Systemische Sklerose – Nachkontrolle und Therapie

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Disclosures

Consultancy relationship with and/or research funding from and/or speaker for the following companies in the area of potential treatments for fibrosis and its complications in the last three calendar years:

Abbvie, Acepodia, Aera, Amgen, Anaveon, Argenx, AstraZeneca, Avalyn, Boehringer Ingelheim, BMS, Calluna, Cantargia, Citus AG, Egle, EMD Serono, Galderma, Fimmcyte, Galderm, Galapagos, Generate Biomedicines, Hemetron, Innovaderm, Kali, Lilly, Mediar, Merck AG, One 30, Oorja Bio, Orion, Oxion, Pliant, Quell, Scleroderma Research Foundation, Skyhawk, Tandem, Topadur, UCB and Umlaut.bio.

Patent issued “mir-29 for the treatment of systemic sclerosis” (US8247389, EP2331143). Co-founder of CITUS AG.

The patient journey



Diagnosis



Screening Treatment



Follow up

ACR/EULAR criteria for the classification of systemic sclerosis (SSc)

Criteria	Sub-criteria	Score
Skin thickening of the fingers of both hands extending proximal to MCP joints		9
Skin thickening of the fingers *(count the higher of the two)*	Puffy fingers Whole Finger, distal to MCP	2 4
Fingertip lesions *(count the higher of the two)*	Digital Tip Ulcers Pitting Scars	2 3
Telangiectasia		2
Abnormal nailfold capillaries		2
Lung Involvement	Pulmonary arterial hypertension (on RHC) and/or Interstitial lung disease (on HRCT)	2
Raynaud's phenomenon		3
Scleroderma related antibodies	Any of anti-centromere, anti-topoisomerase I (anti-ScL 70), anti-RNA polymerase III	3

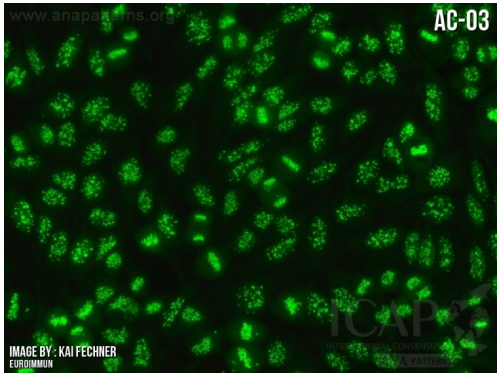
Total score of ≥ 9 is classified as SSc

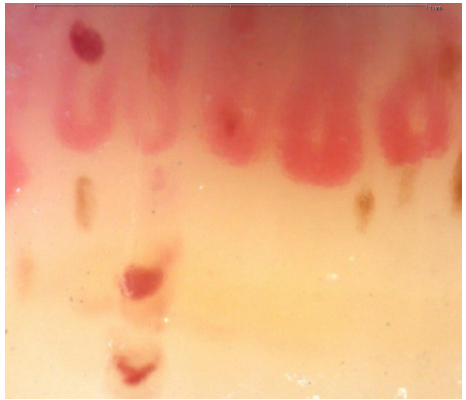
van den Hoogen F et al Ann Rheum Dis 2013; 72;1747-55 and Arthritis Rheum 2013, 65:2737-47.

Classification is not diagnosis: Pre-SSc/VEDOSS

- Raynaud phenomenon
- ANA/SSc-antibodies
- SSc-specific capillaroscopy changes
- Puffy fingers
- No skin fibrosis
- No organ involvement



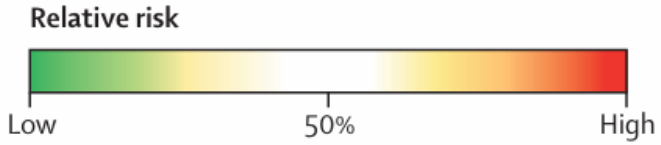






Risk factors to progress from pre-SSc into definitive SSc

Proportion fulfilling 2013 ACR–EULAR criteria		ANA	Ssc-Ab	SSc pattern on NVC	Puffy fingers
In the presence of	ANA	**58·9%**	70·2%	75·0%	79·0%
	SSc-Ab	70·2%	**70·2%**	82·2%	94·1%
	SSc-Ab pattern on NVC	75·0%	82·2%	**70·1%**	69·2%
	Puffy fingers	79·0%	94·1%	69·2%	**70·8%**
In the absence of	ANA	**10·8%**	31·0%	40·4%	47·5%
	SSc-Ab	31·0%	**31·0%**	41·9%	49·6%
	SSc-Ab pattern on NVC	40·4%	41·9%	**41·5%**	50·9%
	Puffy fingers	47·5%	49·6%	50·9%	**47·9%**



