Treatments for IPF

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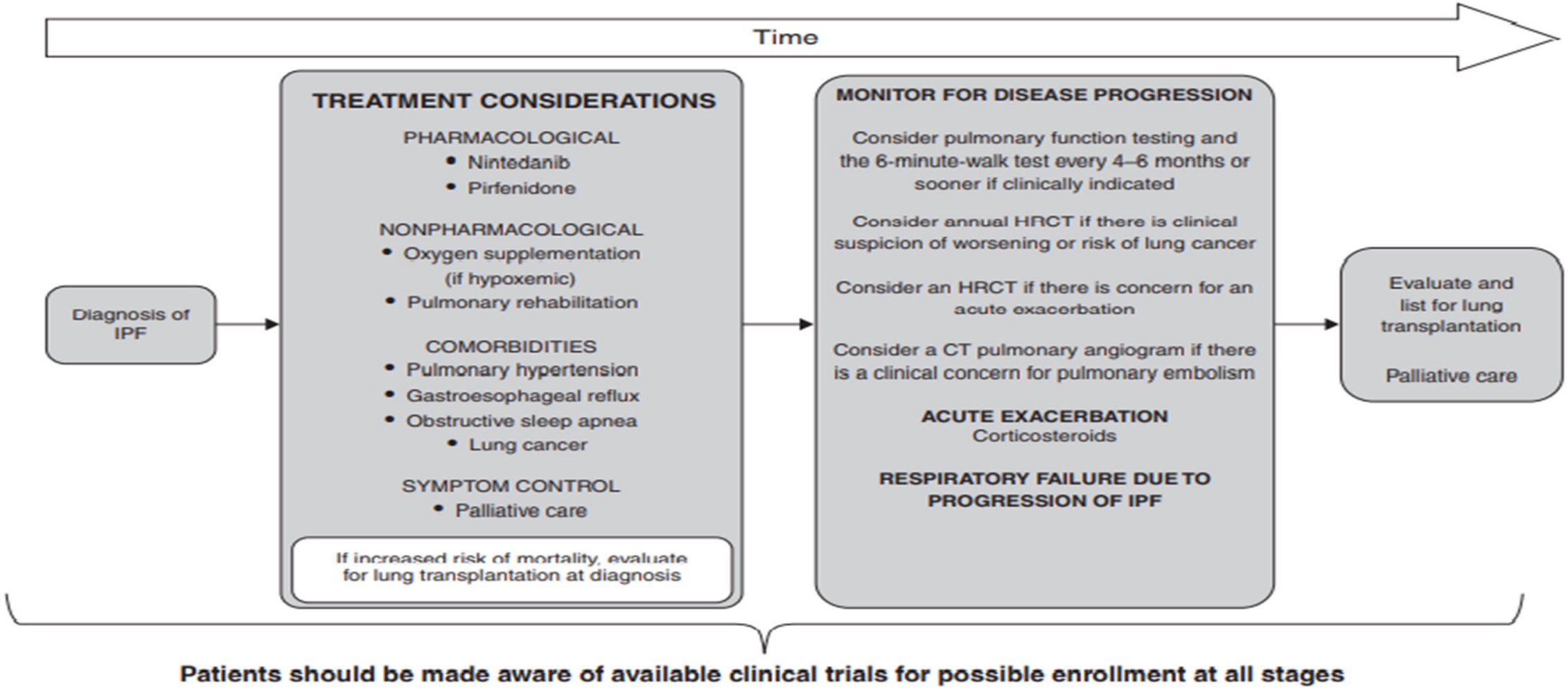
- **Anti-fibrotics**
- **GERD Treatments**
- **Pulmonary Hypertension Therapies**
- **Clinical Trials**
- **Acute Exacerbation Management**



Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022

Anti-fibrotics

When to start?

Which one to chose?

How do you know if it's working?

When do you consider switching?

When to stop?

Anti-fibrotics

When to start?

Immediately upon diagnosis

vs.

At a particular severity stage

vs.

Beyond a certain rate of lung function loss

vs.

