Management of Idiopathic Pulmonary Fibrosis

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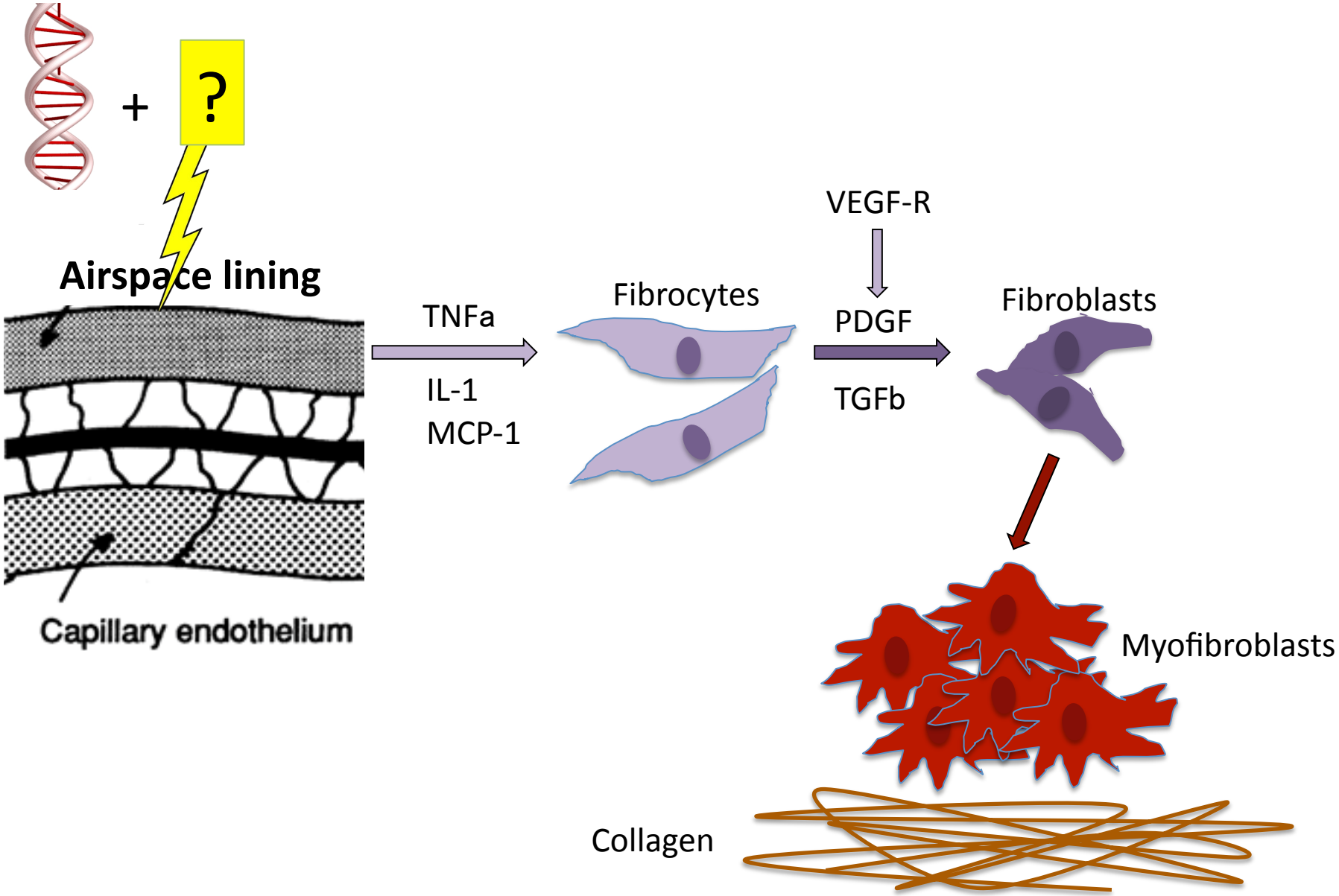
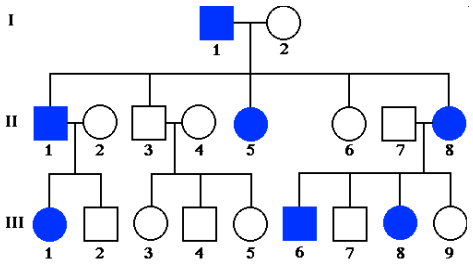
Disclosures

