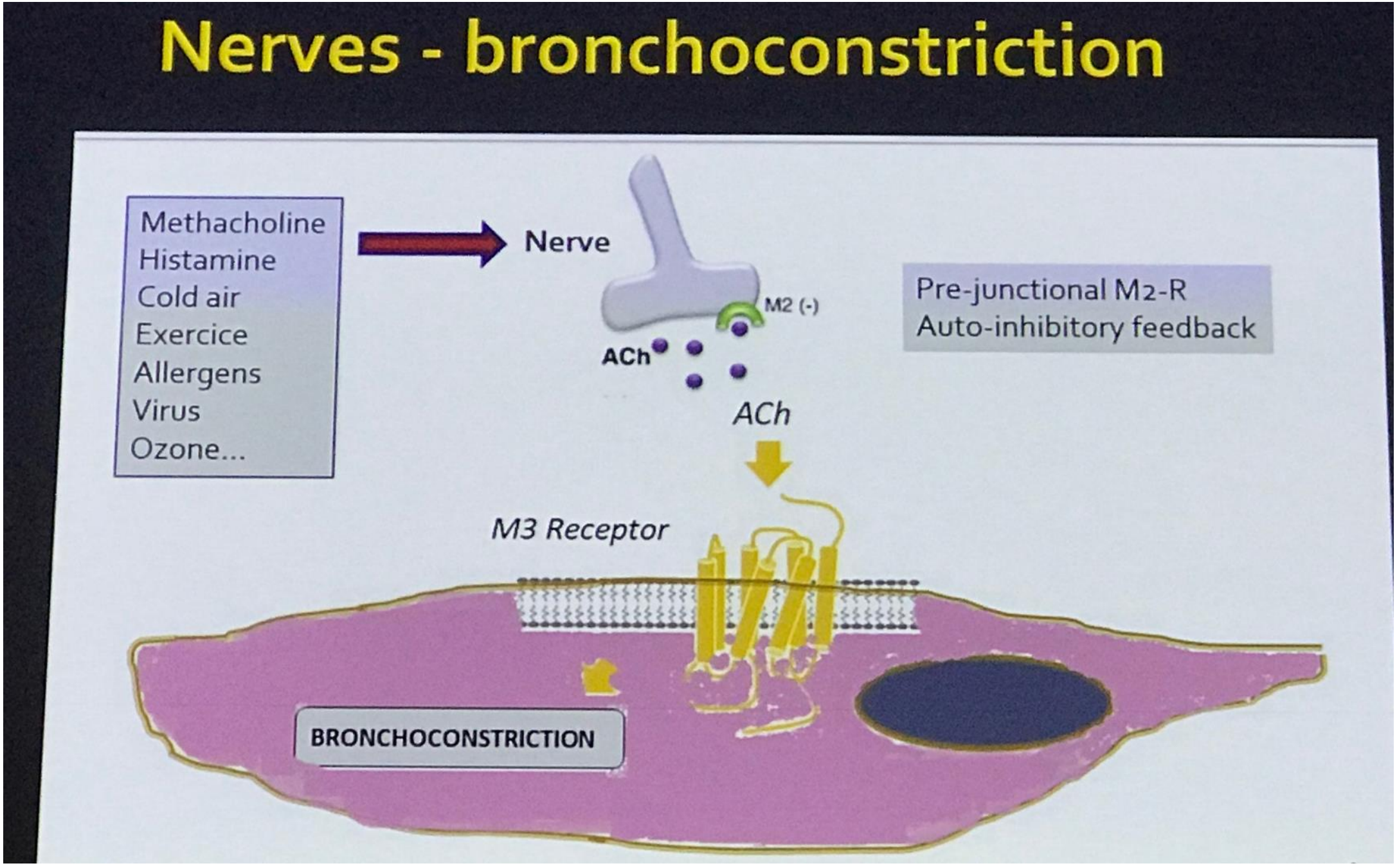
RSDC
Respiratory Sleep Disorder

Eosinophilic asthma



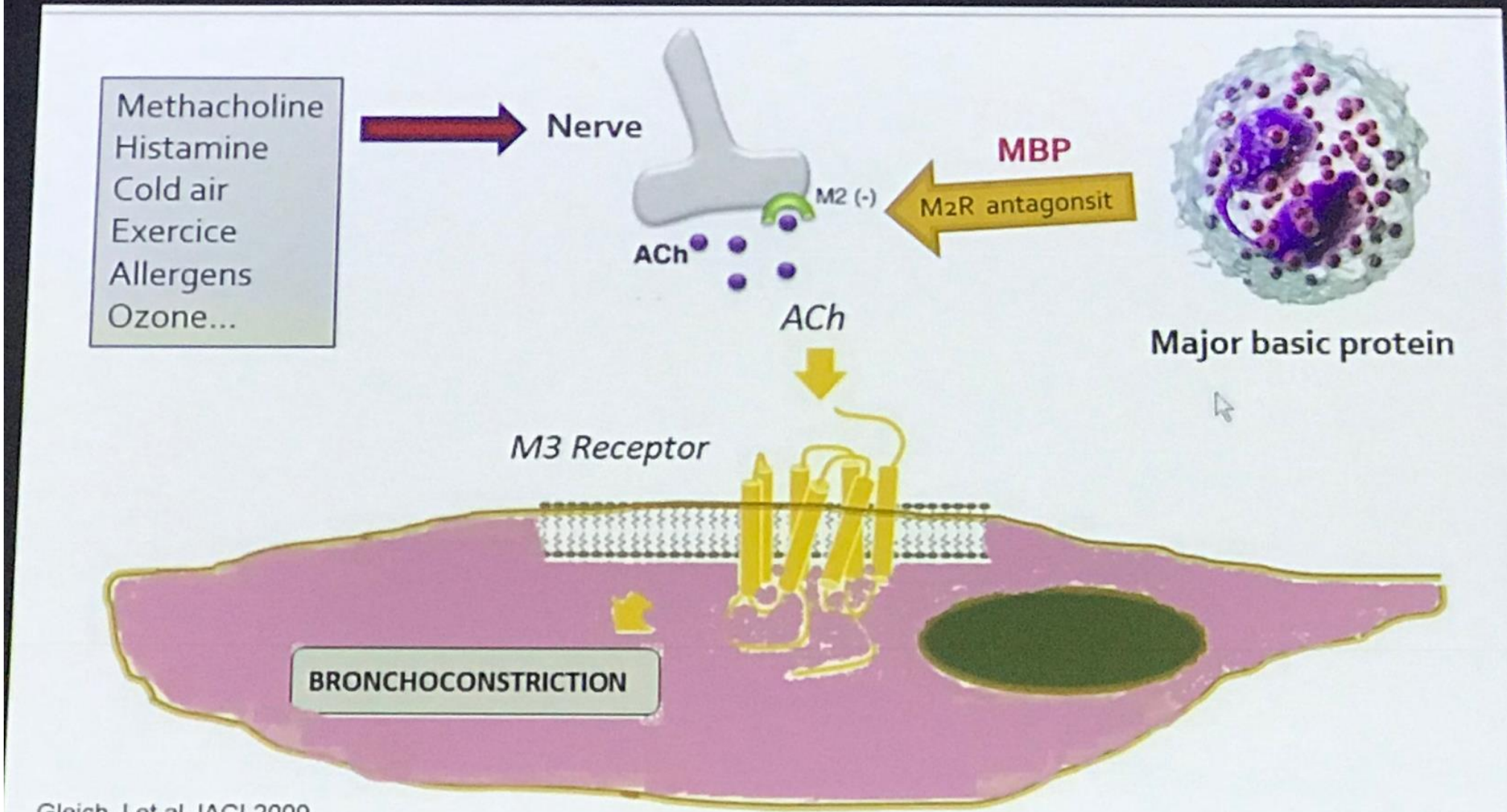
RSDC
Respiratory Sleep Disorder

