# «Πνευμονικές εκδηλώσεις στη Συστηματική Σκληροδερμία: αντιμετώπιση στο εξωτερικό / ιδιωτικό ιατρείο»

**Στυλιανός Πανόπουλος**

Ρευματολόγος

Α’ Προπαιδευτική Παθολογική Κλινική, ΓΝΑ «ΛΑΙΚΟ»

- Δεν υπάρχει σύγκρουση συμφερόντων

# Pulmonary complications in Systemic Sclerosis

- Interstitial lung disease
- Pulmonary Hypertension

- Pleural effusion
- Malignancy
- Pulmonary aspirations

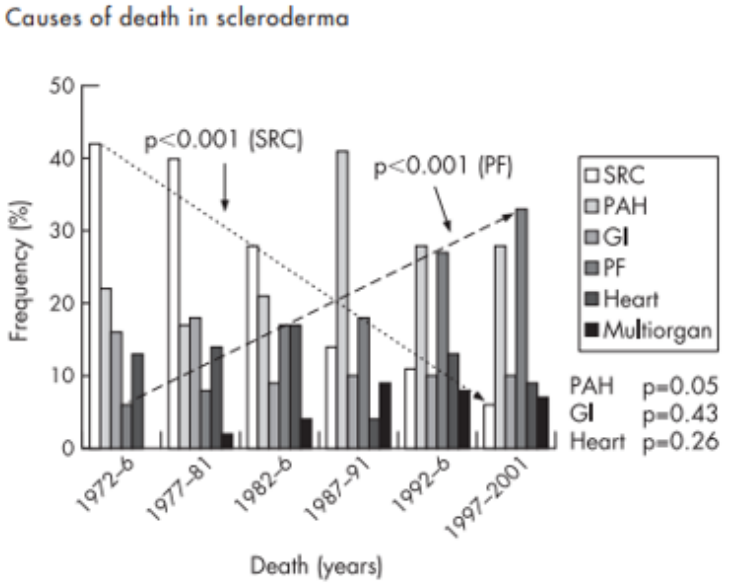
- Other rare conditions

# Interstitial lung disease

- ILD findings evident in HRCT in up to 80% of SSc patients (autopsy up to 90%)
- 30–40% of patients will develop clinically significant ILD
- ILD in most cases within the first 3 years of SSc diagnosis

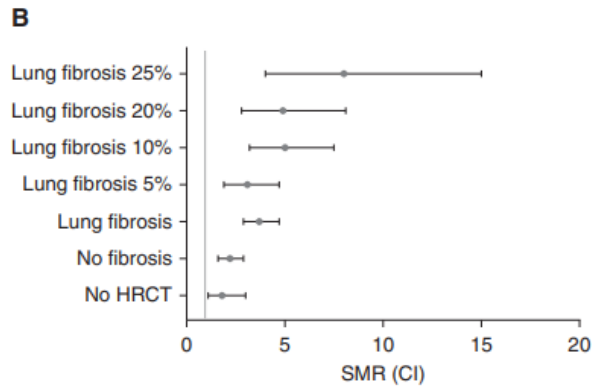
1st SSc-related cause of death (35% of SSc-related deaths)

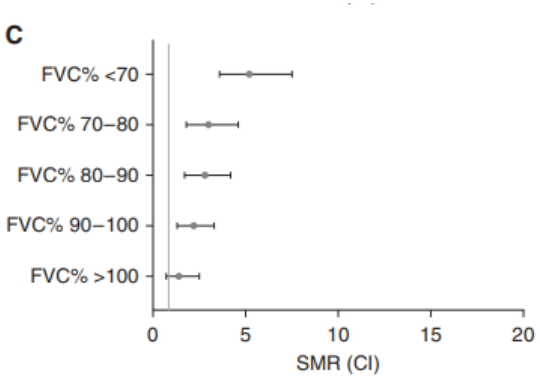
- 2 to 3-fold incrased mortality risk in case of SSc-ILD
  6-fold increased risk in case of ILD+PH

