La Cronicità:

Dall’Ospedale al territorio, una realtà in evoluzione

Malattie respiratorie: terapia e aderenza terapeutica nel paziente anziano

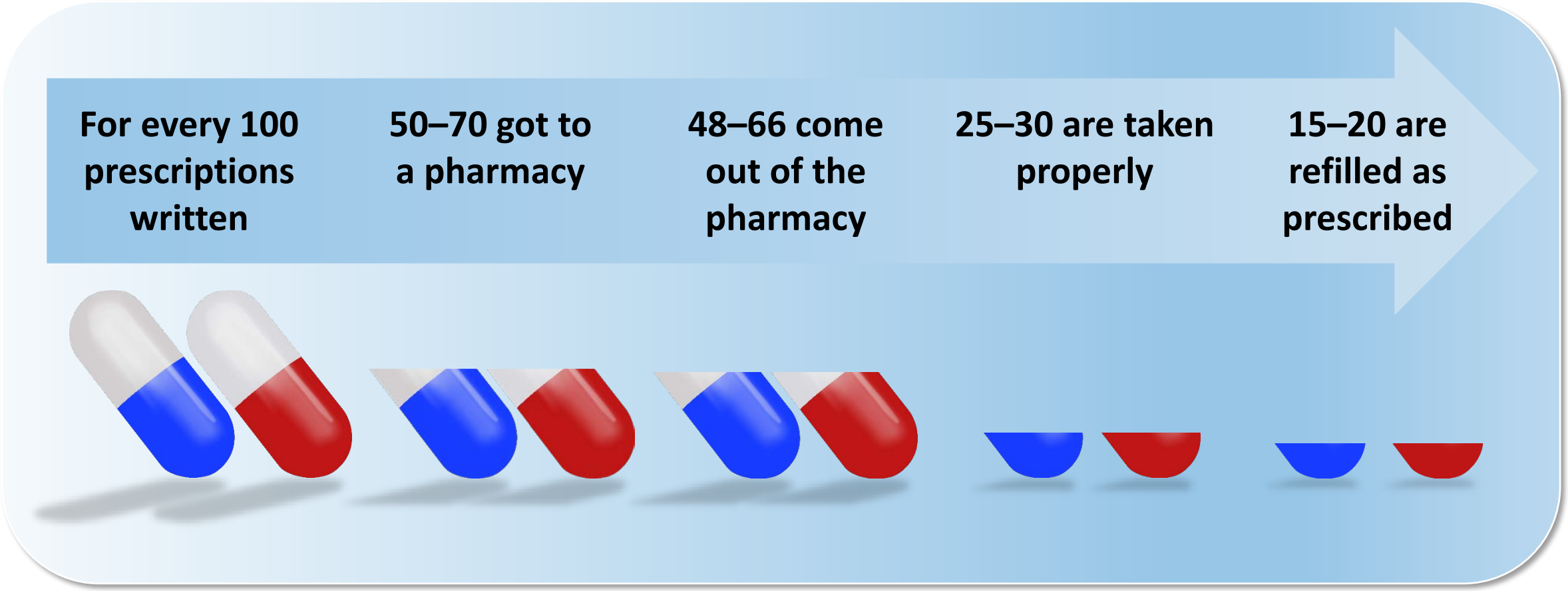
Dr. Sergio Harari
U.O. di Pneumologia
Ospedale San Giuseppe – MultiMedica IRCCS
Milano

'Drugs don't work in patients who don't take them'

'Increasing the effectiveness of adherence interventions might have a far greater impact on health than any improvement in specific medical treatments'

Everett Koop, surgeon general of the United States under R. Reagan
Haynes RB et al. Cochrane Database Sys Rev 2000;2:CD000011

In general, there is a gap between a written prescription and actual medication use



National Association of Chain Drug Stores, Pharmacies: Improving Health, Reducing Costs, July 2010. Based on IMS Health data

Think of yourself…

- Medication adherence amongst doctors and nurses
  - For short-term medication: 77%
  - For long-term medication: 84%

It seems unreasonable, then, to expect that patients can achieve better adherence than providers without provider intervention

Corda RS, et al. *South Med J* 2000;93:565–569

Treatment requires flexibility

The patient and physician need to work together to maintain treatment over the long term

Adherence
Percent of doses taken as prescribed[1]

Flexibility is required

+

Persistence
Days taking medication without exceeding permissive gap[1]

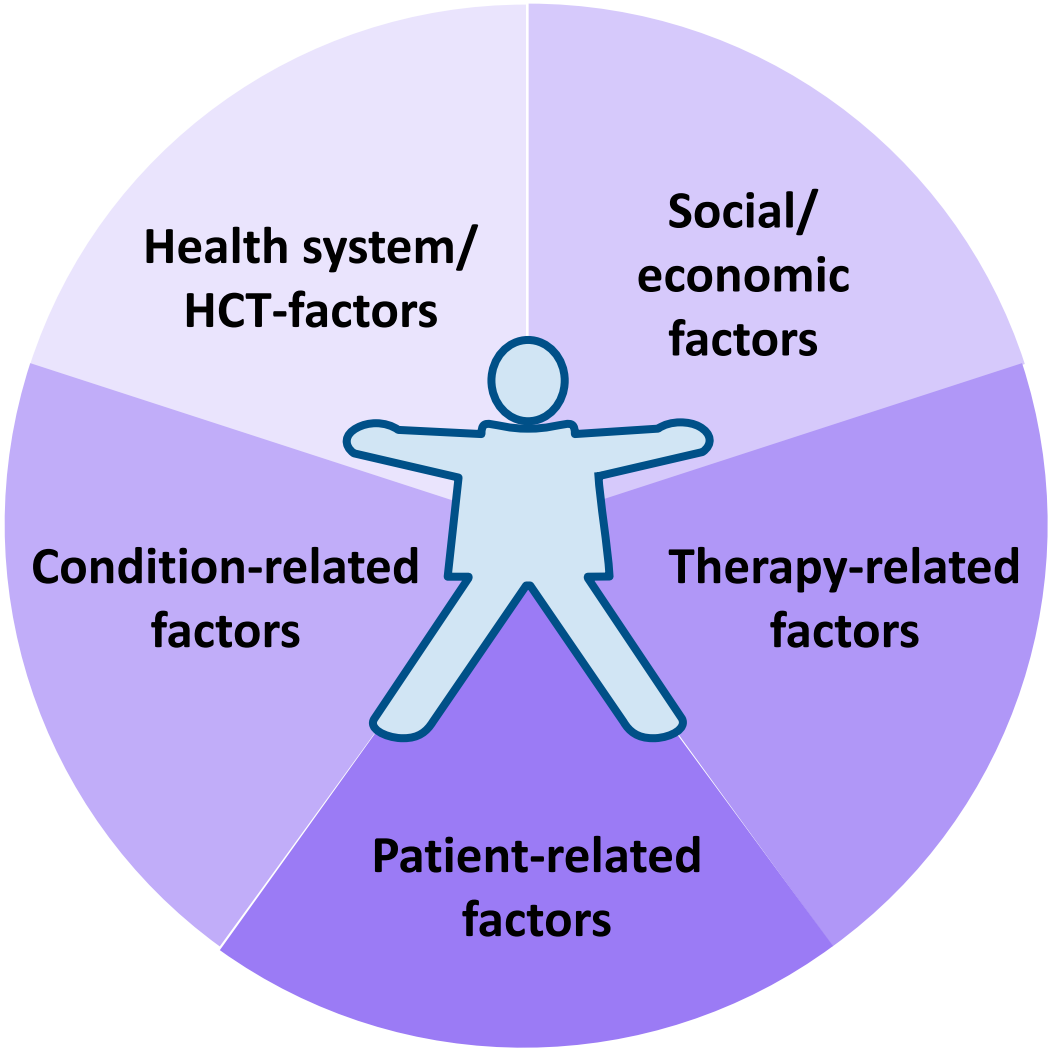
=

Desired medication use

While ideally the correct dose will be prescribed from the outset, if required, dose reductions help maintain patients on treatment

Cramer JA, et al. *Value Health* 2008;11:44–47

Adherence is not merely a patient-driven problem



HCT, healthcare team

World Health Organisation. Adherence to long-term therapies, evidence for action. 2003

How do I maintain patients on treatment?

- What factors influence adherence and persistence of treatment?
- **What do we know about adherence to IPF treatments?**
- How do we improve and maintain adherence?