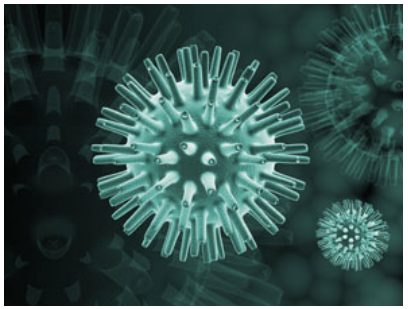
- No financial disclosures

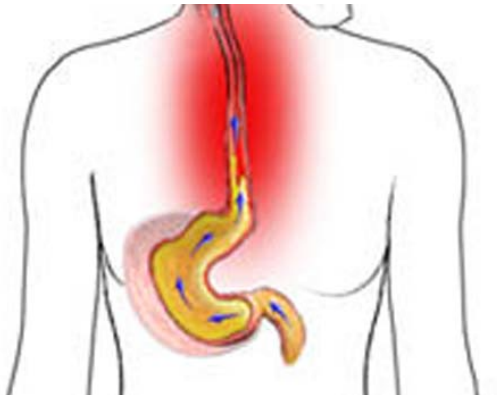
What causes IPF?



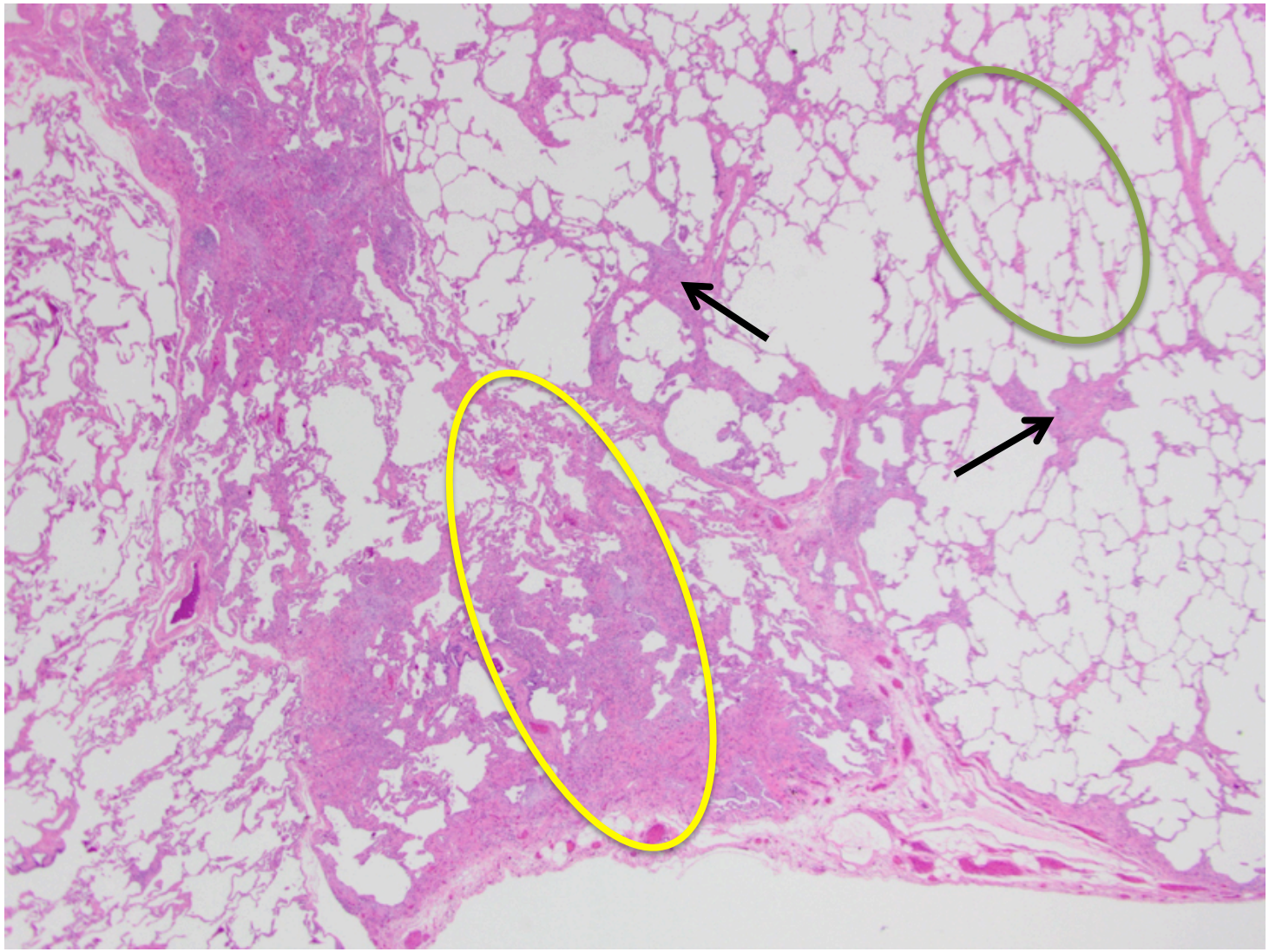
Risk factors







Patches of Scar Tissue In the Lung



Courtesy of Paul Vanderlaan, MD

Treatment

"To know where we're going, we must first know from where we have come"

Failed therapies

No Significant Benefit	Worse outcomes