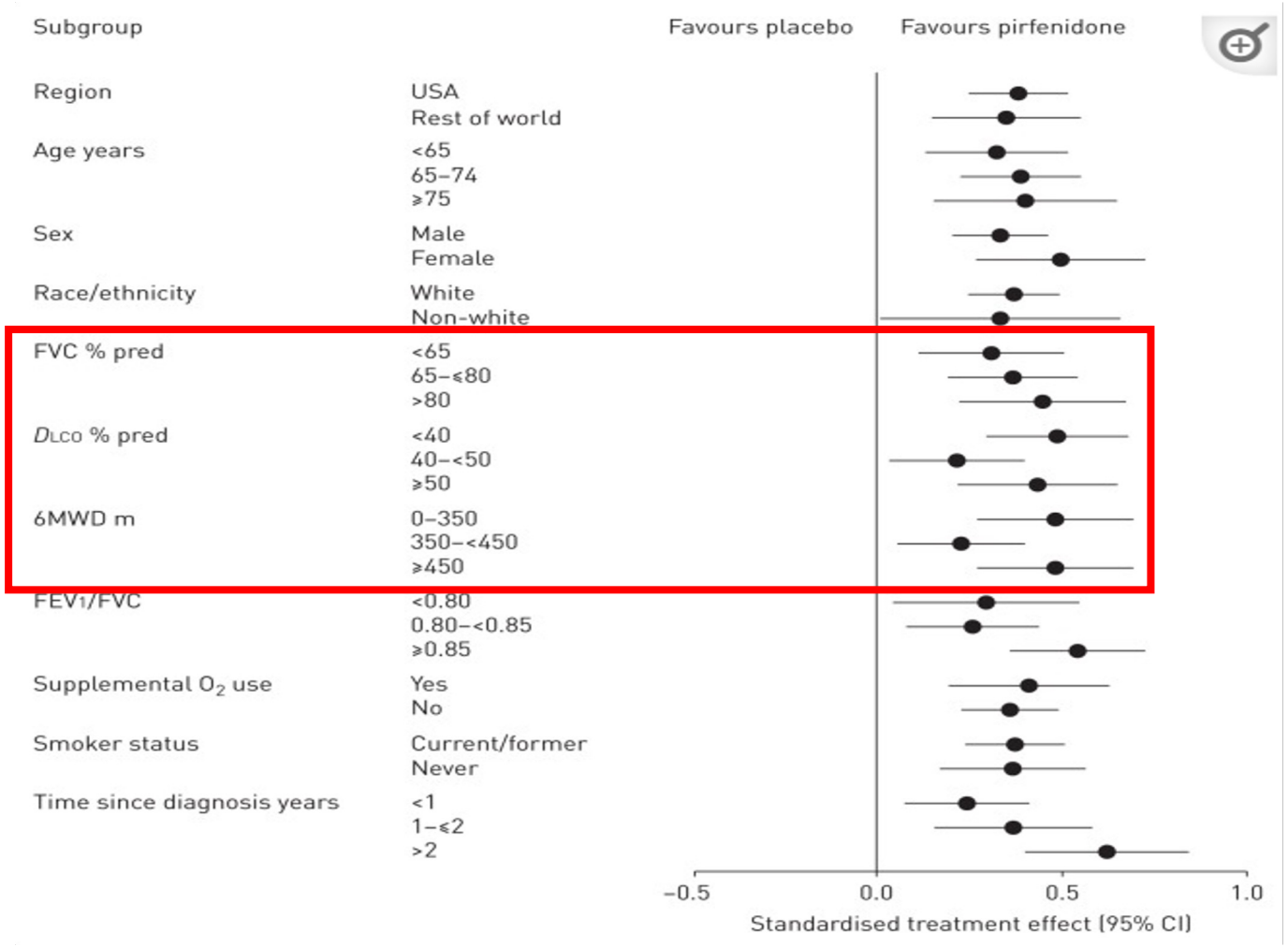
Never – hope not

Anti-fibrotics

When to start?

At a particular severity stage?

Pirfenidone Pooled Data, n = 1247



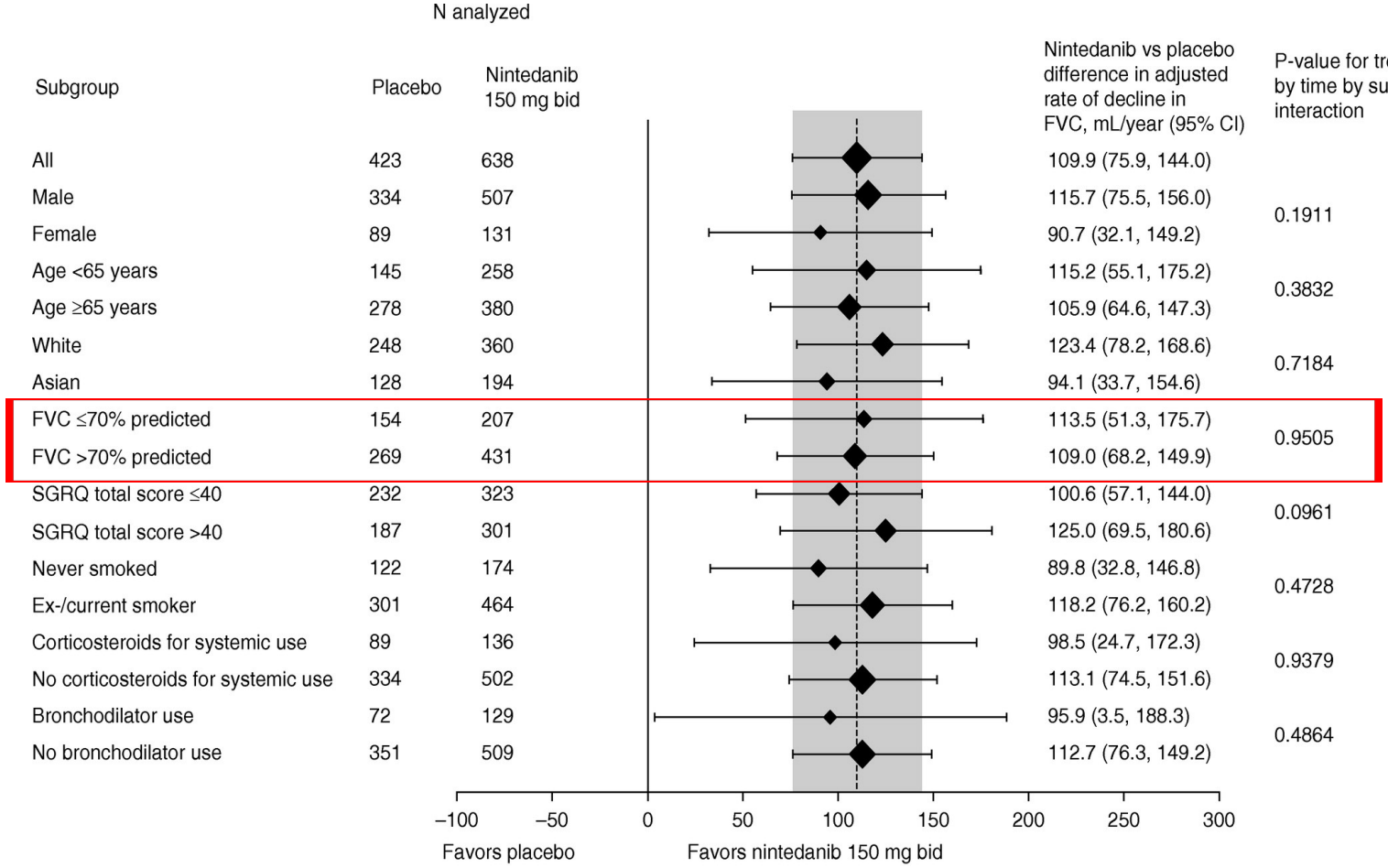
Noble P, et al. Eur Respir J. 2016 Jan; 47(1): 243–253.