TEAEs leading to discontinuation in pirfenidone and nintedanib trials

% patients	CAPACITY and ASCEND trials		TOMORROW and INPULSIS trials	
	Pirfenidone (N=623)	Placebo (N=624)	Nintedanib (N=723)	Placebo (N=508)
Any TEAE,%	99.0	97.9	95.3	89.8
Any serious TEAE, %	27.0	28.5	30.0	30.1
Any TEAE leading to treatment discontinuation, %	**14.6**	**9.6**	**20.6**	**15.0**

Main reasons for discontinuation:

- Diarrhoea (5.3%)
- Nausea (2.4%)
- Progression IPF (2.1%)
- Decreased appetite (1.5%)

Most common reasons for treatment discontinuation were:

- Worsening of IPF (11.5%)
- Rash (2.2 %)
- Nausea (1.7%)
- Photosensititivity (0.5%)

While a large proportion of patients experience AEs, the rate of AEs is not a key element to adherence

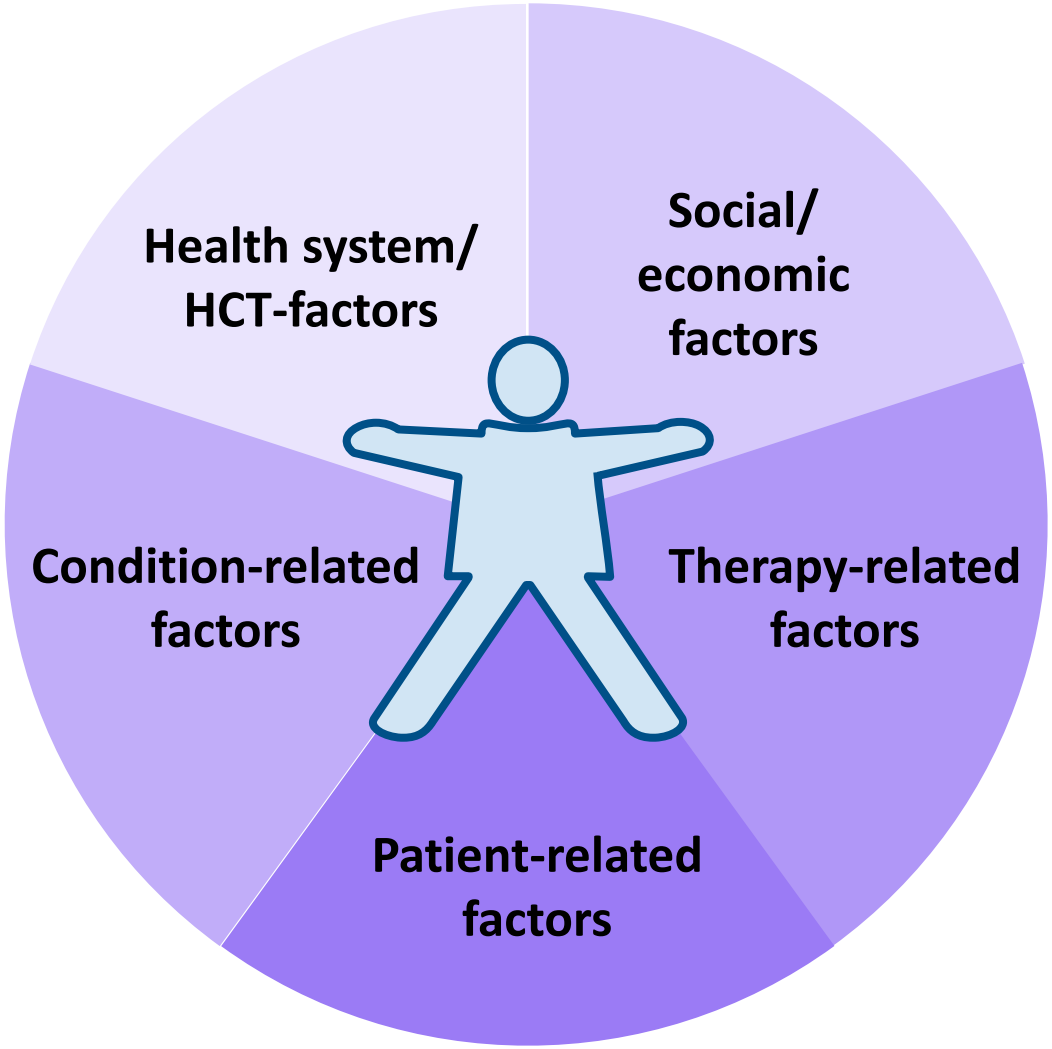
AE, adverse event; TEAE, treatment-emergent adverse event

Lancaster L, et al. *BMJ Open Respir Res* 2016;3:e000105;
Richeldi L, et al. *Respir Med* 2016;113:74–79;
Cottin V. *Exp Opin Drug Safety* 2017;16:857–865

How do I maintain patients on treatment?

- What factors influence adherence and persistence of treatment?
- What do we know about adherence to IPF treatments?
- **How do we improve and maintain adherence?**

Patients need to be supported, not blamed, for non-adherence



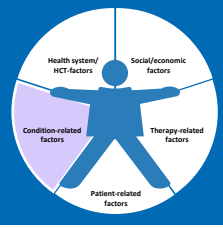
World Health Organisation. Adherence to long-term therapies, evidence for action. 2003

Take into account socioeconomic and health system factors

- Educational level
- Social support networks
- Financial situation
- Treatment centre factors
  - Time
  - Team
  - Communication
- Collaboration with other care providers
- Bias
  - Age
  - Race
  - Language
  - Level of education?

World Health Organisation. Adherence to long-term therapies, evidence for action. 2003

Condition-related factors



Sometimes asymptomatic

Sometimes severely impaired

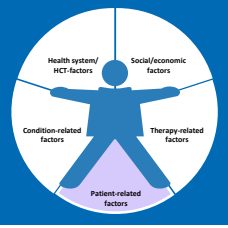
Rapid progression, no cure

Co-morbidities

All impact patients' risk perception and adherence motivation

World Health Organisation. Adherence to long-term therapies, evidence for action. 2003

Patient-related factors



Awareness of disease and treatment benefits

Lack of symptoms delaying pursuit of medical help

Lack of motivation to pursue medical consultation

Expectations

Anxiety about disease / possible AE treatment

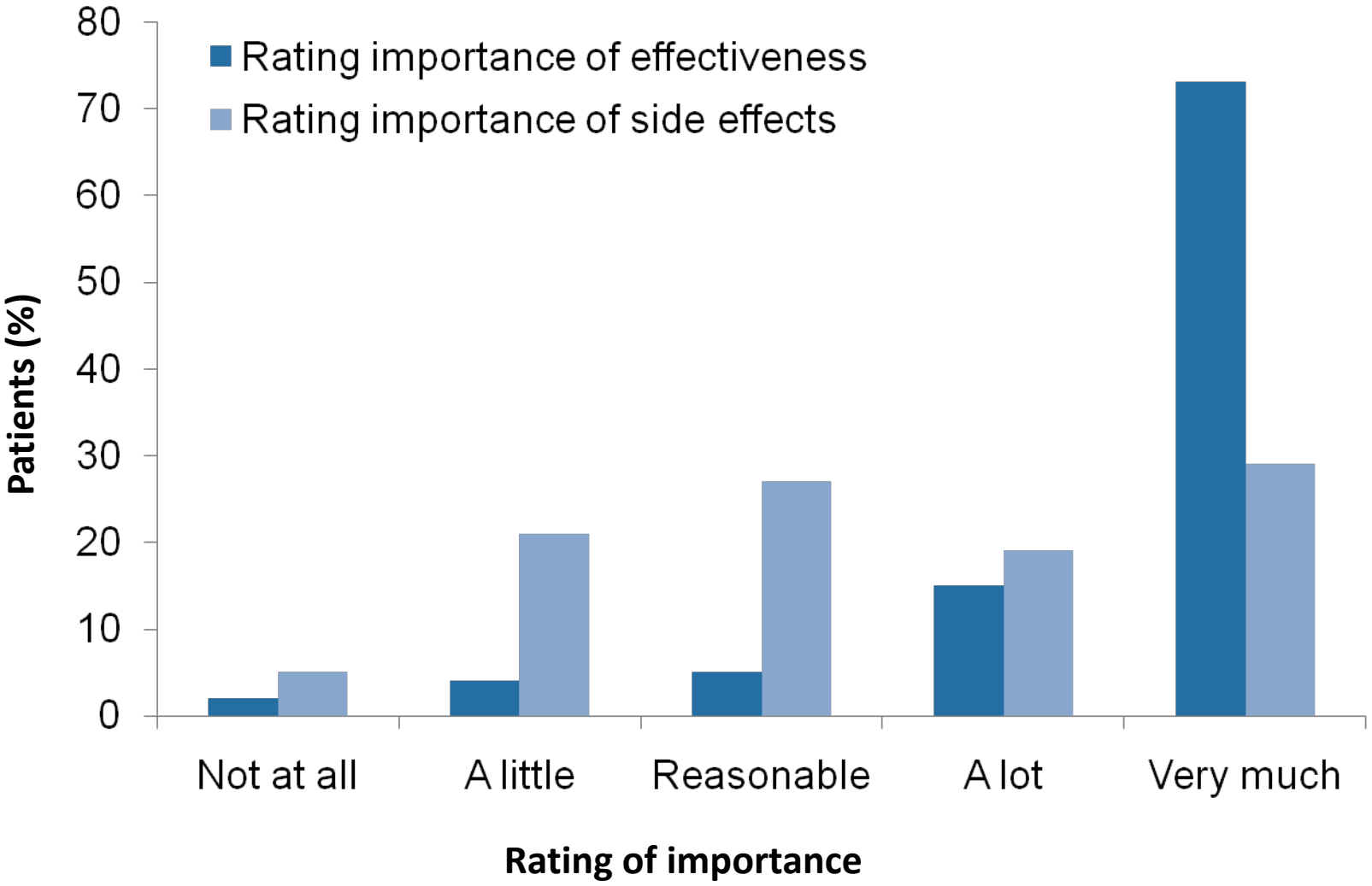
Negative views in general about medicines