Prednisone	Azathioprine + NAC + Prednisone
Imatinib	Ambrisentan
N-acetylcysteine	Coumadin
Bosentan	
Macitentan	
Sildenafil	

Treatment of Idiopathic Pulmonary Fibrosis (IPF)

Pirfenidone (InterMune/Roche--Esbriet):

Reduces fibroblast proliferation, TGF-b production, and TGF-b regulated collagen production

Three pills, three times a day

$95,500/yr

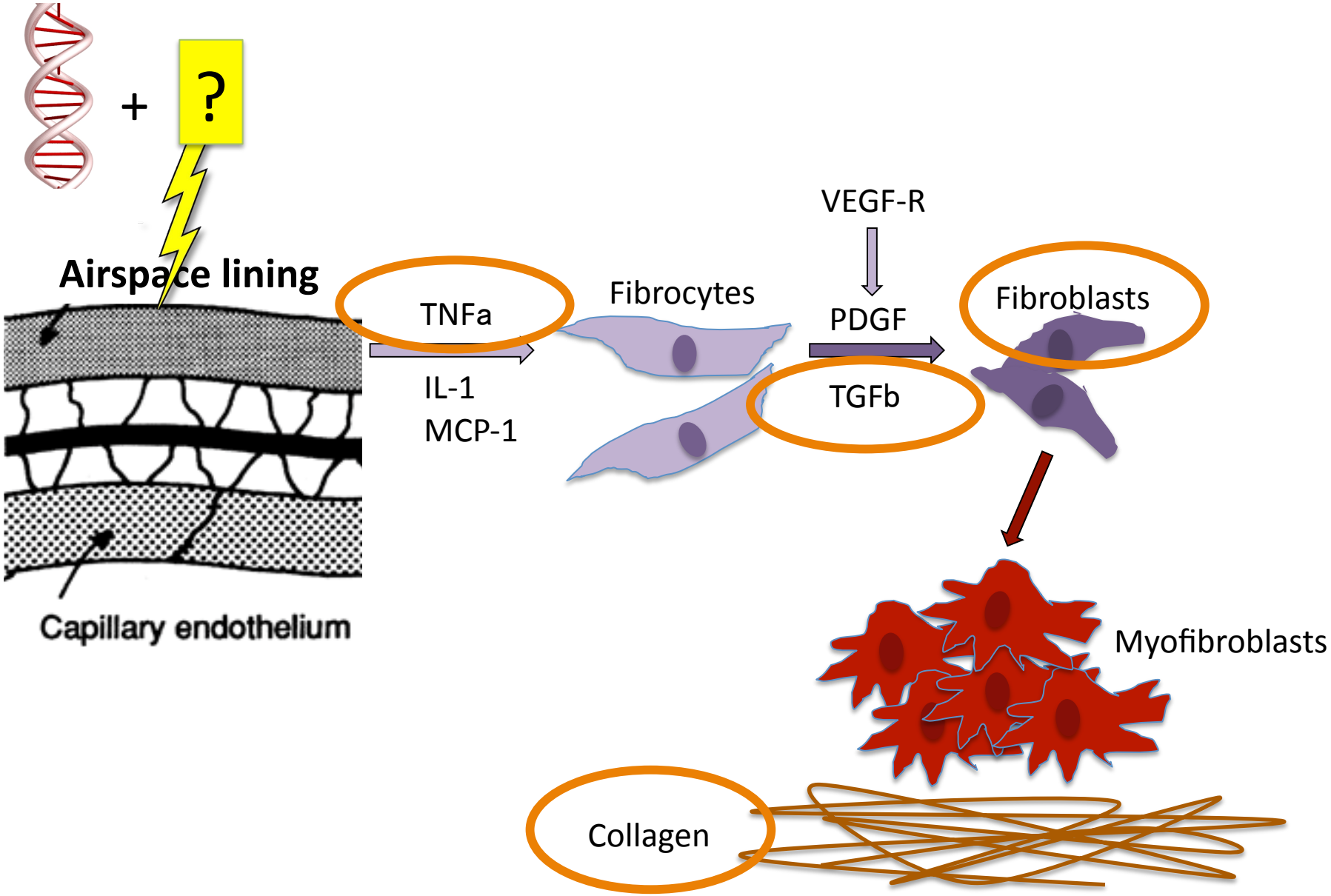
Nintedanib (Boehringer Ingelheim--Ofev):