Anti-fibrotics

When to start?

At a particular severity stage?

Nintedanib Pooled Data, n = 1061

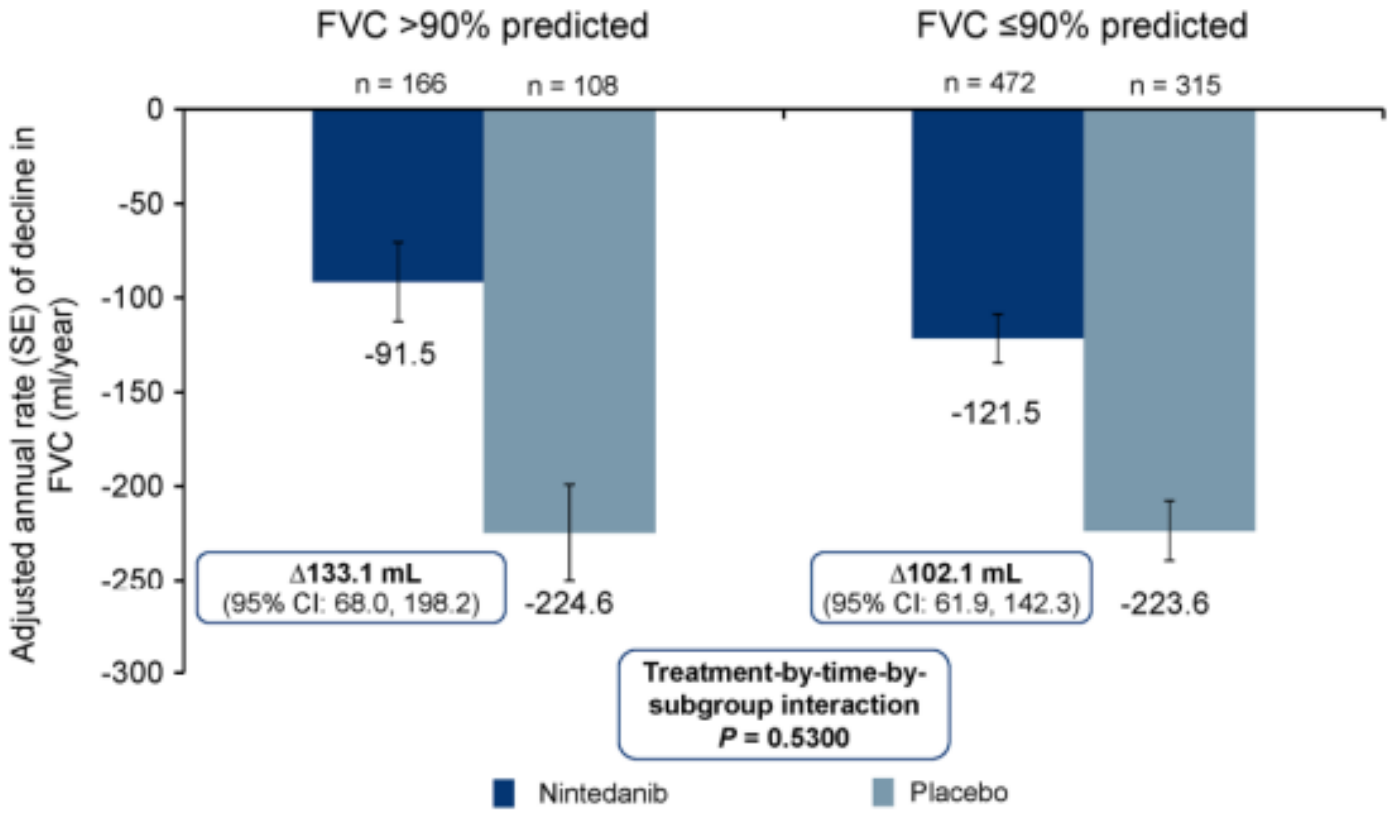


Costabel U, et al. AJRCCM Vol 193, Iss 2, pp 178–185, Jan 15, 2016.

Anti-fibrotics

When to start?

At a particular severity class?