Confidence in self-management

Cost–benefit ratio: unlikely to be an issue, but physicians should be aware that some patients think about this

World Health Organisation. Adherence to long-term therapies, evidence for action. 2003

Patients considered effectiveness of pirfenidone and nintedanib more important than side effects

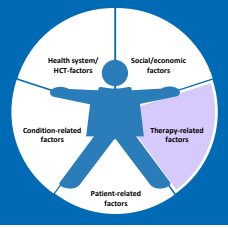


Graph: patients about to start on either pirfenidone or nintedanib (n=134) were asked about effectiveness vs side effects and their expectations of the drugs

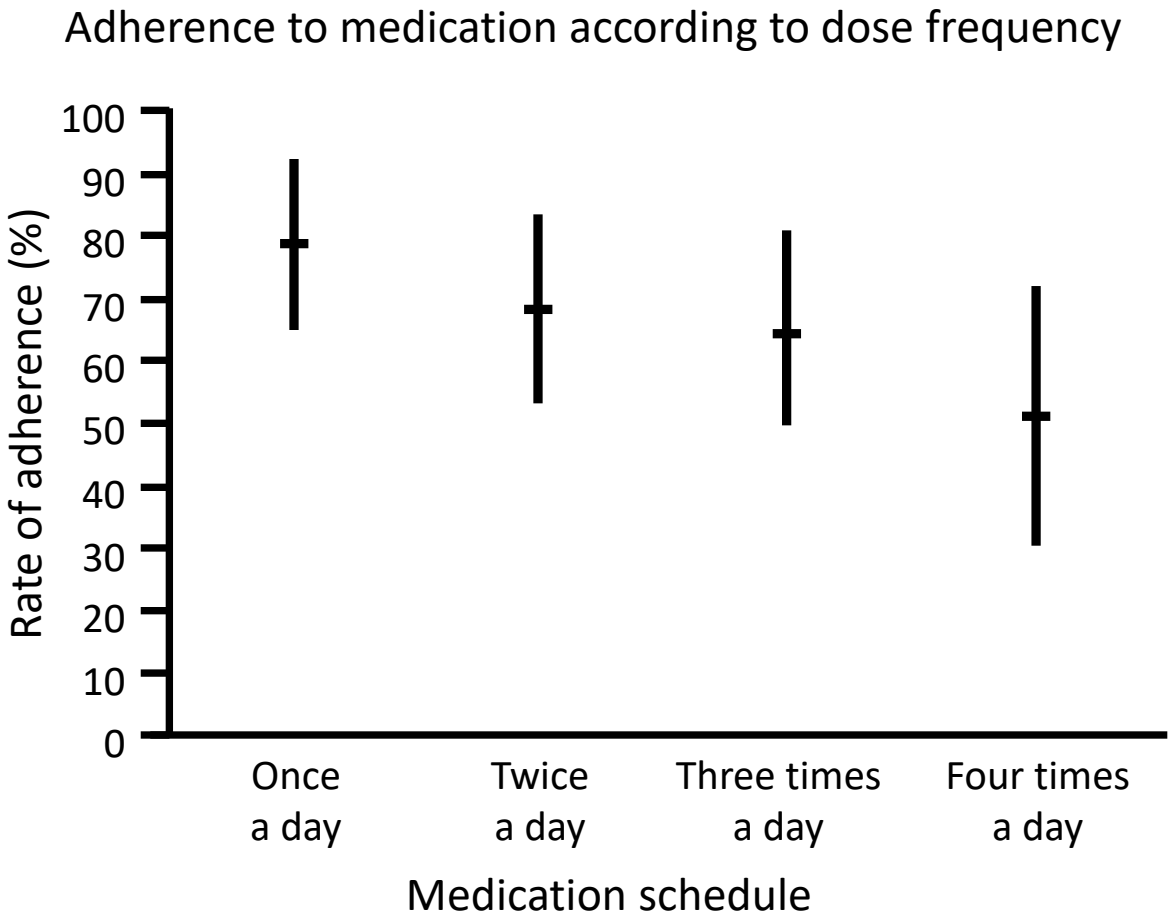
Also: a 2016 online patient survey indicated that most patients (n=52, 87%) felt that the ability of antifibrotics to slow disease progression was more important than possible side effects

Presenter's unpublished data; Maher et al, *ATS* 2017: A1123

Therapy-related factors

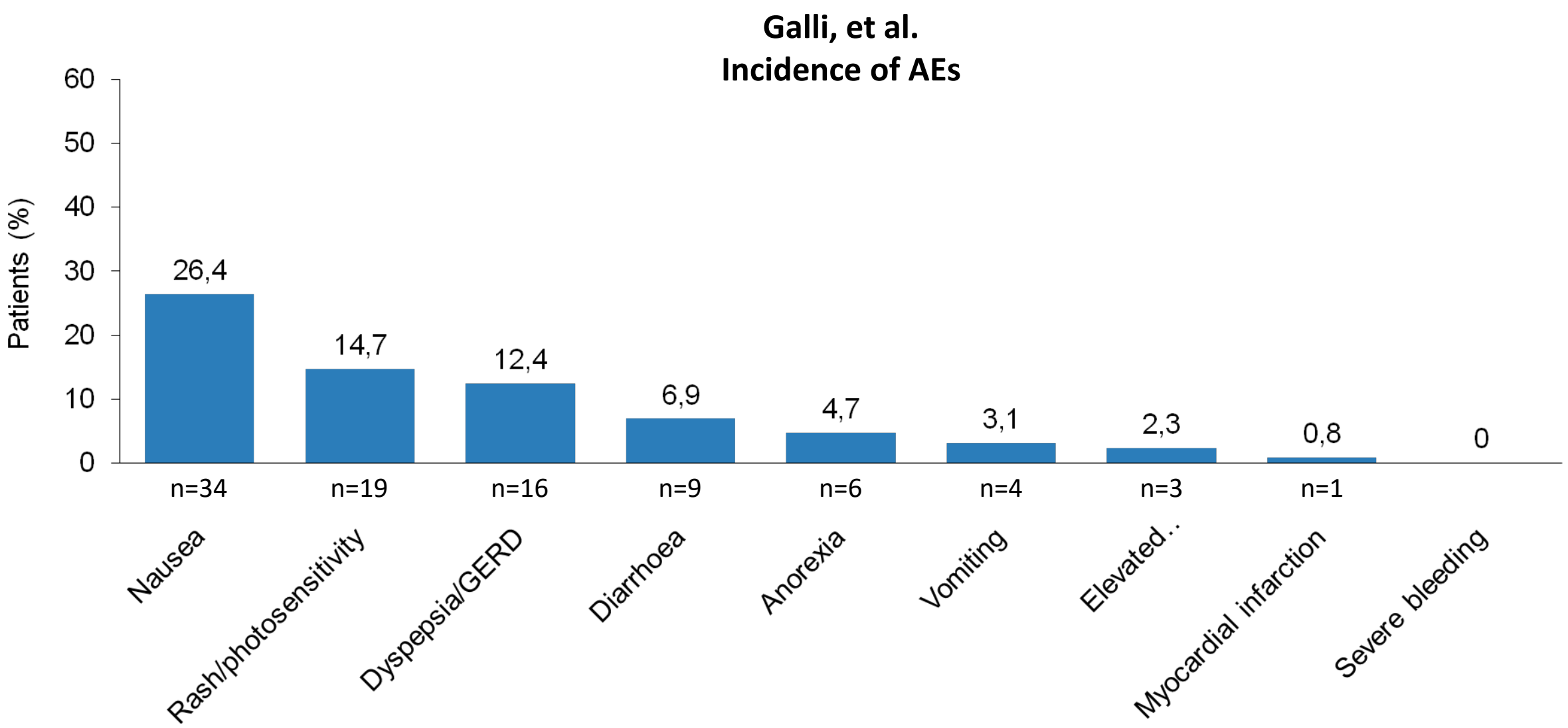


- Complexity of regimen
- Duration of treament
- Limited or no tangible effect
- Side effects and the availabitly of medical support to deal with them