Blocks several receptor tyrosine kinases: PDGFR; FGFR; VEGFR

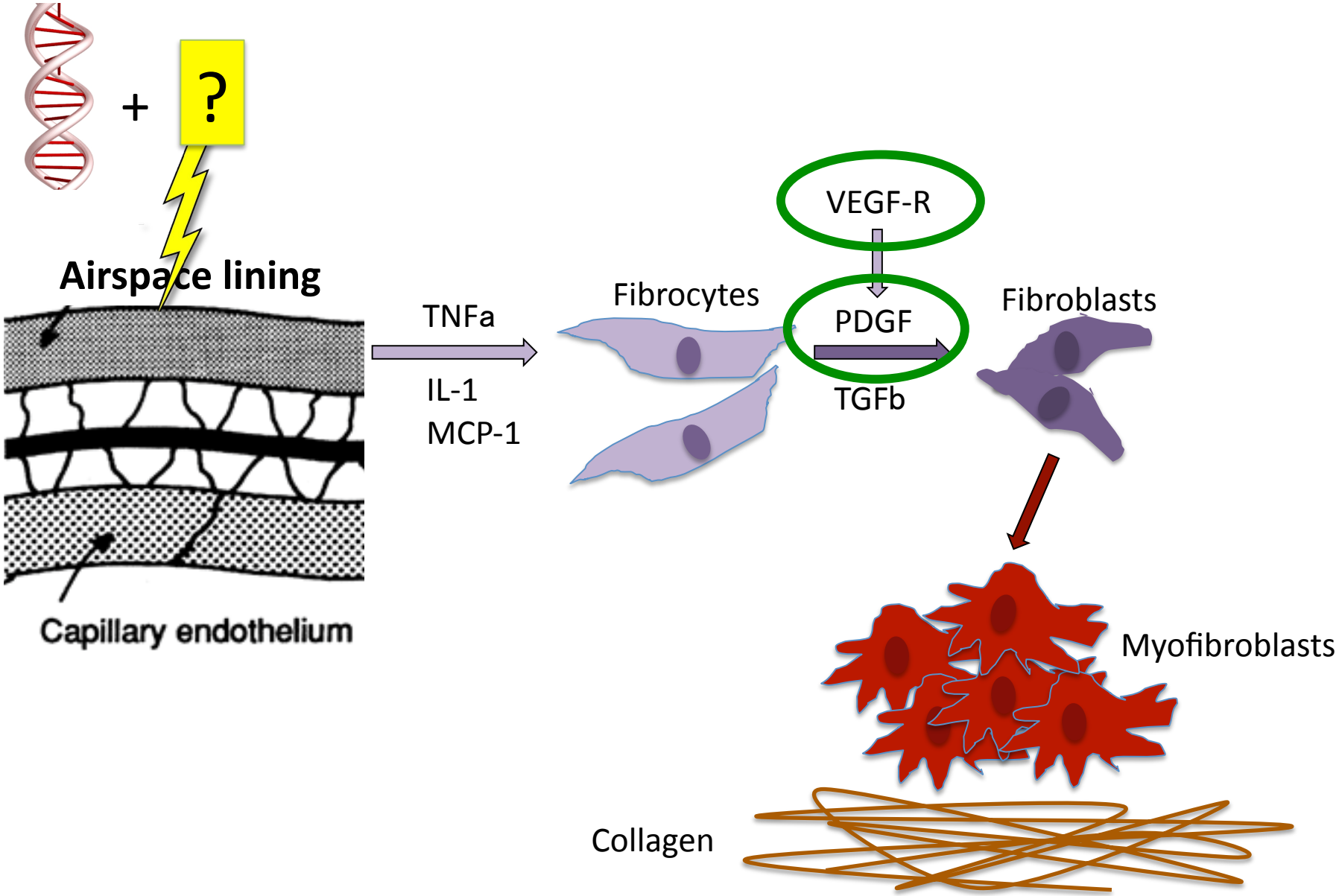
One pill, twice a day

$98,000/yr

Pirfenidone



Nintedanib


+
?
Airspace lining
Capillary endothelium
TNFa
IL-1
MCP-1
Fibrocytes
VEGF-R
PDGF
TGFb
Fibroblasts
Myofibroblasts
Collagen