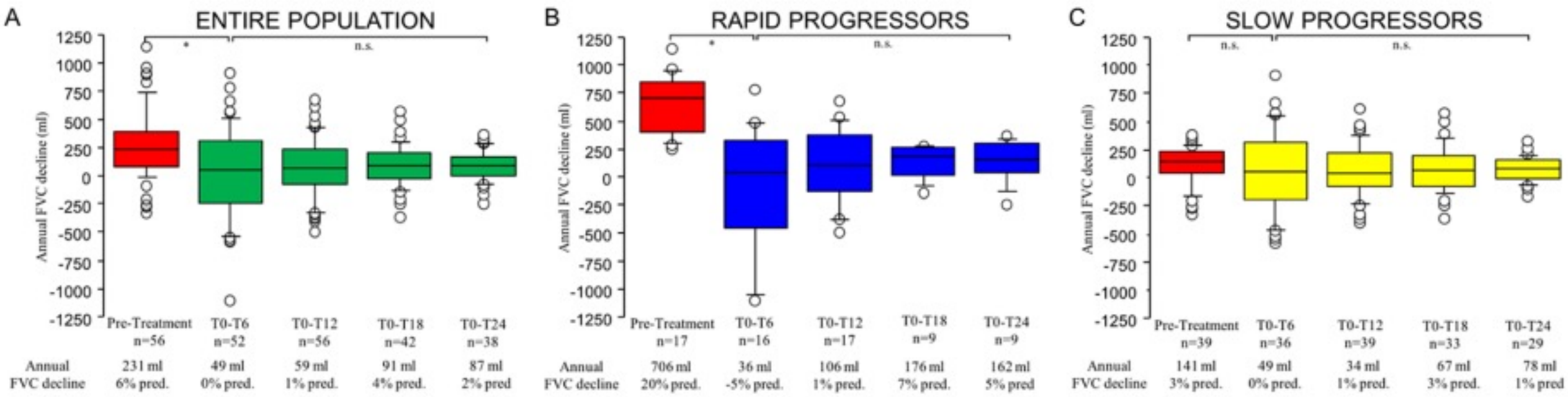


Data suggests it's beneficial to start right away

Kolb M, et al. Thorax 2017;72:340–346.

Anti-fibrotics

When to start?
Beyond a certain rate of lung function loss? Leave slow progressors alone?



Biondini D, et al. Sci Rep 8, 5961 (2018).

This particular question is far from answered

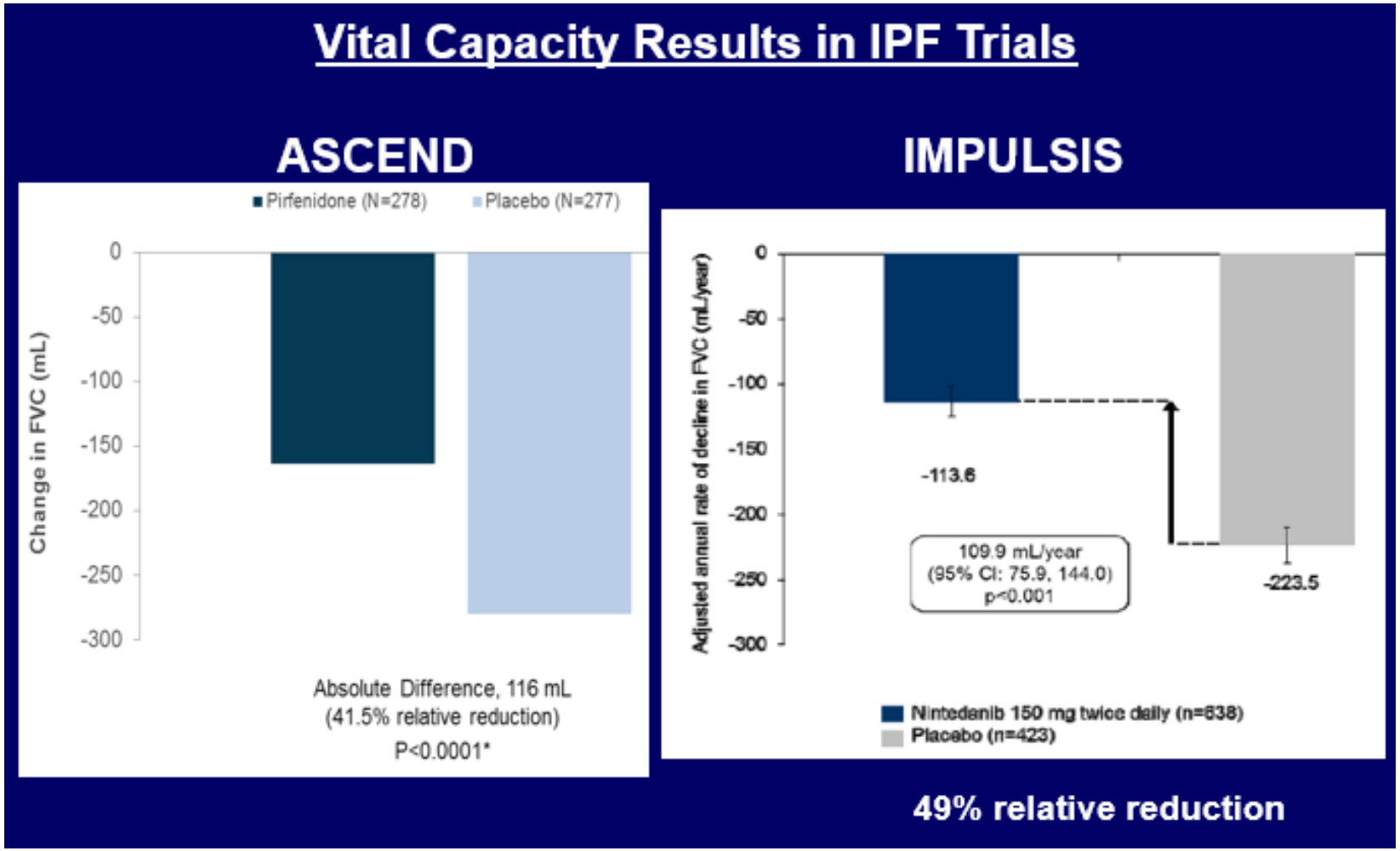
Anti-fibrotics

Which one to chose?