Osterberg L, et al. *N Engl J Med* 2005;353:487-497;
World Health Organisation. Adherence to long-term therapies, evidence for action. 2003

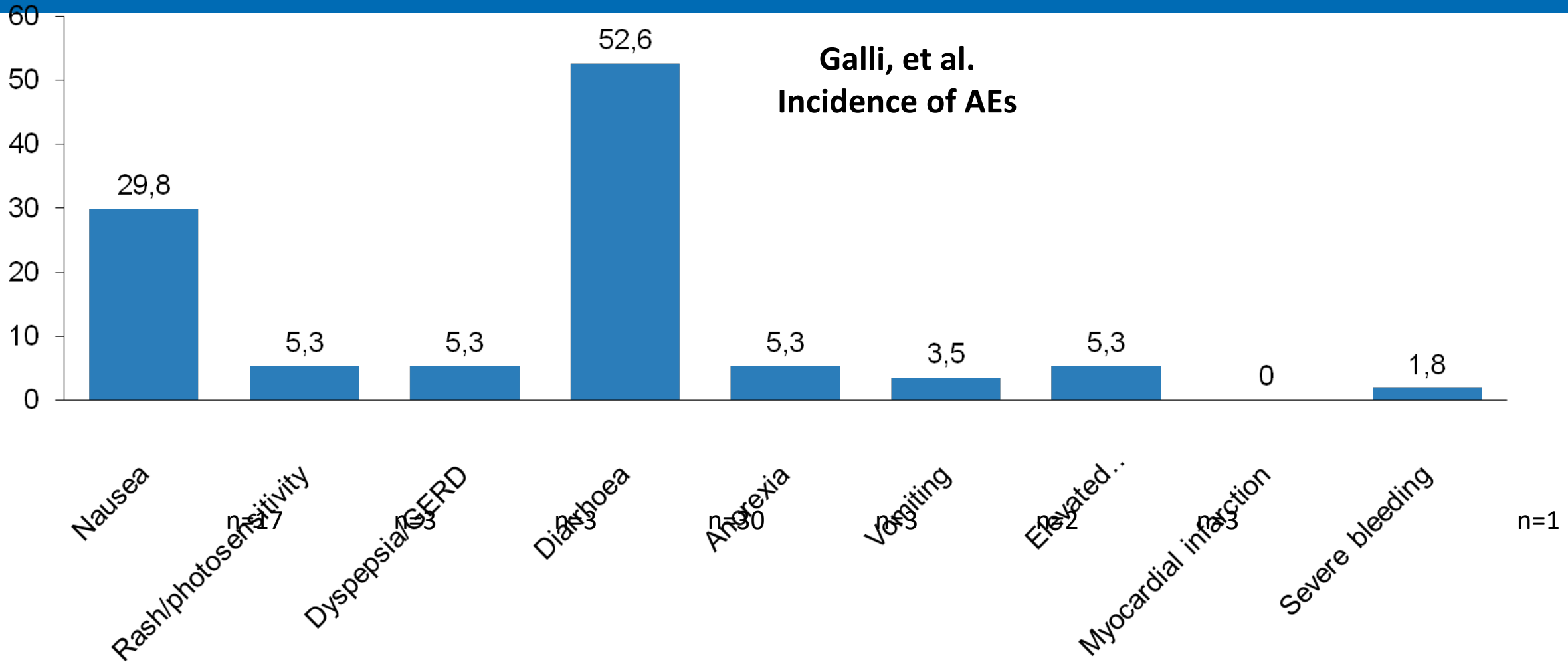
Real-world AE frequency with pirfenidone



GERD, gastroesophageal reflux disease

Galli JA, et al. *Respirology* 2017;epub ahead of print

Real-world AE frequency with nintedanib



GERD, gastroesophageal reflux disease

TEAE leading to discontinuation: pirfenidone trials and real-world data

CAPACITY and ASCEND – any TEAE leading to treatment discontinuation: 14.6%

Real-world data – discontinuation due to TEAEs ranging from ~6% to ~38%

	Total number of patients	Patients discontinued
Bando	502	15.3%
Chaudhuri	40	15%
Duck	465	8%
Galli	129	20.9%
Hughes	351	29%
Kaur	49	18.4%

	Total number of patients	Patients discontinued
Lalla*	1291	23.8%
Okuda	76	18.4%
Salih	113	16%
Skold	33	6.1%
Strock	40	38%
Wijsenbeek	63	19%

*Includes discontinuations due to non-TEAE causes

Bando M, et al. *Intern Med* 2016;55:443–448; Chaudhuri N, et al. *Respir Med* 2014; 108:224–226; Duck A, et al. *Adv Ther* 2015;32:87–107; Galli JA, et al. *Respirology* 2017;epub ahead of print; Hughes G, et al. *J Clin Med* 2016;5:E78; Kaur R, et al. *Am J Respir Crit Care Med* 2017;195:A5388; Lalla D, et al. *Am J Respir Crit Care Med* 2017;195:A5351; Okuda R, et al. *Respir Med* 2013;107:1431–1437; Salih GN, et al. *Eur Clin Respir J* 2016;9:32608; Skold CM, et al. *Eur Clin Respir J* 2016;18:32035; Strock S, et al. *Am J Respir Crit Care Med* 2017;195:A5404; Wijsenbeek M, et al. *Adv Ther* 2015;32:691–704

TEAEs leading to discontinuation: nintedanib trials and real-world data

TOMORROW and INPULSIS – any TEAE leading to treatment discontinuation: 20.6%

Real-world data – discontinuation due to TEAEs ranging from 3% to ~34%

	Total number of patients	Patients discontinued		Total number of patients	Patients discontinued
Brunnemer	60	3%	Noma	18	22.2%
Galli	57	26.3%	Oliveira	15	13.3%
Hughes	124	19%	Sakamoto	14	7.1%
Kaur	40	17.5%	Strock	20	20%
Lalla*	1040	33.5%	Toellner	187	20%

*Includes discontinuations due to non-TEAE causes

Brunnemer E, et al. *Eur Respir J* 2016;48:PA2093; Galli JA, et al. *Respirology* 2017;epub ahead of print; Hughes G, et al. *J Clin Med* 2016;5:E78; Kaur R et al. *Am J Respir Crit Care Med* 2017;195:A5388; Lalla D, et al. *Am J Respir Crit Care Med* 2017;195:A5351; Noma S, et al. *Am J Respir Crit Care Med* 2017;195:A5400; Oliveira S, et al. *Am J Respir Crit Care Med* 2017;195:A6779; Sakamoto K, et al. *Am J Respir Crit Care Med* 2017;195:A5379; Strock S, et al. *Am J Respir Crit Care Med* 2017;195:A5404; Toellner H, et al. *Am J Respir Crit Care Med* 2017;195:A5384

Nintedanib with add-on pirfenidone in idiopathic pulmonary fibrosis: results of the INJOURNEY trial

- 105 patients were randomized to receive nintedanib 150mg bid alone (n=52) or nintedanib 150mg bid with add-on pirfenidone titrated to 801 mg tid (n=53)

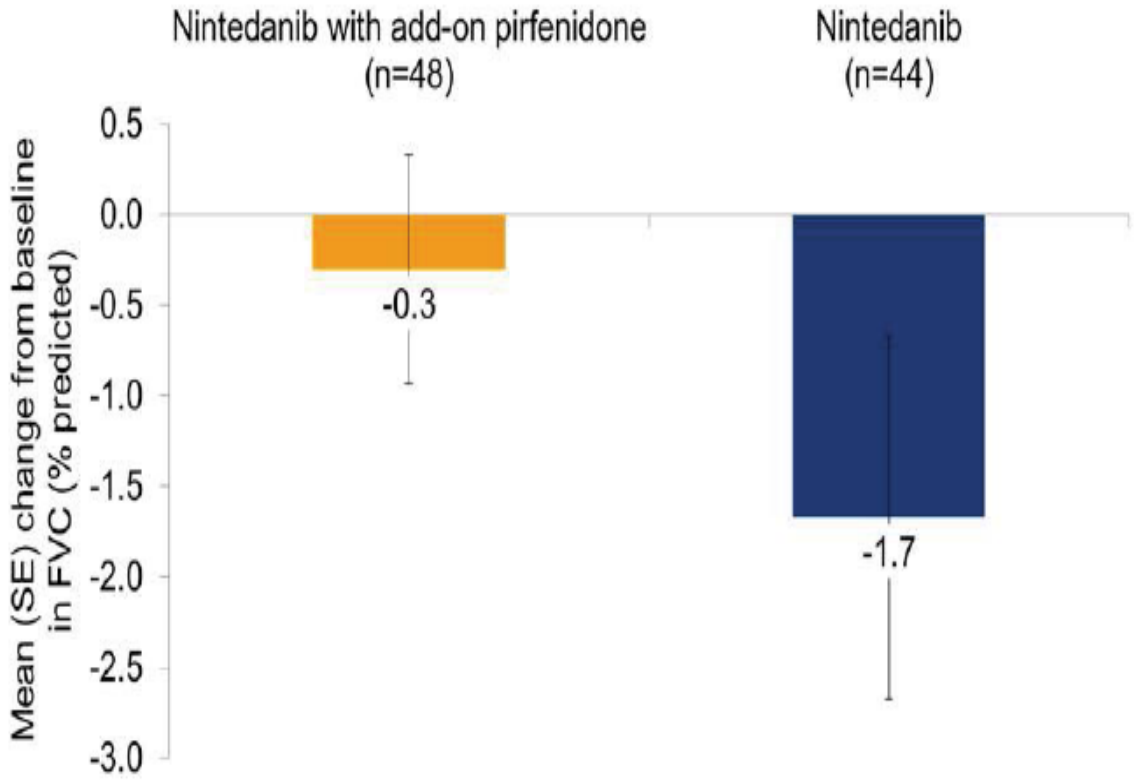
- Nintedanib with add-on pirfenidone had a manageable safety and tolerability profile in patients with IPF, in line with the adverse event profiles of each drug