Pirfenidone—CAPACITY trials

Capacity 004 (72 weeks): 435 patients (174 high-dose; 87 low; 174 placebo)
FVC change: -8% vs -12.4% (p=0.001)
Change in 6MWT (m) -60.4 vs -76.8 (p=0.171)

Capacity 006 (72 weeks): 344 patients (171 high-dose; 173 placebo)
FVC change: -9% vs -9.6% (p=0.51)
Change in 6MWT (m) -45.1 vs -76.9 (p=0.0009)

Pooled data (72 weeks):
FVC change: -8.5% vs -11% (p=0.005)
Mortality:
No statistical difference

Lancet. 2011;377(9779):1760.

Pirfenidone—ASCEND trial

555 patients followed 52 weeks (278 high-dose; 277 placebo)
FVC 10% decline or death: 46 [16.5%] vs. 88 patients [31.8%]) p<0.001
FVC no decline: 63 patients [22.7%] vs. 27 patients [9.7%]) p=0.001

Mortality:
No statistical difference

Pooled mortality (ASCEND + CAPACITY high-dose cut off at 52 weeks)
Overall deaths: 22 (3.5%) vs 42 (6.7%) p=0.01
IPF-related deaths: 7 (1.1%) vs 22.5 (3.5%) p=0.006

N Engl J Med. 2014;370(22):2083

Nintedanib—INPULSIS trials

INPULSIS-1 (52 weeks) 513 patients (309 drug; 204 placebo)

FVC decline (52 weeks): −114.7 ml vs −239.9 (p<0.001)

Time to first exacerbation: HR 1.15 (P = 0.67)

INPULSIS-2 (52 weeks) 548 patients (329 drug; 219 placebo)

FVC deline (52 weeks): −113.6 ml vs −207.3 (p<0.001)

Time to first exacerbation: HR 0.38 (P = 0.005)

Pooled mortality from any cause:

No statistical difference

N Engl J Med. 2014;370(22):2071

Side Effects

Pirfenidone

Nausea (36%)

Diarrhea (26%)

Abdominal pain (24%)

Photosensitivity (9%)

Nintedanib

Nausea (24%)

Diarrhea (62%)

Vomiting (12%)

N Engl J Med. 2014;370(22):2071
N Engl J Med. 2014;370(22):2083

Combination therapy?

IPF involves disregulation of multiple, complex pathways.

Barriers:

- Cost
- More GI side effects
- Hard to show efficacy
- Pirfenidone decreases nintedinib levels