VEDOSS study, Del Galdo et al, Lancet Rheumatol 2021 Dec;3(12):e834-e843

The patient journey



Diagnosis

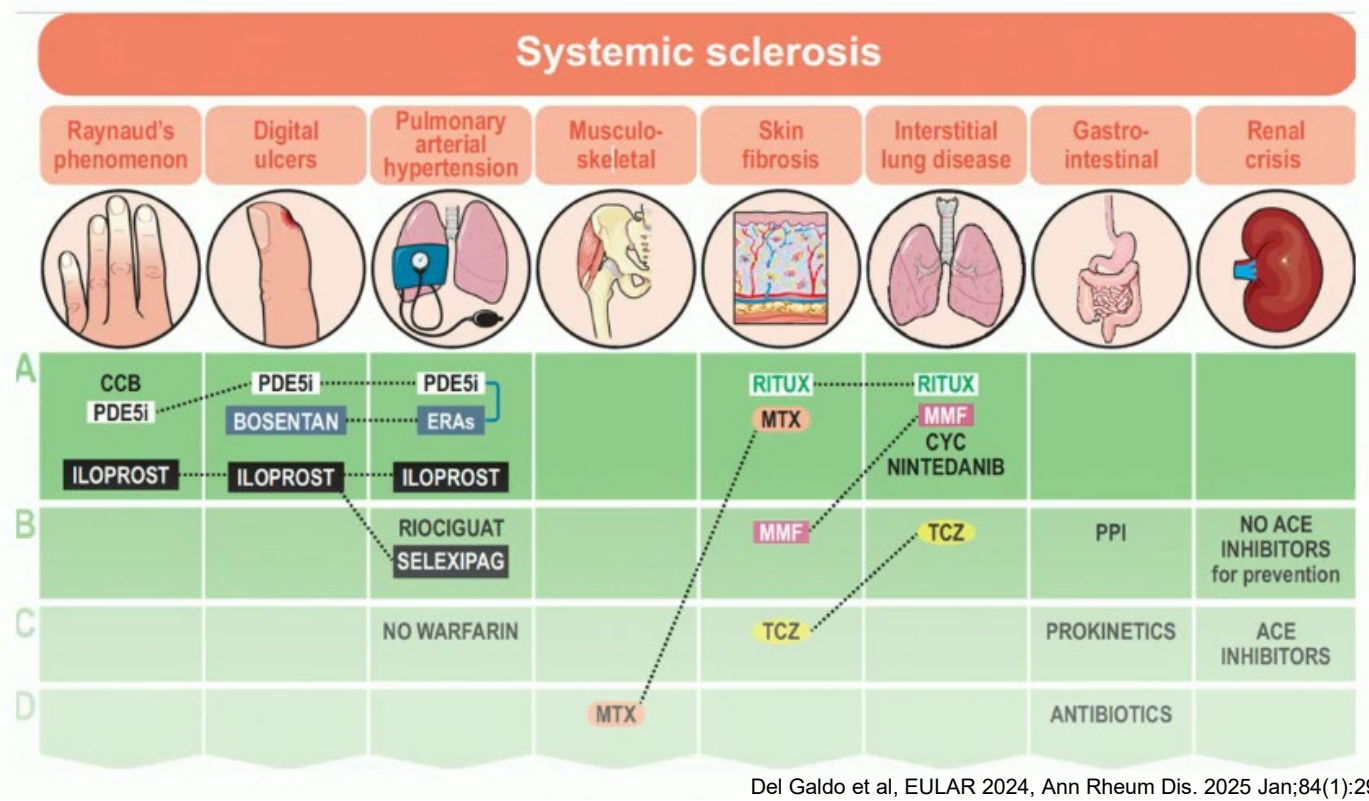


Screening Treatment



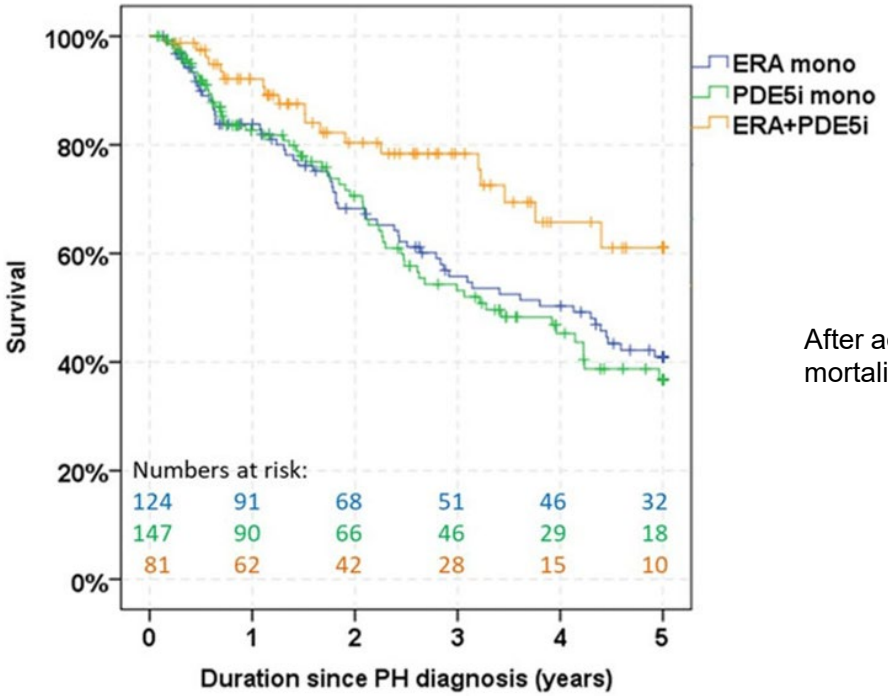
Follow up

Screening, risk assessment and treatment selection is organ-based



Del Galdo et al, EULAR 2024, Ann Rheum Dis. 2025 Jan;84(1):29-40

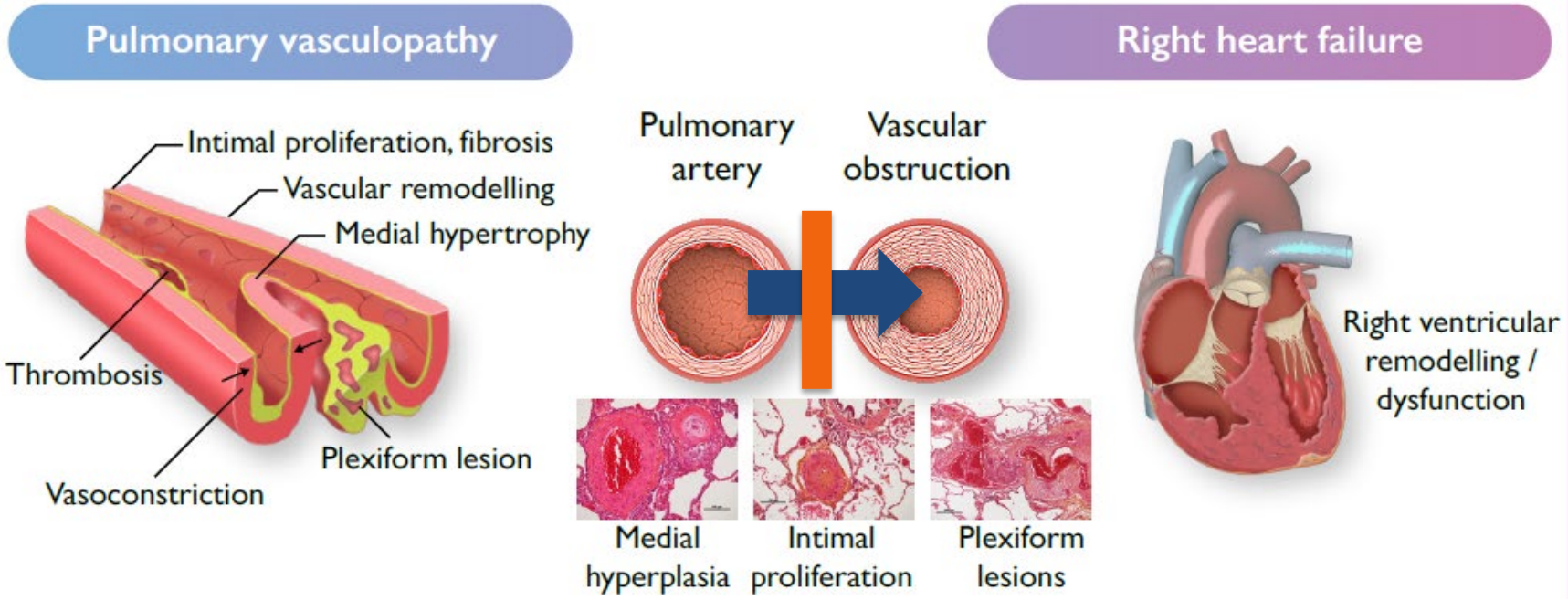
PAH is a deadly disease manifestation which can be treated



After adjustment for mortality confounders

Distler et al, Rheumatology, 2024, 63, 1139–1146

When pulmonary arterial hypertension becomes evident significant damage has already occurred



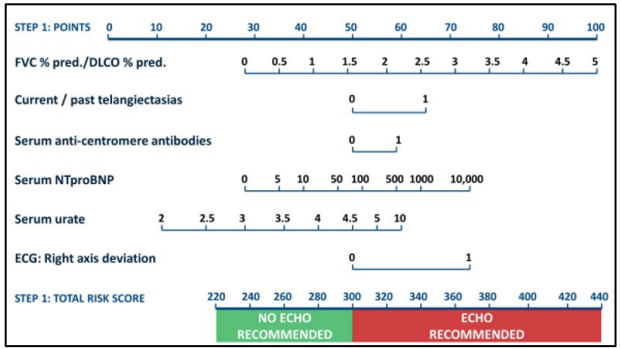
Humbert et al, European Heart Journal (2022) 00, 1–114

Different screening methods are available for early detection

Peak TRV (m/s)	Presence of other echocardiographic PH signs	Echocardiographic probability of PH
≤ 2.8 or not measurable	No	Low
≤ 2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
> 3.4	Not required	

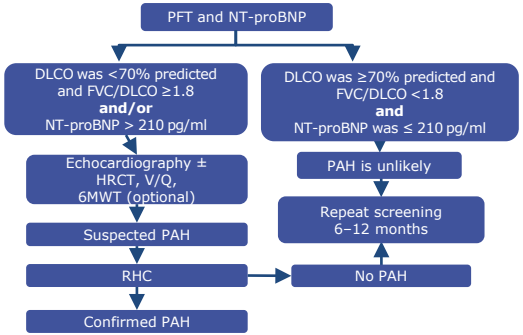
Echocardiography[1] (TTE)