	Nintedanib 150 mg bid with add-on pirfenidone (n=53)	Nintedanib 150 mg bid (n=51)
Any adverse event(s)	47 (88.7)	45 (88.2)
Most frequent adverse events*		
Diarrhea	20 (37.7)	16 (31.4)
Nausea	22 (41.5)	6 (11.8)
Vomiting	15 (28.3)	6 (11.8)
Fatigue	10 (18.9)	6 (11.8)
Upper abdominal pain	7 (13.2)	4 (7.8)
Decreased appetite	6 (11.3)	5 (9.8)
Dyspnea	2 (3.8)	8 (15.7)
Headache	7 (13.2)	1 (2.0)
Any serious adverse event(s)†	2 (3.8)	5 (9.8)
Any fatal adverse event(s)	0	0

Vancheri et al.
Am J Respir Crit Care Med 2017 Sep 10. [Epub ahead of print]

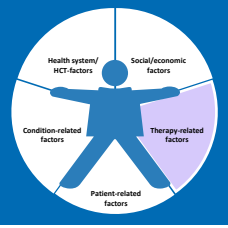
Nintedanib with add-on pirfenidone in idiopathic pulmonary fibrosis: results of the INJOURNEY trial

- Pre-dose plasma trough concentrations of nintedanib were similar at each time point, irrespective of whether nintedanib 150 mg bid was administered alone or with add-on pirfenidone.
- A smaller numerical decline in FVC over 12 weeks was observed in patients treated with nintedanib with add-on pirfenidone compared with nintedanib alone.
- However, as this trial was not powered for this endpoint and was too short for conclusions to be drawn about the efficacy of combination therapy, these findings should be interpreted with caution

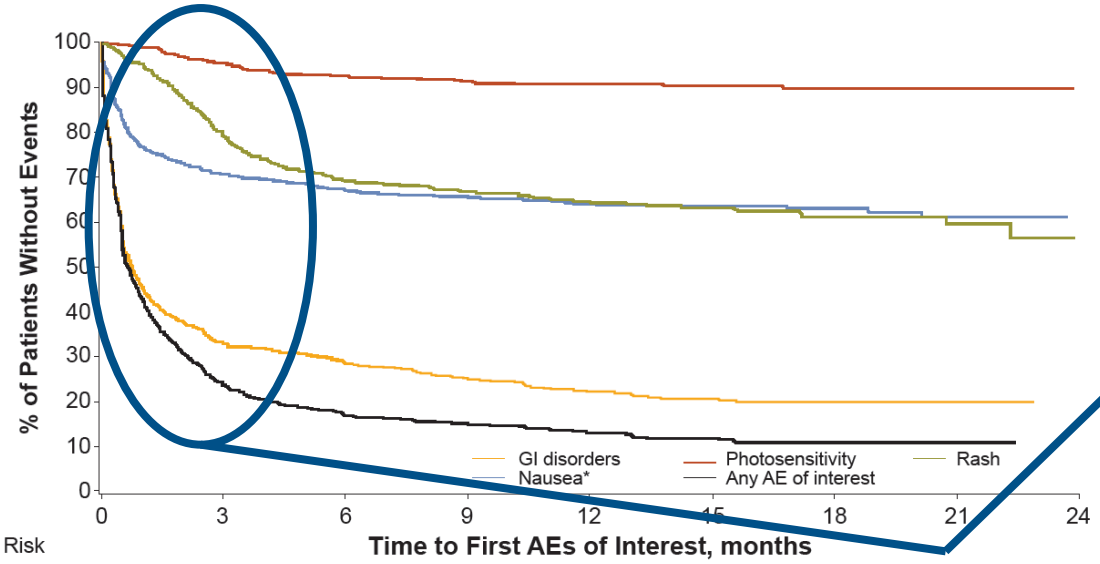


Vancheri et al. Am J Respir Crit Care Med 2017 Sep 10. [Epub ahead of print]

Coaching is crucial in first period



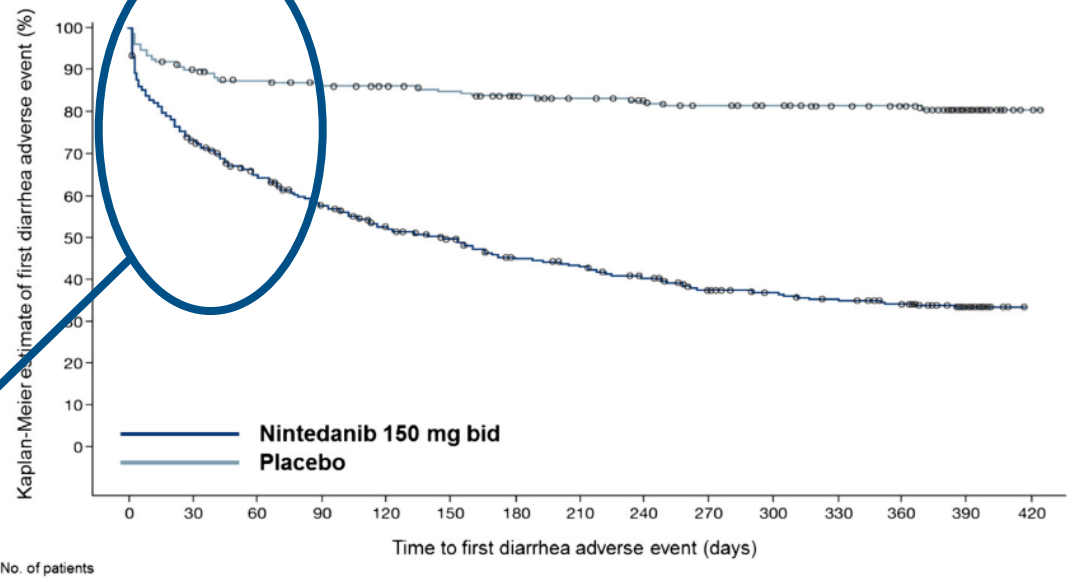
Pirfenidone



Patients at Risk

GI disorders	623	199	166	139	86	64	25	12	0
Photosensitivity	623	574	530	499	343	258	118	66	6
Rash	623	478	395	366	244	176	81	36	5
Nausea*	623	427	385	361	248	188	87	43	4
Any AE of interest	623	143	100	87	56	38	12	5	0