Nerves - bronchoconstriction



RSDC
Respiratory Sleep Disorder

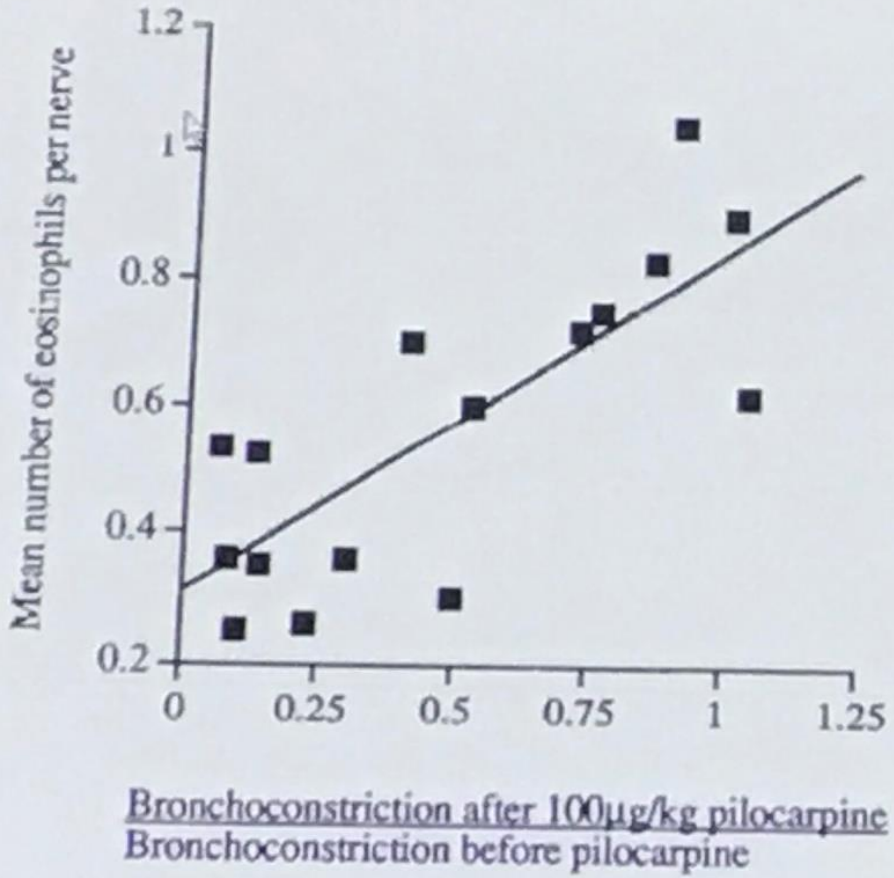
Nerves – eosinophils interaction



Gleich J et al JACI 2000

RSDC
Respiratory Sleep Disorder

Nerves – eosinophils interaction



Loss of M2 R function is associated with increased eosinophils around the nerves.