Eur Respir J 2015; 45: 1382–1392

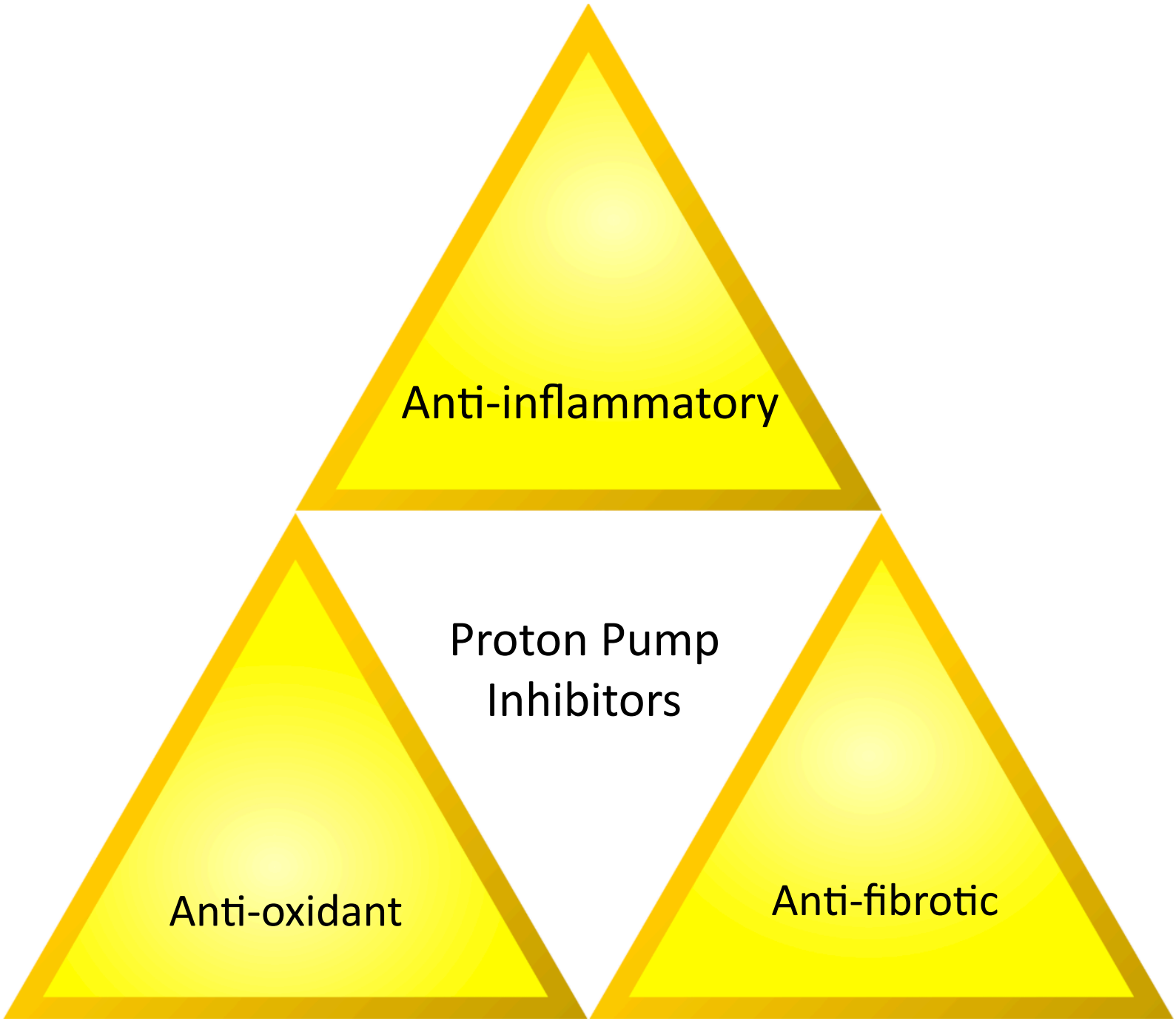
Additional therapies

- Acid suppression
- Pulmonary rehab
- CPAP machines for sleep apnea
- Oxygen

GERD and IPF

- 90% of patients with IPF have at least silent GERD
- Causative or simply the result of changes in intra-thoracic pressure?
- Chronic, low grade inflammation from acidic aspiration?

Am J Respir Crit Care Med Vol 192, Iss 2, pp e3–e19


Anti-inflammatory
Proton Pump Inhibitors
Anti-oxidant
Anti-fibrotic

Esomeprazole effects *in the test tube*

- ⬇ Lung fibroblast proliferation
- ⬇ Lung fibroblast collagen synthesis
- ⬇ Bleomycin-induced fibrosis (mouse model)