Nintedanib



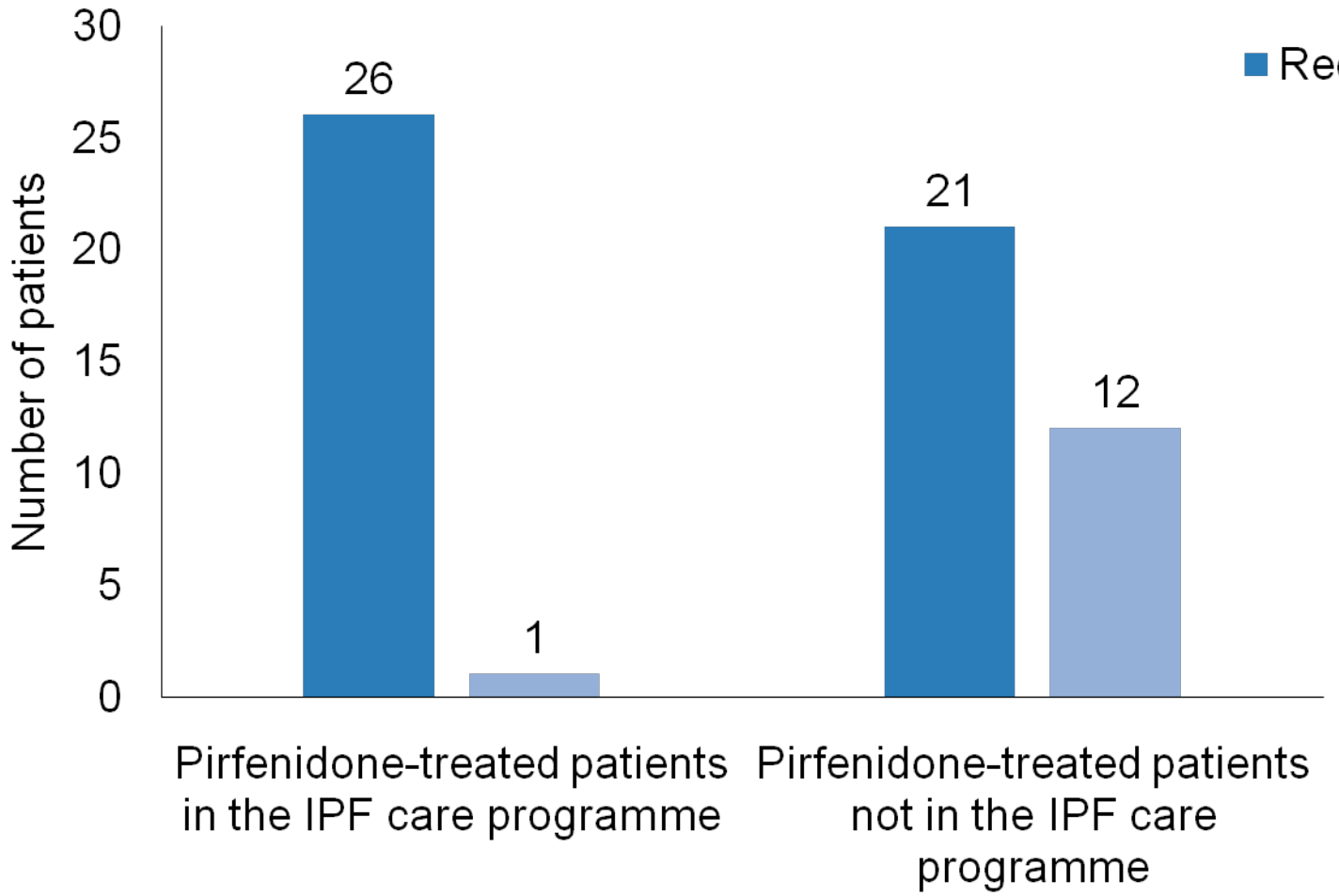
No. of patients

Nintedanib	638	462	401	345	309	286	255	242	221	199	191	180	169	131
Placebo	423	378	361	353	347	340	329	321	314	304	299	293	287	218	2

Most TEAEs occur in the first months of treatment, but they may also occur later in the course of disease

Mason WR, et al. *Am J Respir Crit Care Med* 2017;195:A6798; Corte T, et al. *Respir Res* 2015;16:116

Real-world support experiences



Patients treated within care programmes have been shown to remain on treatment for longer than those not in care programmes

Duck A, et al. *Adv Ther* 2015;32:87–107

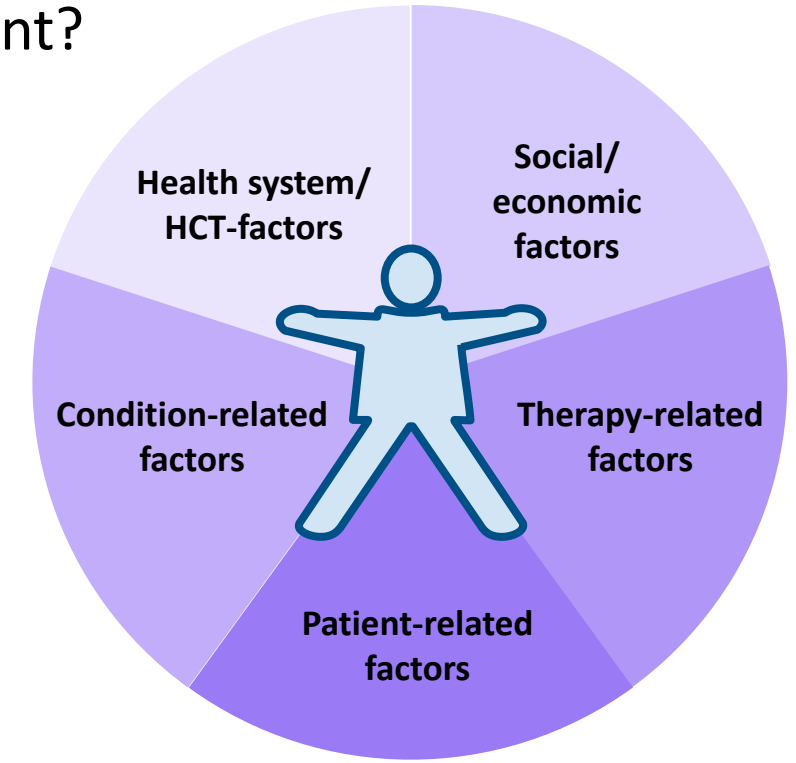
Conclusions in daily practice: be flexible and approachable

1. Patient education
2. Prevention of AEs
3. In case of AEs and no spontaneous resolution → treat symptoms
4. If symptom treatment does not have desired effect → reduce dose
5. If persistent symptoms → temporarily discontinue treatment
6. If symptoms resolved slowly, reintroduce or consider a switch when possible

Adapted from: Costabel U, et al. *Adv Ther* 2014;31:375–391

Conclusions: maintain patients on treatment

- What factors influence adherence and persistence of treatment?
  - Social/economic factors
  - Therapy-related factors
  - Patient-related factors
  - Condition-related factors
  - Health system/HCT-factors
- What do we know about adherence to IPF treatments?
  - Rates of discontinuation with IPF treatments are too high, leaving room for improvement
- How do we improve and maintain adherence?
  - Adherence is a dynamic process that needs to be followed-up



REPOSI Registry

- The REPOSI study is a collaborative study between the Italian Society of Internal Medicine (SIMI), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano and the IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milano
- It was designed with the purpose of setting up a network of internal medicine wards to investigate the prevalence and correlates of multimorbidity and polypharmacy in hospitalized elderly patients.
- Participation was voluntary, but in the choice of participating centers, we were careful to ensure they were representative in terms of country-wide distribution and size.

REPOSI Registry

Aims

The Register was specifically designed:

- to describe the prevalence of multiple concurrent diseases and treatments in hospitalized elderly patients,
- to correlate the patient's clinical characteristics with the type and number of diseases and treatments,
- to evaluate the main clinical outcomes at discharge and at 3 – 12 months of follow-up.

REPOSI Registry

Inclusion criteria

Patients are eligible if:

1. they are admitted to one of the participating internal medicine or geriatric wards during one of the four annual index weeks;
2. they are 65 years or older;
3. they sign the informed consent.

Each ward must enrol at least the first five consecutive eligible patients during each index week.

REPOSI Registry

All data (Minimin Data Set) obtained from the patient medical records enter in a standardized web-based Case Report Form (CRF).

The following data are recorded for each patient:

- basic socio-demographic details,
- clinical and laboratory parameters,
- diagnoses (comorbidities)
- cognitive function (Belssed test)
- disability (Barthel index)
- depression (Geriatric Depression Scale, 4 items)
- drugs at hospital admission, during hospital stay at discharge and follow-up
- clinical adverse events
- outcome at discharge and 3-12 months follow-up.

REPOSI

REGISTER OF MULTIMORBIDITY AND POLYPHARMACY

REPOSI is a collaborative study promoted by the Italian Society of Internal Medicine (SIMI), IRCCS Ca' Granda Foundation Hospital and the Institute of Pharmacological Research Mario Negri of Milan, Italy.

Starting 2008:

- Pre-hospital
- In-hospital

From 2010

- **2010:** 3-months follow-up
- **2012:** 12-months follow-up

From 2014

- **REPOSI Spanish Network**

Main outcomes

- mortality (in-hospital, 3-12 months);
- re-hospitalization;
- changes in multimorbidity and polypharmacy (at admission, at discharge and at 3-12 months).