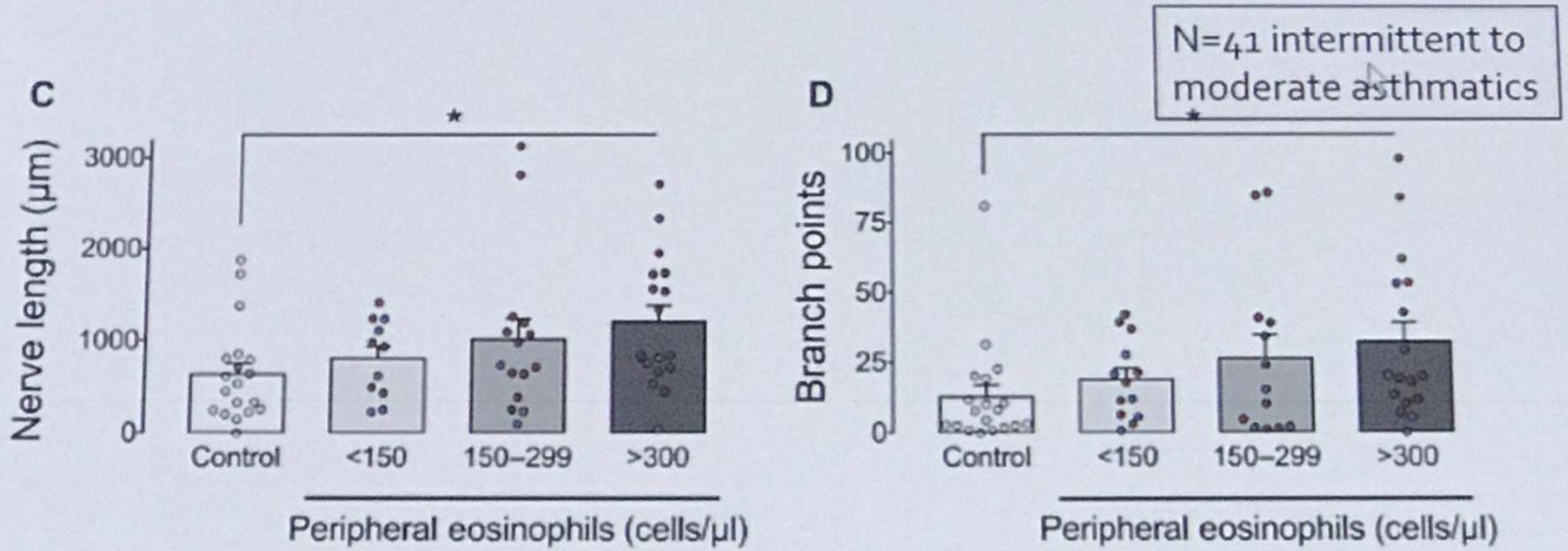
Parasympathetic and sensory nerves recruite eosinophils by releasing eotaxin-1 after antigen challenge.

Costello , Am J Physiol 1997

RSDC
Respiratory Sleep Disorder

Airway epithelial sensory nerves undergo remodeling in Eos asthma

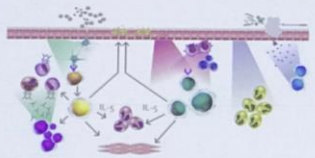
- Immunofluorescence and 3D nerve modeling in biopsies
- Blood eos ≥300/mm³: longer airway nerves



RSDC
Respiratory Sleep Disorder

IL5 - eosinophils

- IL-5 is an essential cytokine in eosinophil development, as it promotes terminal differentiation, growth and survival, as well as the activation of eosinophils



Adapted from Brusselle G, et al. Ann Am Thorac Soc. 2014;11:S322-S328.