ESC/ERS 2015 guidelines recommend the use of annual resting TTE as a screening test in asymptomatic patients with SSc and in symptomatic patients with other CTDs



DETECT[2]

A 2-step algorithm using non-echocardiographic and echocardiographic variables to screen for PH



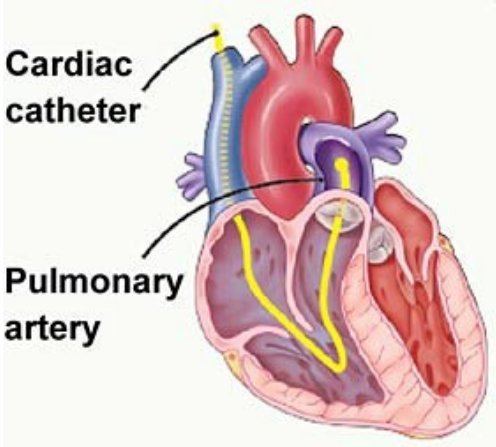
Australian Scleroderma Interest Group[4,5]

An Australia-wide screening program where enrolled patients were recommended to have PFTs, ECG, TTE, and NT-proBNP measurement; and if abnormal, RHC and 6MWD[4,5]

6MWD: 6-minute walk distance; CTD: connective tissue disease; DLCO: diffusing capacity for carbon monoxide; ECG: electrocardiogram; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAH: pulmonary arterial hypertension; PFT: pulmonary function test; PH: pulmonary hypertension; RHC: right heart catheterisation; SSc: systemic sclerosis; TRV: tricuspid regurgitation velocity; TTE: transthoracic echocardiography.

1. Galiè N, *et al. Eur Heart J* 2016; 37:67-119; 2. Coghlan JG, *et al. Ann Rheum Dis* 2014; 73:1340-9; 3. Hoffmann-Vold A, *et al. RMD Open* 2019; 5:e000826; 4. Morrisroe K, *et al. Arthritis Res Ther* 2017; 19:42; 5. Thakkar V, *et al. Arthritis Research & Therapy* 2013; 15:R193.