Efficacy vs. SE profile vs. bid/tid

nausea/reflux/sun sensitivity
vs.
diarrhea

Pick your poison…



N Engl J Med. 2014 May 29; 370(22):2083-92.

N Engl J Med 2014; 370:2071-2082.

Nintedanib related diarrhea – imodium, lomotil, others?

Anti-fibrotics

How do you know if it's working?

Well, you usually don't

Consider rate of pre-treatment FVC loss c/w rate of FVC loss while on treatment (if sufficient data available) – is there an improvement?

While on treatment, if rate of FVC loss > 200 mL / year, at minimum entertain idea that anti-fibrotic isn't effective (large trials demonstrated that on average those with IPF lose < 200 mL / year while on treatment)

Anti-fibrotics

When do you consider switching from a med that is generally being tolerating?

When there's concern that antifibrotic is ineffective

Ongoing side effects baked into consideration – the more bothersome the side effects, the lower the threshold to change

Does switching help?

Anti-fibrotics

When do you consider switching from a med that is generally being tolerating? Does switching help?

Management of Progressive Disease in Idiopathic Pulmonary Fibrosis (PROGRESSION)

Goal:

Evaluate the efficacy and tolerance of combined pirfenidone and nintedanib as compared to "switch monotherapy“ in patients with worsening IPF despite receiving either pirfenidone or nintedanib

Eligibility:

- **Stable dose of pirfenidone or nintedanib prescribed as first-line therapy for at least 6 months**
- **Worsening of respiratory symptoms AND worsening fibrosis according to PFTs, CT**

Intervention – 24 weeks of:

- **pirfenidone 2403 mg per day in combination with nintedanib 300 mg per day**
- **switch from one monotherapy to alternative**
- **cont current therapy**

Enrollment : 378 participants

Will likely complete study in 2023

Primary Outcome Measure : Slope of the decline in FVC

Anti-fibrotics

When do you stop?

Will continue during very late stages when…

- **Well tolerated**
- **Providing psychological boost**

Individualized decision that requires ongoing patient – MD communication

Prior to lung transplant –

Anti-fibrotic therapy and lung transplant outcomes in patients with idiopathic pulmonary fibrosis
Astor T, et al.
Submitted, under review

GERD Treatments

- GER is very common in IPF
- Hiatal hernias seen more often in IPF than general population
- Chronic, recurrent micro-aspirations may contribute to pathogenesis of IPF

Should all patients with IPF receive treatment for GERD, regardless of presence/absence of GER symptoms?

ATS IPF Guidelines ‘11

Recommendation: Asymptomatic gastroesophageal reflux disease should be medically treated in the majority of patients with IPF (weak recommendation, very low-quality evidence).

ATS IPF Guideline Update ‘15

No change in recommendation

ATS IPF Guidelines ’22

Antacid medication and other interventions may be appropriate for patients with both IPF and symptoms of gastroesophageal reflux disease (GERD) for the purpose of improving gastroesophageal reflux (GER)–related outcomes in accordance with GER-specific guidelines – do not manage GER for the purpose of improving respiratory outcomes.

GERD Treatments

Should all patients with IPF receive treatment for GERD, regardless of presence/absence of GER symptoms?

ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease
The American Journal of Gastroenterology: January 2022 - Volume 117 - Issue 1 - p 27-56.

SAGES guidelines for the surgical treatment of gastroesophageal reflux (GERD)
Surg Endosc. 2021 Sep;35(9):4903-4917. doi: 10.1007/s00464-021-08625-5. Epub 2021 Jul 19.

RCTs are needed for IPF patients with symptomatic and/or confirmed GER
More to come…

Pulmonary hypertension

Prevalence: **RHC during transplant eval** 46% 9%

Variable	$\bar{P}_{pa}$ <25 mmHg	$\bar{P}_{pa}$ ≥25 mmHg	$\bar{P}_{pa}$ >40 mmHg
Subjects n	1362	932	231

Shorr AF, et al. Eur Respir J 2007; 30: 715–721.

Before embarking upon work-up, determine whether PH will be treated if discovered?

Treatments:

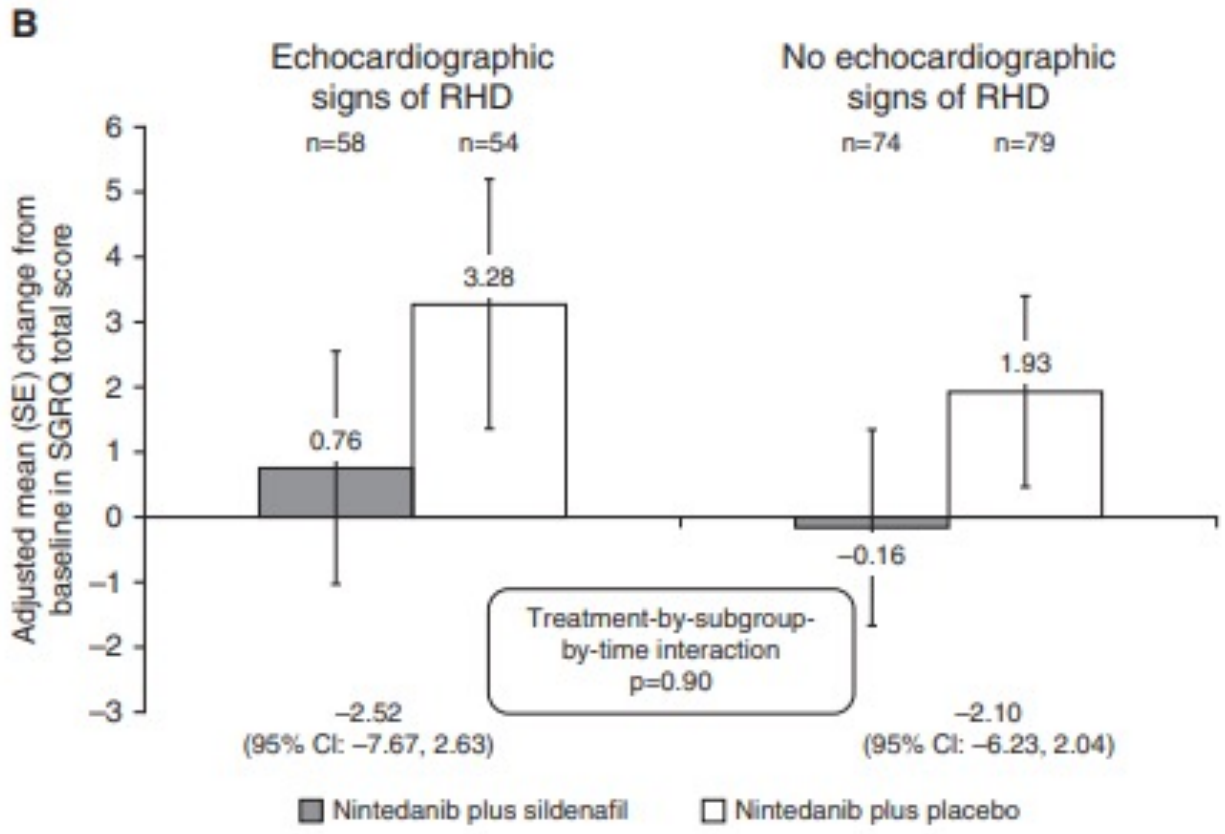
O2
PDE5 inhibitors
PGI2 analogs

Pulmonary hypertension

Sildenafil data

INSTAGE (NEJM '18) subgroups at 24 weeks

Behr J, et al. AJRCCM Vol 200, Iss 12, pp 1505–1512, Dec 15, 2019.



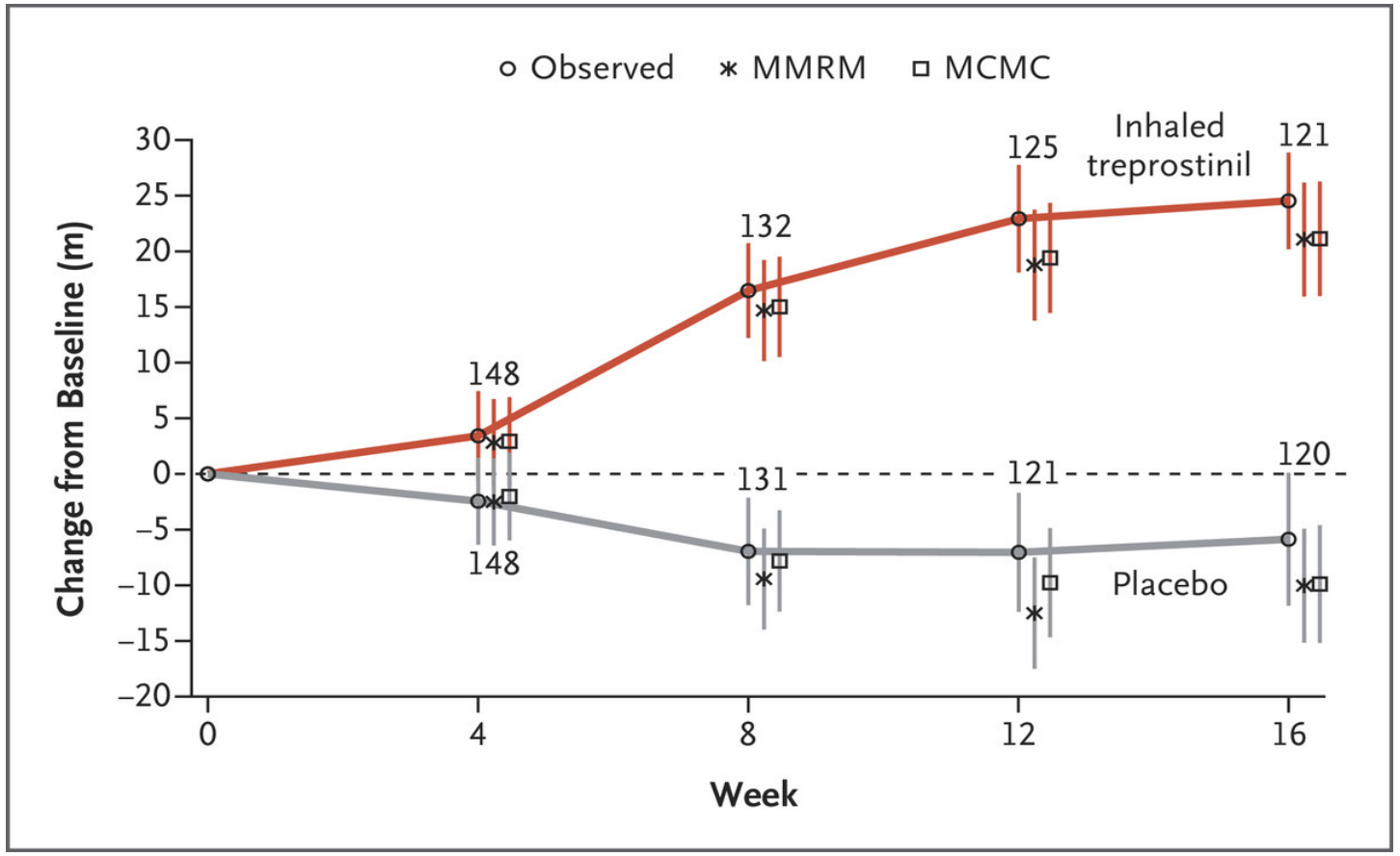
Pirfenidone version of INSTAGE : Behr J, et al. Lancet Respir Med 2021; 9: 85–95.