Study flow chart

Recruitment of the hospitals

Definition of the Minimum Data Set

Standardization of the procedures for data collection

Patients recruitment in each index week

Basic assessment

In hospital monitoring

Discharge

Follow-up 3*-12** months

Coding and data inputi

Control of data quality

* From 2010
** From 2012

REPOSI

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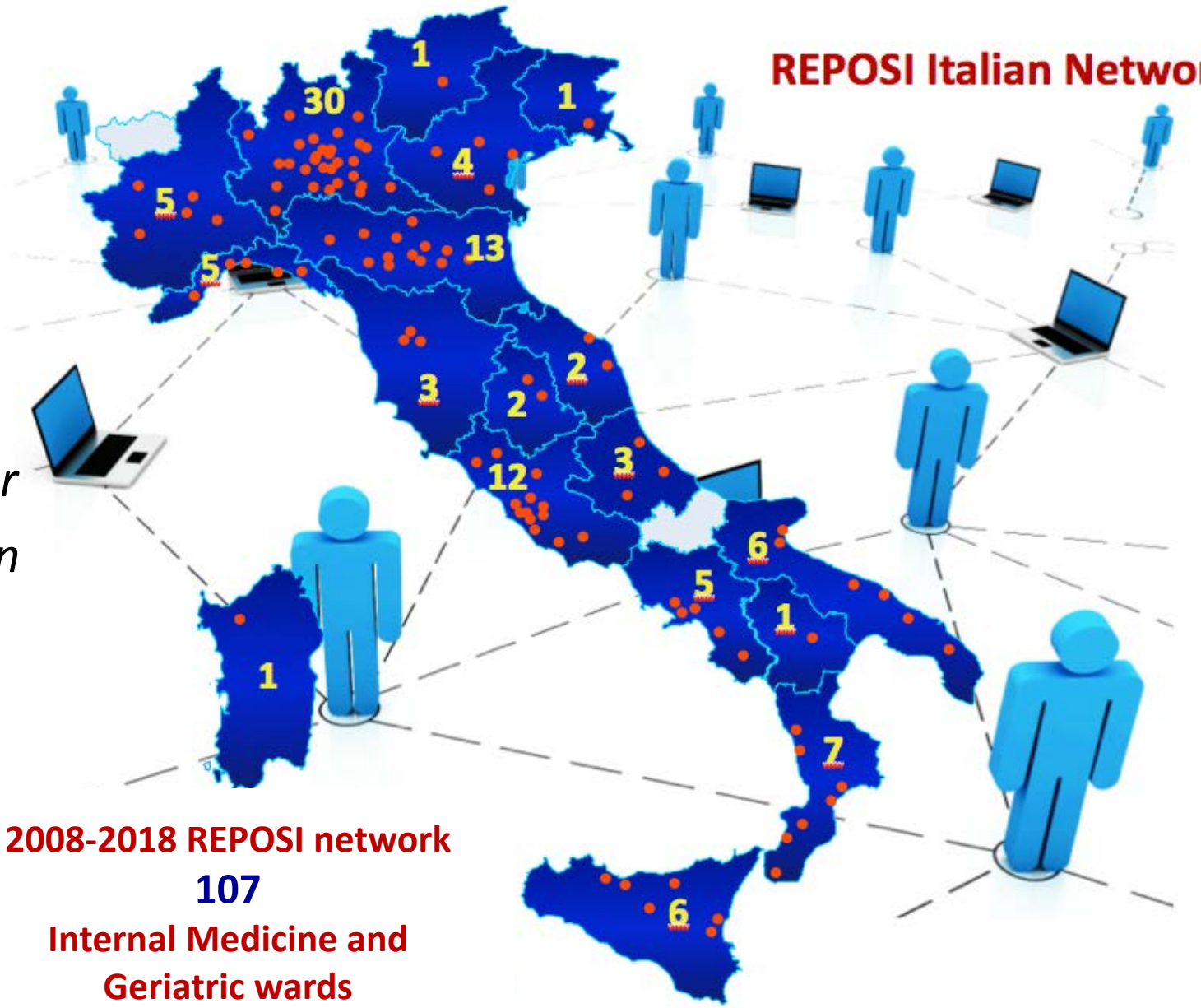
REPOSI is a collaborative study promoted by the Italian Society of Internal Medicine (SIMI), IRCCS Ca' Granda Foundation Hospital and the Institute of Pharmacological Research Mario Negri of Milan, Italy.

From 2008

7,014 patients *aged 65 years or older by* ***107 Italian and 15 Spanish*** *(only in 2014-2015)* ***internal medicine and geriatric wards*** *and more than* ***300 clinical investigators***