PAH must be diagnosed by right heart catheterization



Metric	Measurement Details	Diagnostic Threshold for PAH	Clinical Purpose
mPAP	Mean Pulmonary Artery Pressure	**> 20 mm Hg**	Confirms the presence of pulmonary hypertension (lowered from the historic ≥25 mm Hg threshold).
PAWP	Pulmonary Artery Wedge Pressure	**≤ 15 mm Hg**	Confirms the problem is "pre-capillary" (originating in the lungs, not due to left-heart failure).
PVR	Pulmonary Vascular Resistance	**> 2 Wood units**	Confirms true physical disease, narrowing, and structural remodeling of the lung's blood vessels.

Risk assessment in PAH- ESC/ERC guidelines

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	Repeated syncope[b]
WHO-FC	I, II	III	IV
6MWD[c]	>440 m	165–440 m	<165 m
CPET	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	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope >44
Biomarkers: BNP or NT-proBNP[d]	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI[e]	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m^2 SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m^2 SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 L/min/m^2 SVI <31 mL/m^2 SvO_2 <60%

Humbert et al, European Heart Journal (2022) 00, 1–114

Simplified 4-strata risk model from COMPERA

TABLE 1 Criteria for refined risk stratification in the three-stratum model and the four-stratum model based on World Health Organization functional class (WHO FC), 6-min walk distance (6MWD) and brain natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP)

	Points assigned			
	1	2	3	4
Three-stratum model				
WHO FC	I or II	III	IV	
6MWD, m	>440	440–165	<165	
BNP,# ng·L^{-1}	<50	50–800	>800	
NT-proBNP,# ng·L^{-1}	<300	300–1100	>1100	
Four-stratum model				
WHO FC	I or II		III	IV
6MWD, m	>440	440–320	319–165	<165
BNP,# ng·L^{-1}	<50	50–199	200–800	>800
NT-proBNP,# ng·L^{-1}	<300	300–649	650–1100	>1100

Hoeper et al, Eur Respir J 2022; 60: 2102311

How we do risk-assessment in SSc-PAH

ESC/ERS four-strata model[19,21]

- ✓3 risk parameters (minimum WHO-FC/6MWD and NT-proBNP/BNP)
- ✓Risk parameters graded 1-4
- ✓The mean score defines four risk groups

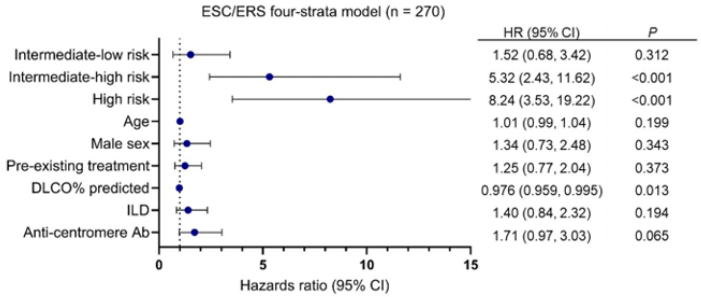
Risk parameters:

- WHO-FC
- 6MWD
- NT-proBNP/BNP

Mean score:

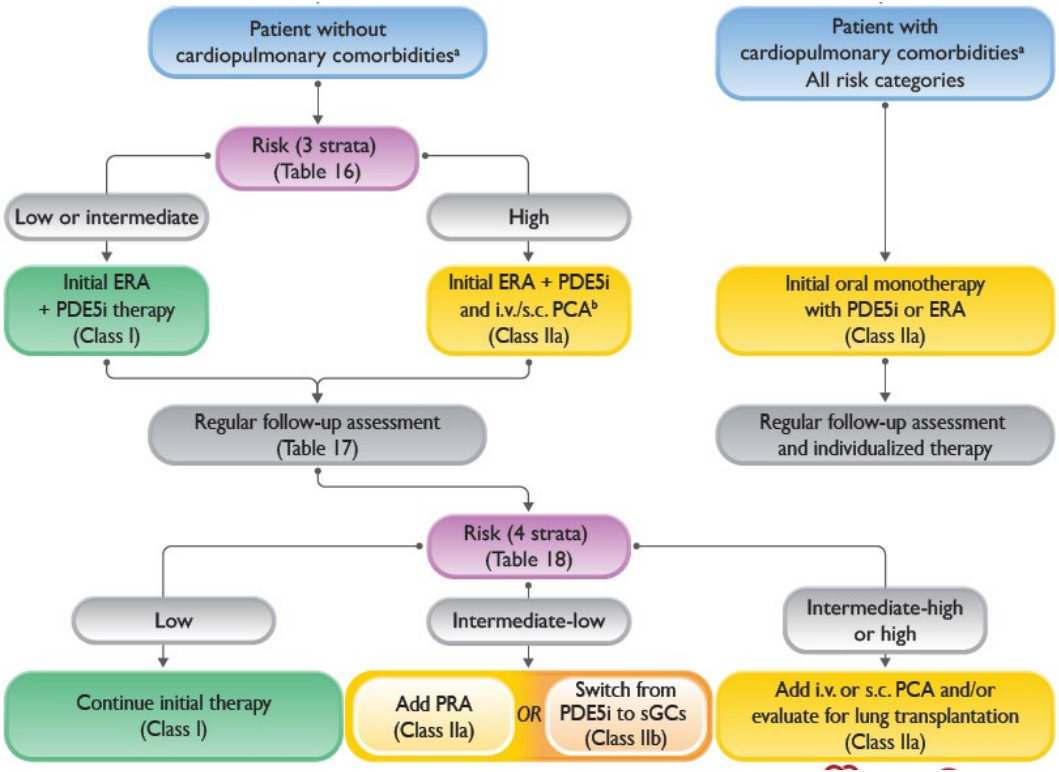
1.0 - 1.49 =	Low risk
1.5 - 2.49 =	Intermediate-low risk
2.5 - 3.49 =	Intermediate-high risk
≥ 3.5 =	High risk