36

Targeting eosinophils

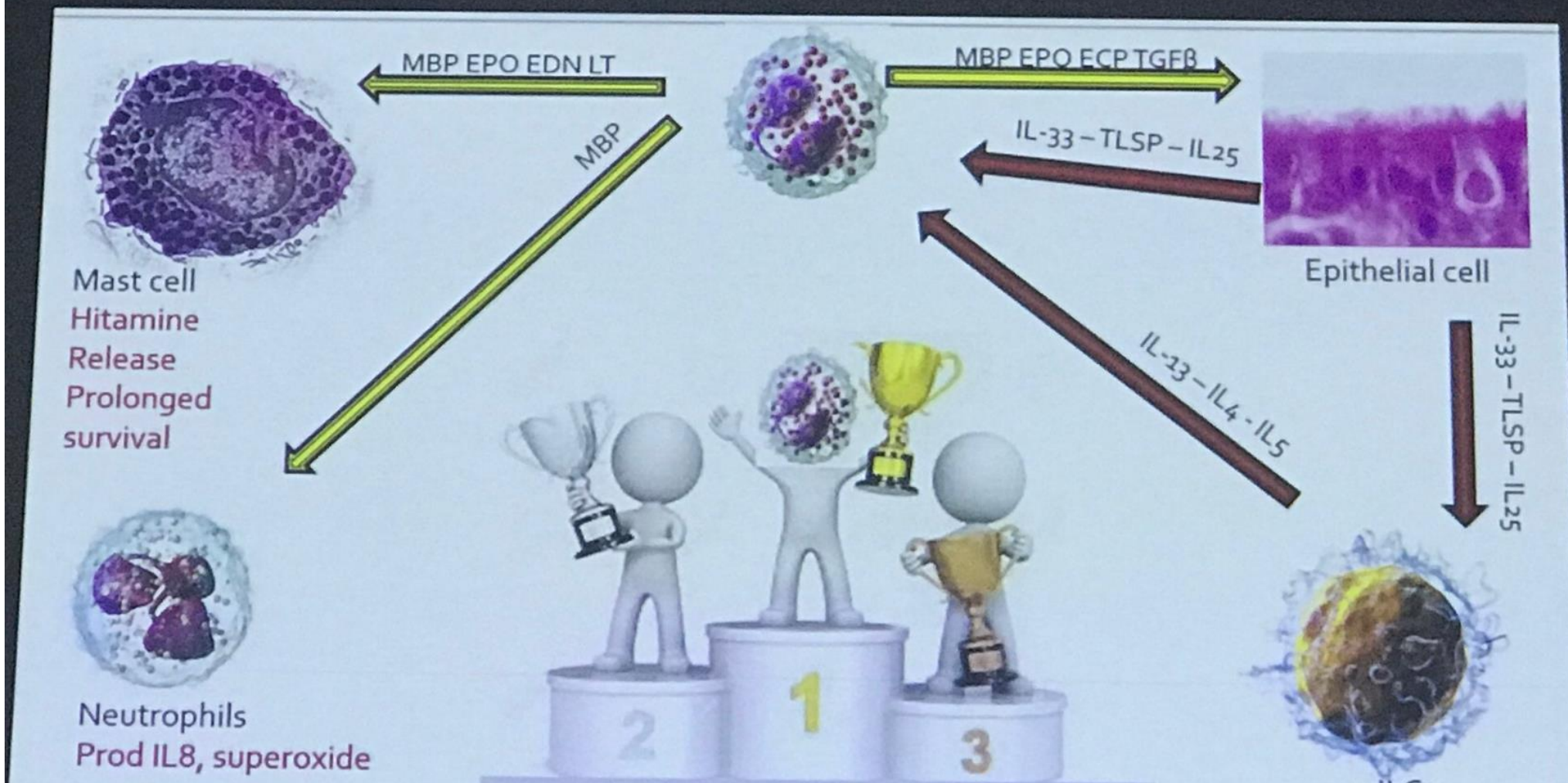
- **Glucocorticoids** (ICS – OCS): eosinophil apoptosis
- **Anti-IL5** (Mepolizumab – Reslizumab) : ↓eos production – recruitment – activation - survival
- **Anti-IL5Rα** (Benralizumab): + cytotoxicity (NK)

Role of eosinophils	Treatment	Treatment effect
Asthma control	Anti-IL5, Anti-IL5R	↑ **Asthma control** (3,5,8,9,10,11)
Exacerbations	Anti-IL5, Anti-IL5R	↓ **Exacerbations** (1,2,3,5,6,7,11,12)
Quality of life	Anti-IL5, Anti-IL5R	↑ **quality of life** 3,5,9,11,12)
Accelerated lung function decline	Anti-IL5, Anti-IL5R	↑ **Lung function** (1,2,3,5,6,8,9,10,11)
Bronchospasm	Anti-IL5, Anti-IL5R Anti-CCR3 ? Anti-ICAM1 ?	↓ bronchoconstriction Prevent eos binding to nerves?

(1) FitzGerald Lancet 2016. (2)SIROCCO (3)Ortega NEJM 2014 MENSA (4) SIRIUS (5) Nair NEJM 2017 (6) Brusselle Pulm Pharmacol Ther 2017 (7) Pavord Lancet 2012; (8) Ortega et al Lancet Respir Med 2016 (9) Bjermer Chest 2016 (10) Corren Chest 2016 (11) Castro, AJRCCM 2011 (12) Chupp Lancet Respir Med 2017 (MUSCA)

RSDC
Respiratory Sleep Disorder

Conclusion



One of the most highly implicated cell

Airway eosinophilia is likely to be determined by different mechanisms including mast cells, epithelial cells...

RSDC
Respiratory Sleep Disorder