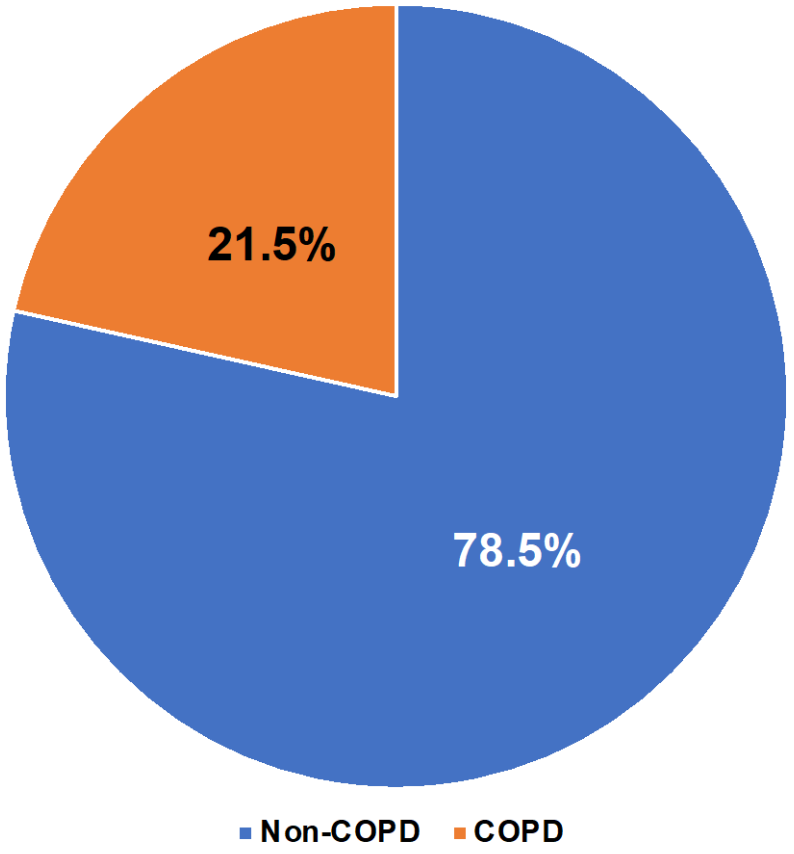


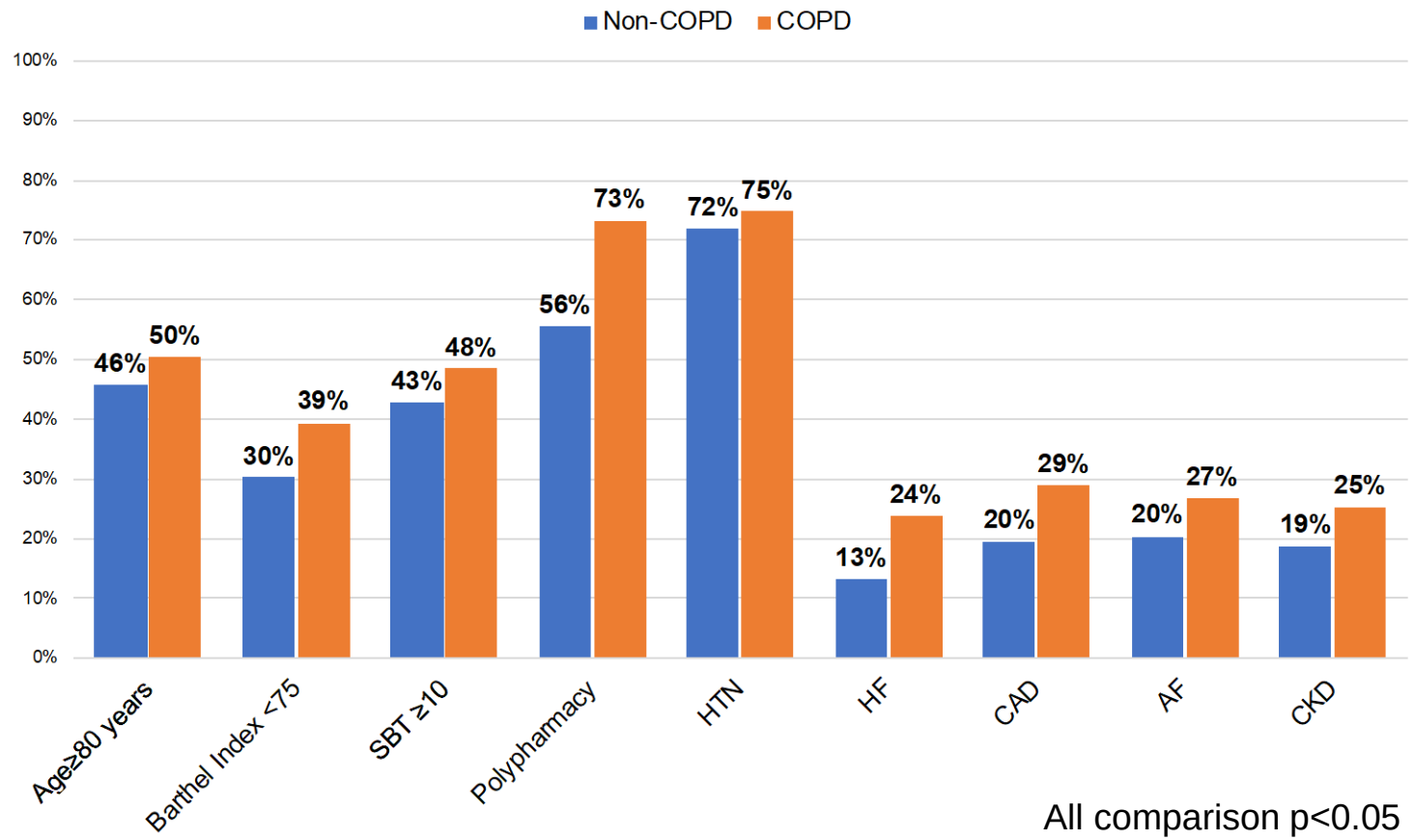
2008-2018 REPOSI network

107

Internal Medicine and Geriatric wards

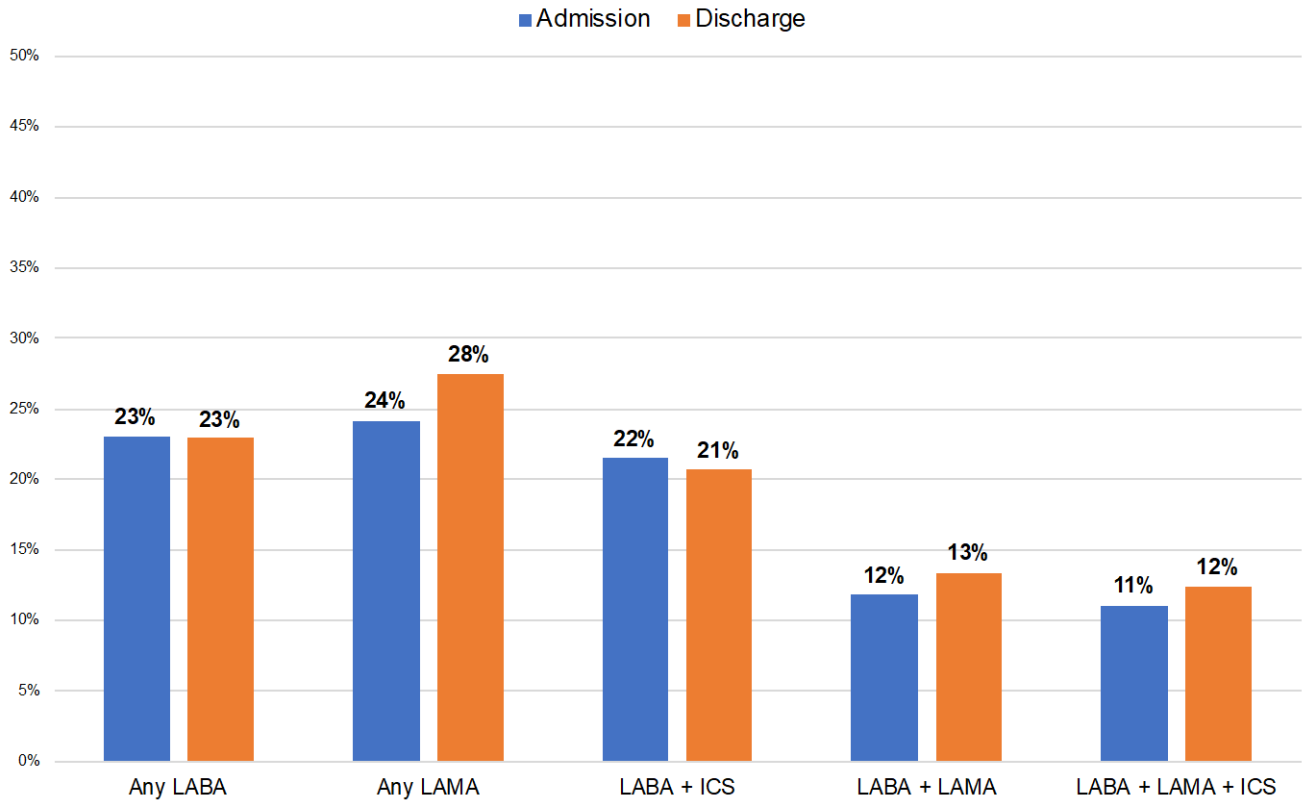
COPD Population in the REPOSI Registry (2008-2016 Data)

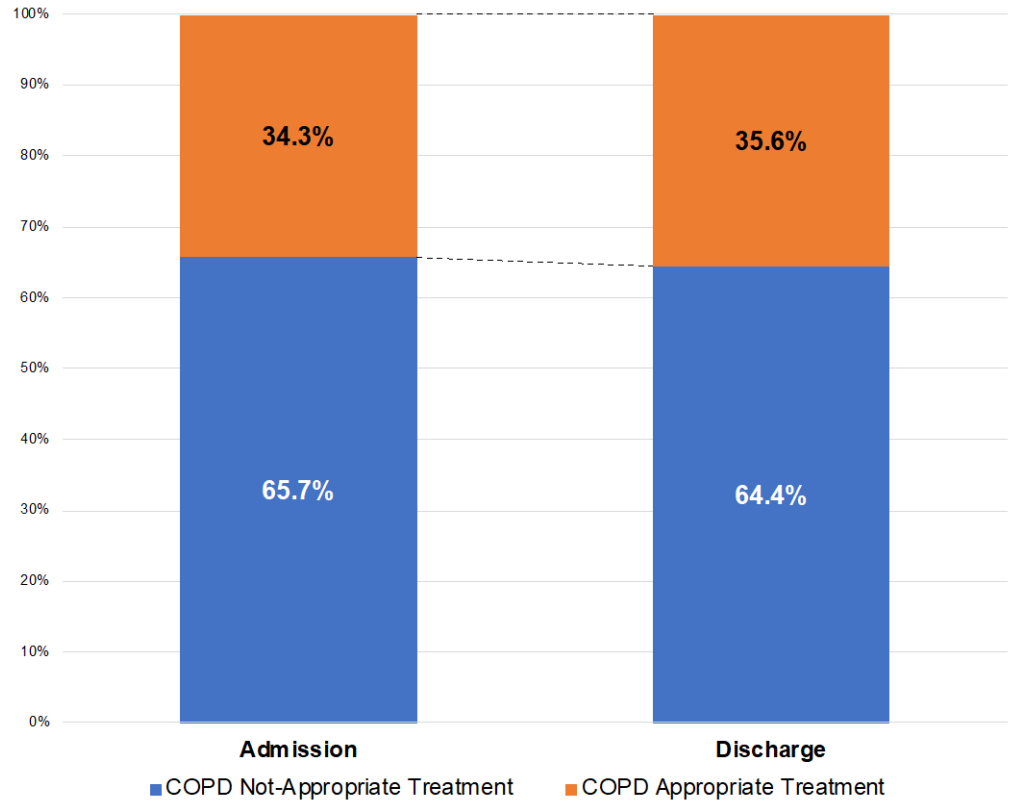




All comparison p<0.05

Use of COPD-related Drugs and Adherence to Appropriate Treatment





Clinical Factors Associated with Appropriate Treatment

	Multivariate		
	OR	**95% CI**	**p**
Appropriate Treatment at Admission			
Polypharmacy	3.28	2.24-4.81	<0.001
History of Acute Exacerbation	2.65	1.44-4.88	0.002
Appropriate Treatment at Discharge			
Smoking Habit	1.45	1.08-1.94	0.012
Polypharmacy	6.76	4.15-11.0	<0.001

COPD and Clinical Outcomes in the REPOSI Registry

COPD vs. Non-COPD	Multivariate		
	OR	**95% CI**	**p**
Any Death	1.33	0.98-1.81	0.071
CV Death	1.66	1.04-2.67	0.034
Respiratory Death	2.14	1.00-4.59	0.051
Hospitalization	1.50	1.08-2.09	0.016
Hospitalization/Respiratory Death	1.60	1.17-2.18	0.003
Hospitalization/Any Death	1.51	1.17-1.95	0.001

Appropriate vs. Non-Appropriate Treatment	Multivariate		
	OR	**95% CI**	**p**
Any Death	0.12	0.02-0.90	0.040