Mortality



Bjørkekjær et al, Rheumatology, 2025, 00, 1–14

Treatment algorithm for PAH (ESC/ERS Guidelines)

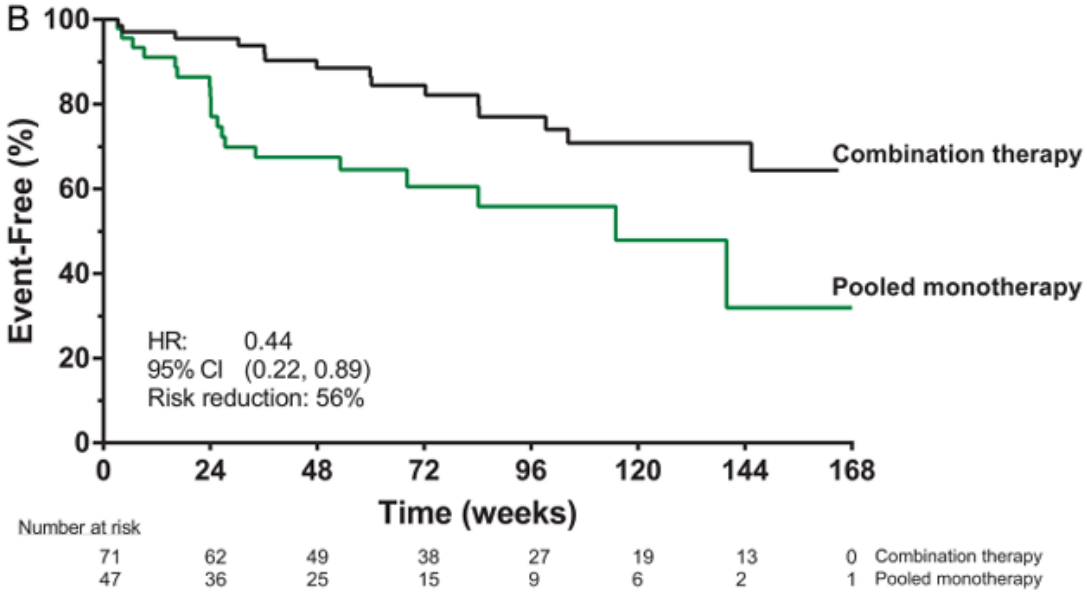


Cardiopulmonary comorbidities are conditions associated with an increased risk of left ventricular diastolic dysfunction, and include obesity, hypertension, diabetes mellitus, and coronary heart disease

Humbert et al, European Heart Journal (2022) 00, 1–114

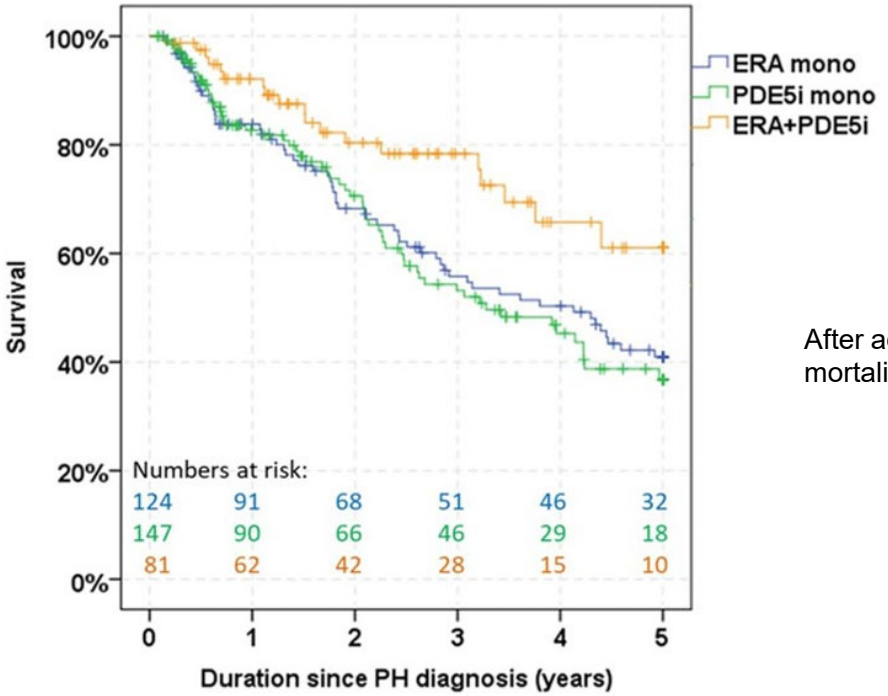
Why combination therapy? SSc-PAH from AMBITION

death, hospitalisation for worsening PAH, disease progression or unsatisfactory long-term clinical response