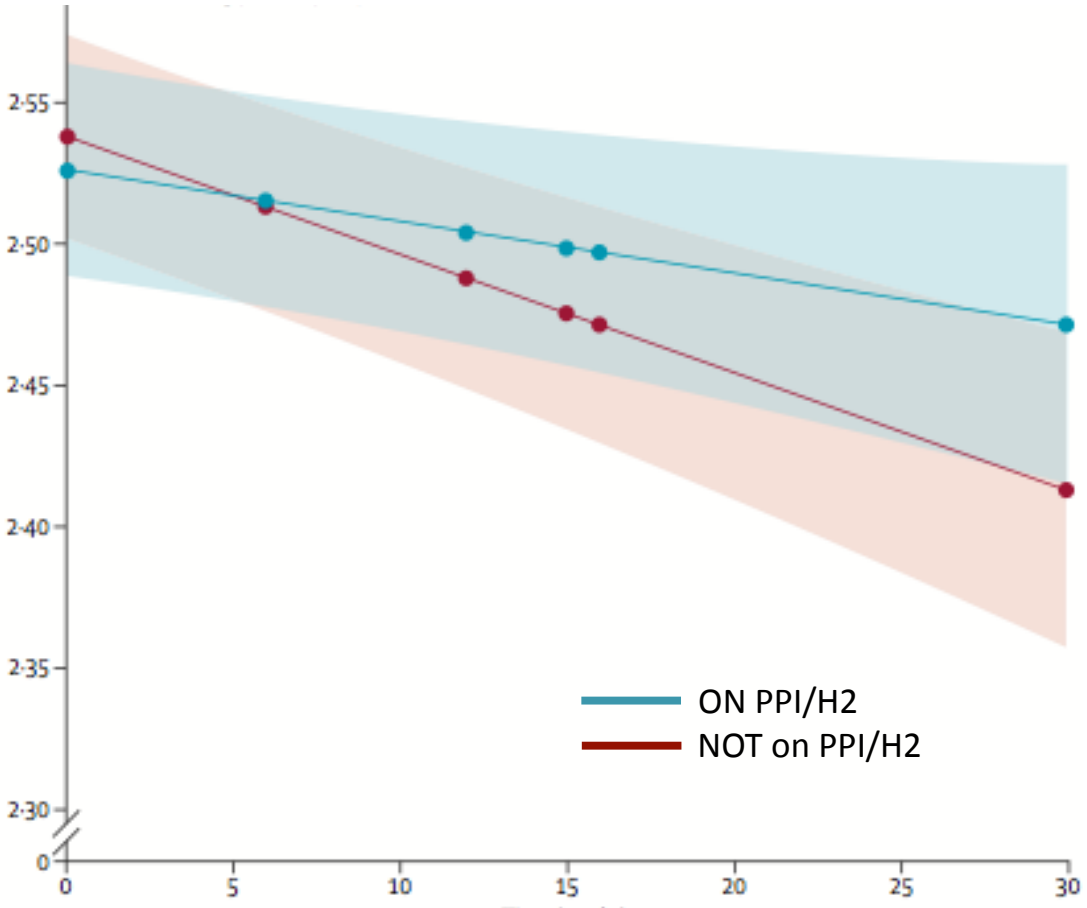
Ghebremariam *et al. J Transl Med (2015) 13:249*

Acid Suppression is associated with a slower decline in FVC

Better

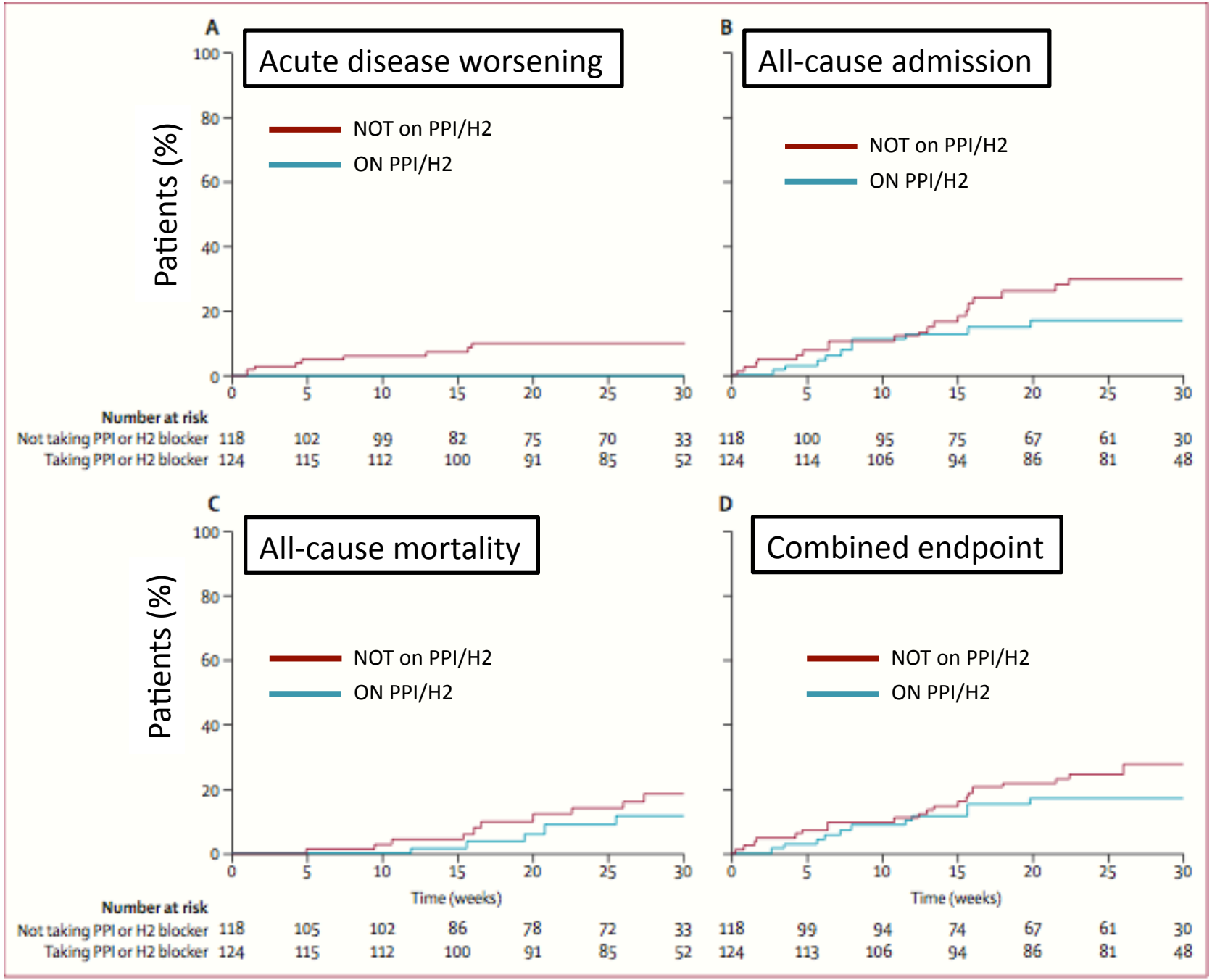
Lung Function (FVC)