No clinical benefit to adding sildenafil to pirfenidone in late-stage IPF

Pulmonary hypertension

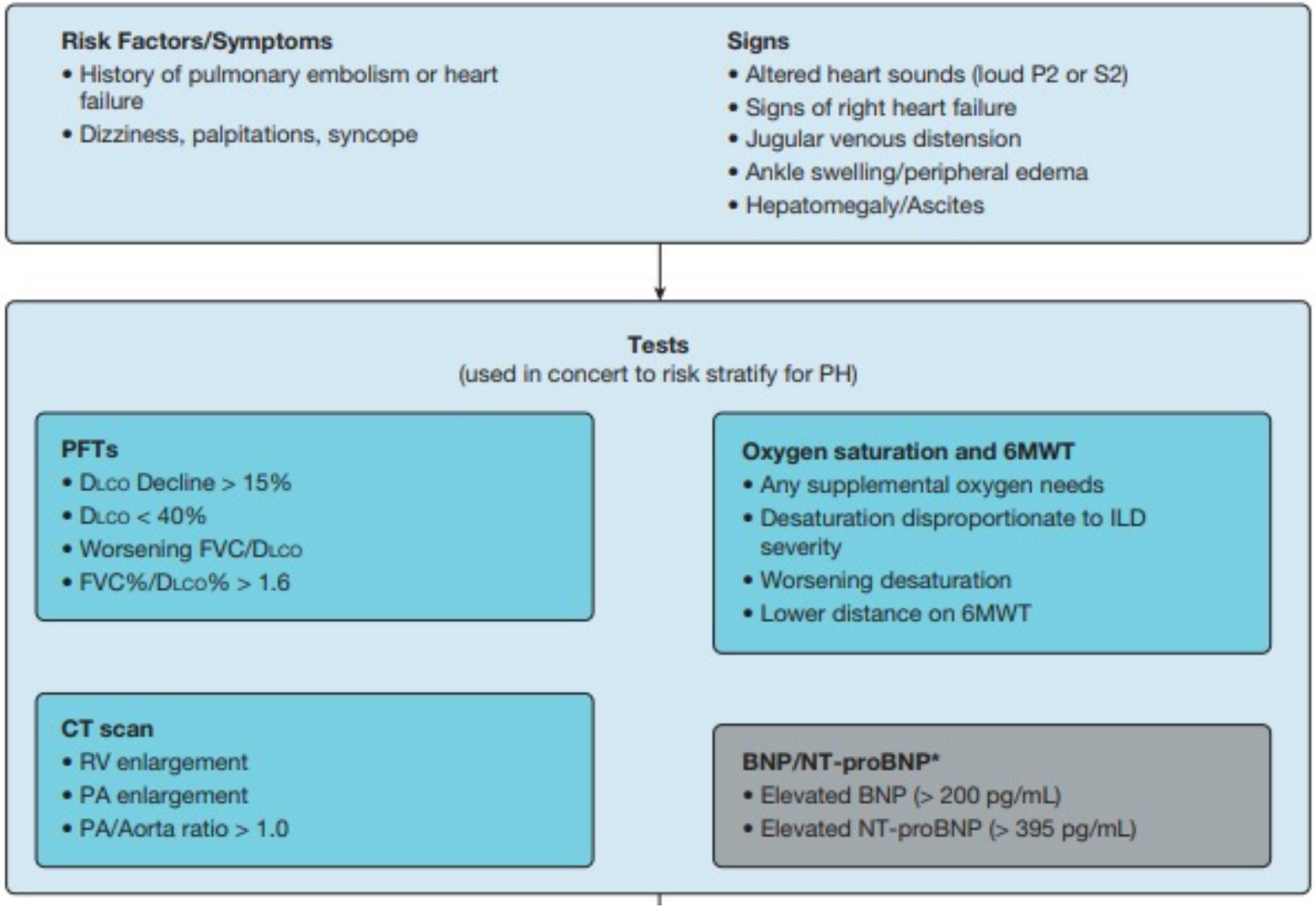
Nebulized treprostinil for ILD-PH

As of 5/22, treprostinil available via DPI qid



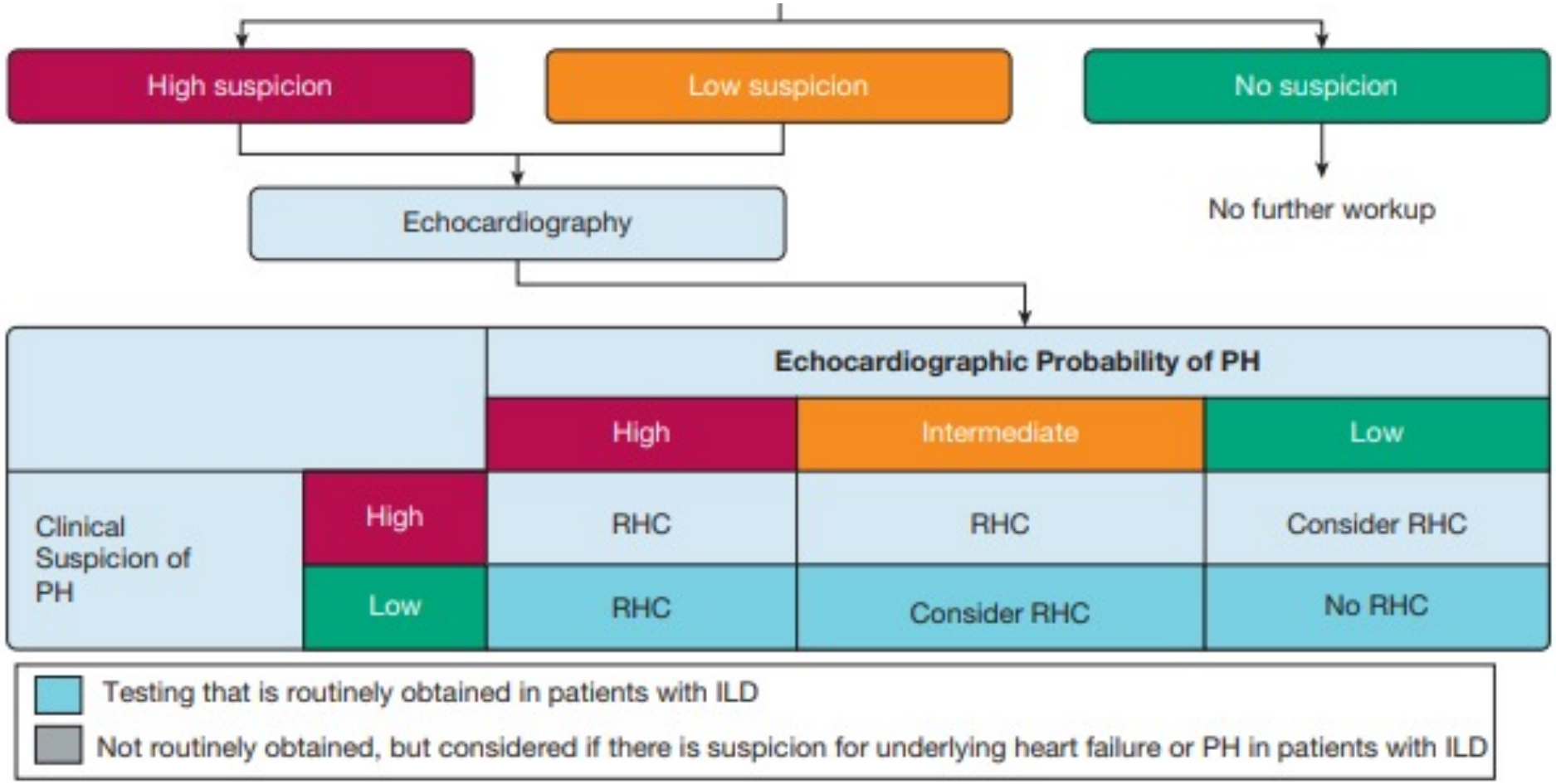
Waxman A, et al. NEJM 2021;384:325-34.

Pulmonary hypertension



Rahaghi F, et al. Chest. 2022 Jul;162(1):145-155.

Pulmonary hypertension



Rahaghi F, et al. Chest. 2022 Jul;162(1):145-155.

Novel Anti-fibrotics

Clinical Trials : www.clinicaltrials.gov

Phase III Trials:

Pamrevlumab (FG-3019)	**Fibrogen**	**CTGF mAB**
PRM-151	**Promedior/Roche**	**recombinant pentraxin-2 (PTX-2) - a.k.a. serum amyloid P**
Treprostinil	**United Therapeutics**	**PGI2 analog**
BI 1015550	**BI**	**PDE4B inhibitor**

Many phase I and II trials

Exacerbations

ATS IPF Guidelines ‘11

Question: Should patients with acute exacerbation of IPF be treated with corticosteroids?
Recommendation: The majority of patients with acute exacerbation of IPF should be treated with corticosteroids, but corticosteroids may not be reasonable in a minority (weak recommendation, very low-quality evidence).Values: This recommendation places a high value on anecdotal reports of benefit and the high mortality of acute exacerbation of IPF.

AE-IPF not mentioned in ATS IPF Guidelines ’15, ‘22

Currently being investigated:

Steroids
PlEx
Rituximab
IVIg

Recently failed:
Cyclophosphamide

Take-homes

Be aggressive with anti-fibrotics

Perhaps less so, for now, with PH and GER therapies

Encourage trial participation

Steroids for exacerbation, more to come re: other therapies