Coghlan et al, Ann Rheum Dis. 2017 Jul;76(7):1219-122

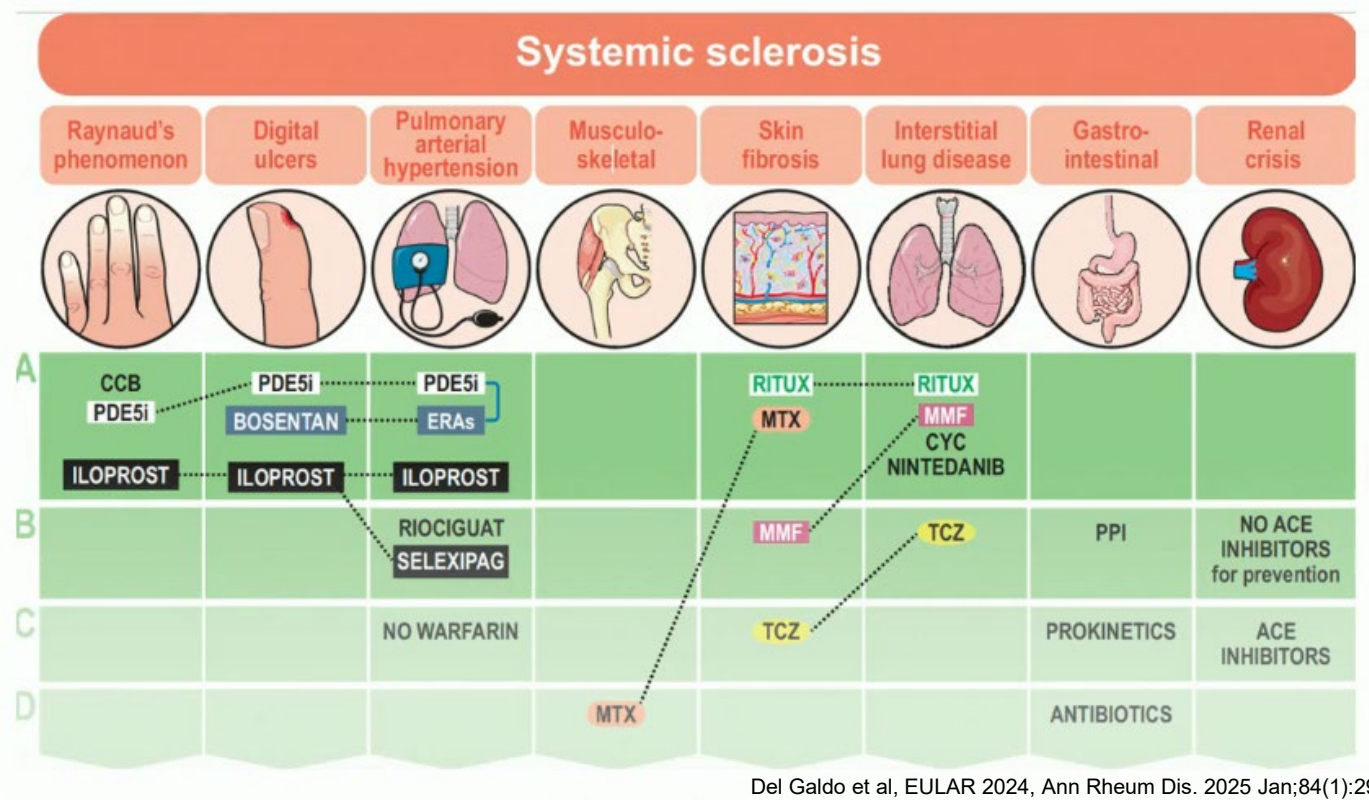
Combination therapy true in real-life? Better long-term survival with combination therapy