Worse



Time (weeks)

Lancet Respir Med 2013;1:369–376


A
Acute disease worsening
B
All-cause admission
C
All-cause mortality
D
Combined endpoint
Patients (%)
NOT on PPI/H2
ON PPI/H2
Time (weeks)
Number at risk
Not taking PPI or H2 blocker 118 102 99 82 75 70 33
Taking PPI or H2 blocker 124 115 112 100 91 85 52
Not taking PPI or H2 blocker 118 100 95 75 67 61 30
Taking PPI or H2 blocker 124 114 106 94 86 81 48
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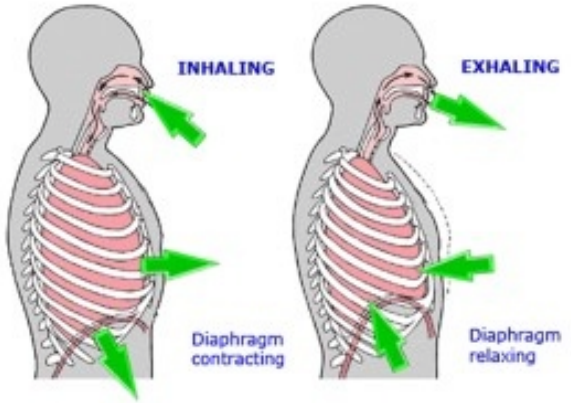
Pulmonary Rehab



A study on the Benefits of Pulmonary Rehab

Structured Rehab (15 patients)

No Rehab (17 patients)

60 min, twice a week
12 weeks

6 min walk distance (81 meters)
Work rate and oxygen consumption
FVC on breathing tests (6% increase)
Dyspnea scores
Quality of life scores

Respiration. 2014;88(5):378-88

Sleep Disordered Breathing

Significant fatigue is a common symptom among IPF patients

Often related to poor sleep quality
- More fragmented sleep
- Never reach deep or REM sleep
- Sleep apnea more common

Consider a sleep study and treatment with CPAP

Sleep Medicine Reviews 26 (2016) 57e63

Supplemental Oxygen

No evidence that it improves outcomes in IPF
(Though there are no good studies)

Data is based on studies in patients with COPD

Use if saturations are less than 89%

Ongoing Clinical Trials

Study Drug	Sponsor
BMS-986020	Bristol-Myers Squibb
FG-3019	Fibrogen
SAR 156597	Sanofi
Lebrikizumab	Hoffmann-La Roche
STX-100	Biogen
AF-219	Afferent
BIBF 1120	Boehringer-Ingelheim
Pirfenidone + Nintedanib	Boehringer-Ingelheim

Questions?