After adjustment for mortality confounders

Distler O et al, Rheumatology, 2024, 63, 1139–1146

Screening, risk assessment and treatment selection is organ-based



Del Galdo et al, EULAR 2024, Ann Rheum Dis. 2025 Jan;84(1):29-40

The patient journey



Diagnosis

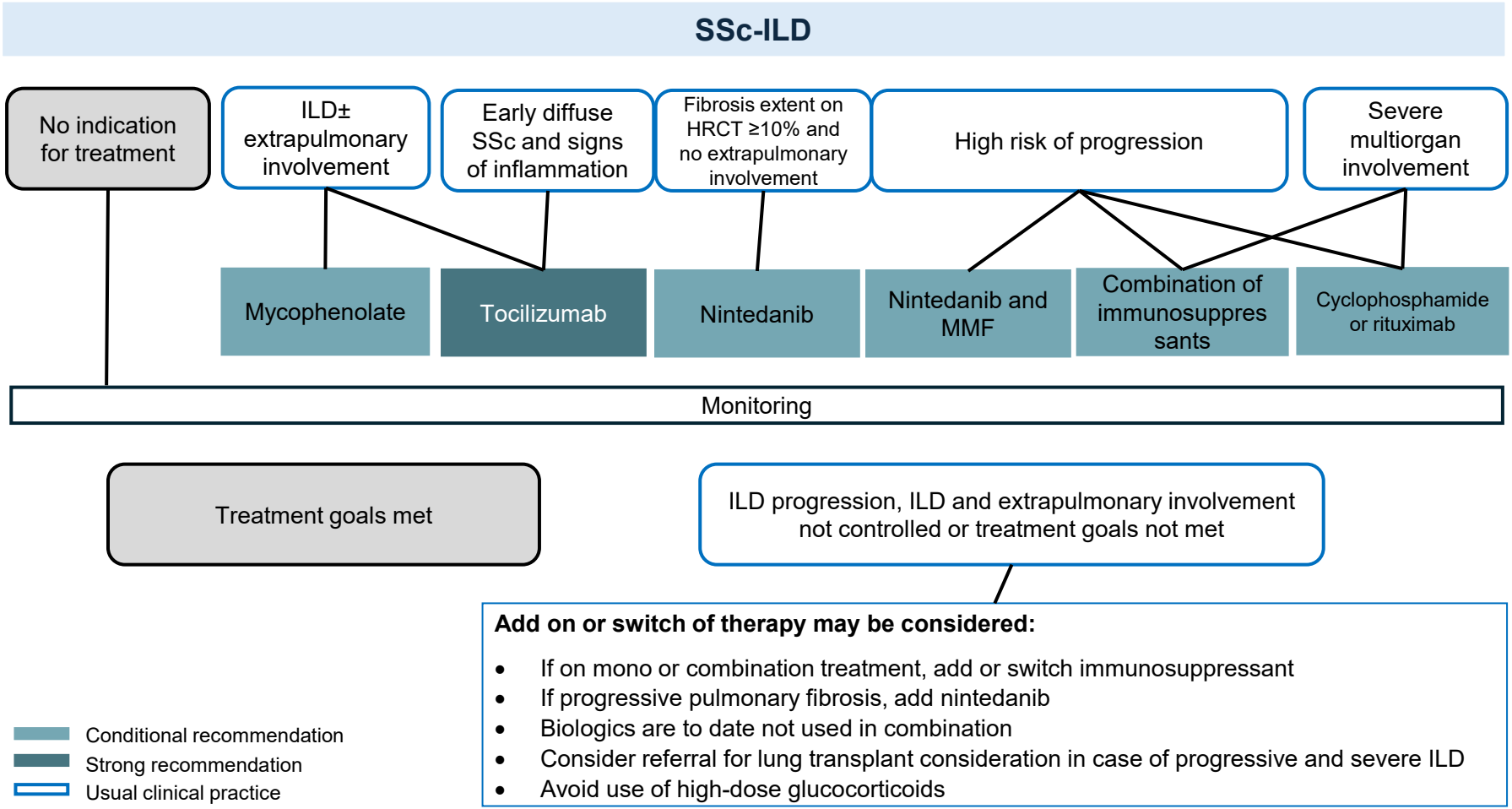


Screening Treatment



Follow up

Treatment of ILD in SSc



The concept of ILD progression

PFT criteria

FVC decline ≥5%

FVC decline ≥5-9% and DLCO decline ≥10/15%

FVC decline ≥10% over 12 months

PPF guideline criteria[1]

Worsening in 2/3 domains over 12 months:

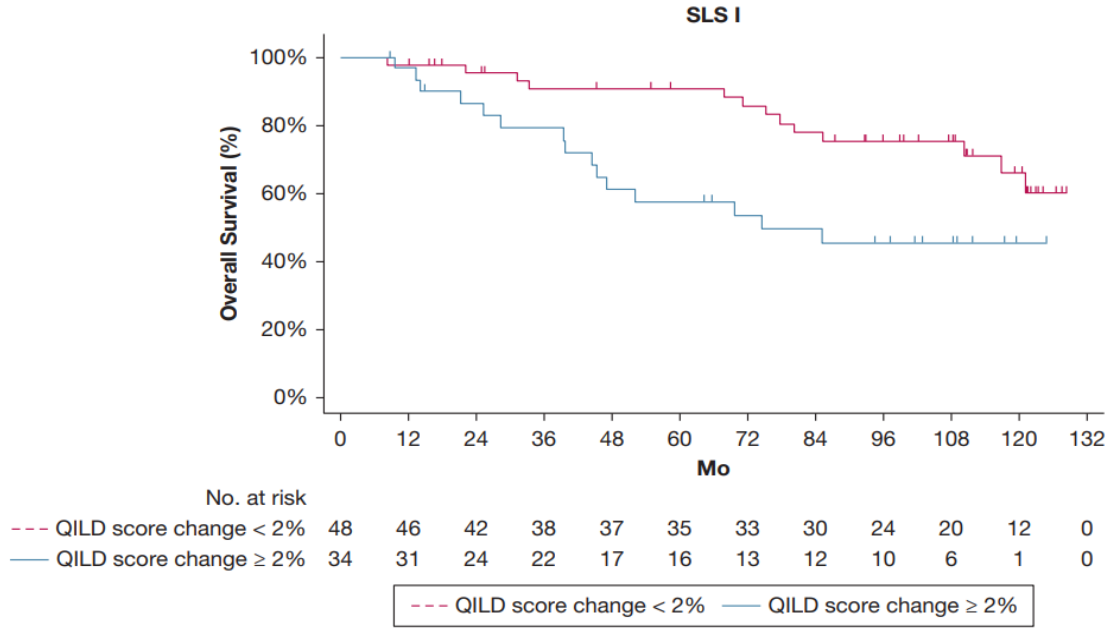
1. Respiratory symptoms
2. Absolute decline in FVC >5% or in DLCO >10%
3. Radiological disease progression

PF-ILD INBUILD[2]

Worsening within 24 months:

1. Relative FVC decline ≥10%
2. Relative FVC decline 5-9% and worsening of respiratory symptoms or increased lung fibrosis on HRCT
3. Worsening of respiratory symptoms and increased lung fibrosis

Minor ILD progression on HRCT is associated with mortality

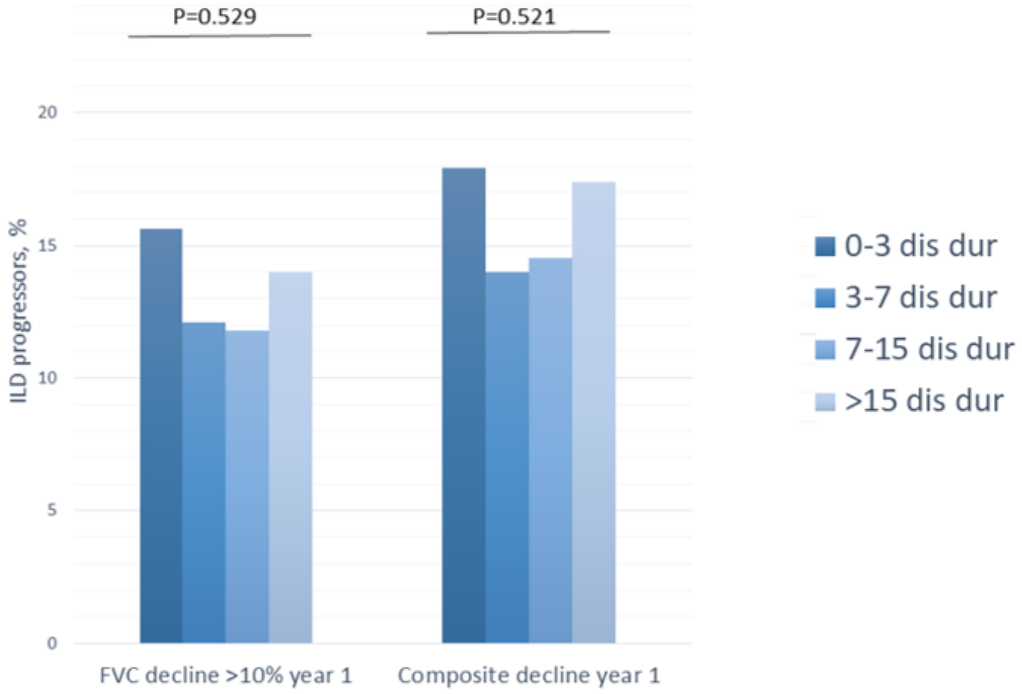


Overall survival for participants with ≥2% vs < 2% increase in QILD score for entire lung from baseline to 12 months in SLS I.
QILD = quantitative interstitial lung disease,

Volkmann ER et al. Chest 2022;161:1310-1319

Progression and damage start early and continue into late stages of SSc-ILD

2259 patients with SSc-ILD from EUSTAR database



Hoffmann-Vold AM et al. POS0063 Abstract presented at EULAR 2022

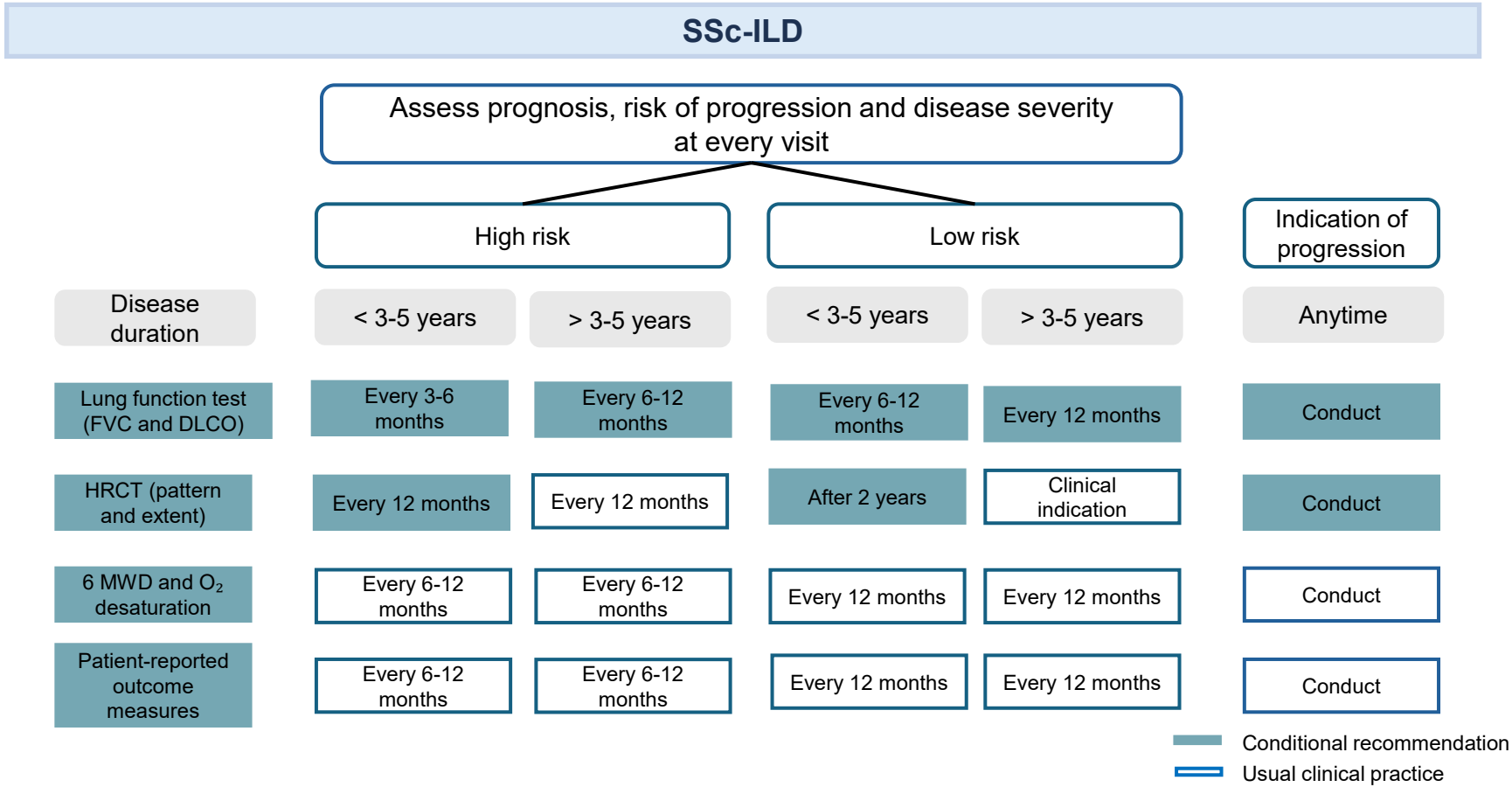
Data from SENSCIS and INBUILD suggest patients with SSc-ILD and RA-ILD should be monitored more frequently than annually

Proportions of patients with ILD progression (absolute decline in FVC % predicted ≥5% or death) in placebo groups

	Week						
	2	4	6	12	24	36	52
Patients with SSc-ILD in SENSCIS (n=288)	7.6	11.1	11.1	16.3	25.0	30.9	36.5
Patients with RA-ILD in INBUILD (n=47)	12.8	12.8	25.5	23.4	40.4	51.1	55.3

Hoffmann, Distler et al, ACR 2024

Monitoring of ILD in SSc



Take home

- Diagnosis is not application of classification criteria
- Screening, diagnosis, risk assessment and treatment selection is organ based
- PAH as an example:
  - DETECT et al for screening
  - Diagnosis with right heart catheterization
  - 4 strata model for risk assessment
  - upfront combination therapy
- Follow up: Based on risk assessment