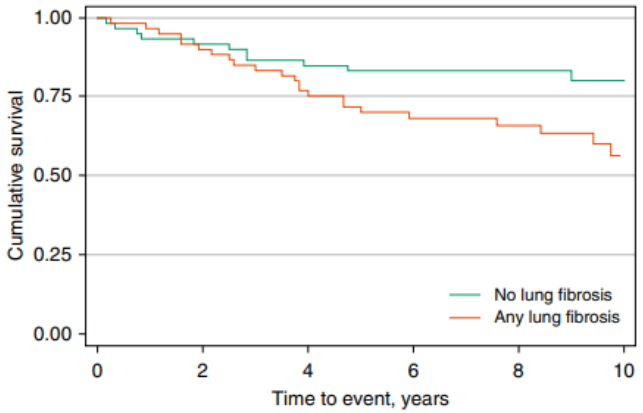


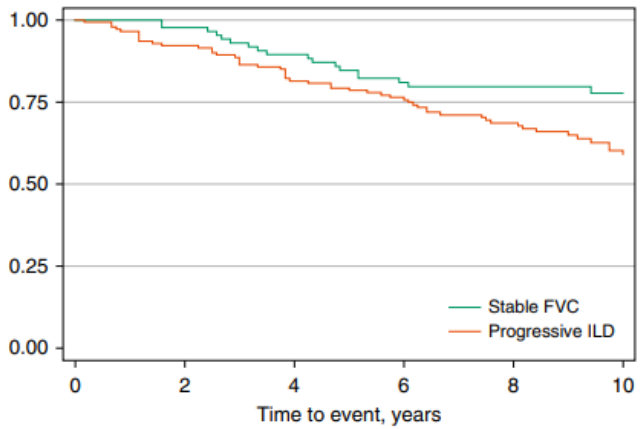
# Delay in diagnosis affects survival

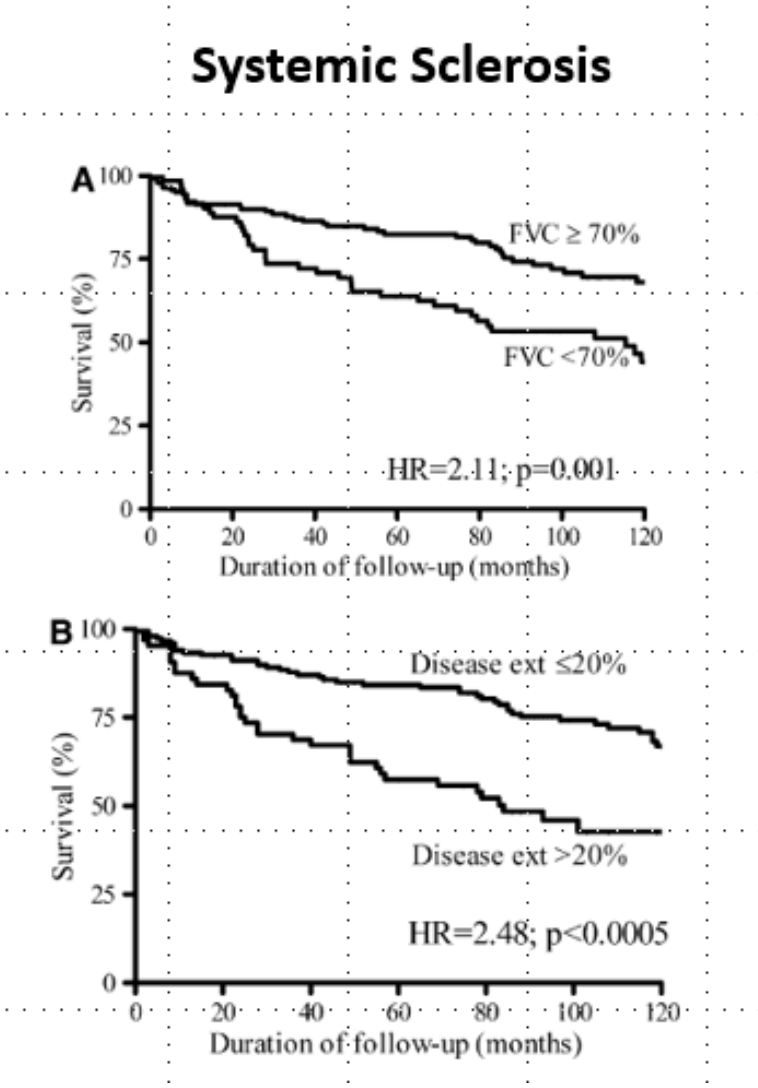
Impact of ILD in Systemic Sclerosis in the entire SSc Norwegian cohort




Hofmmann-Vold et al. Am Jour Resp Med Crit Care.2019;200:1258-1266

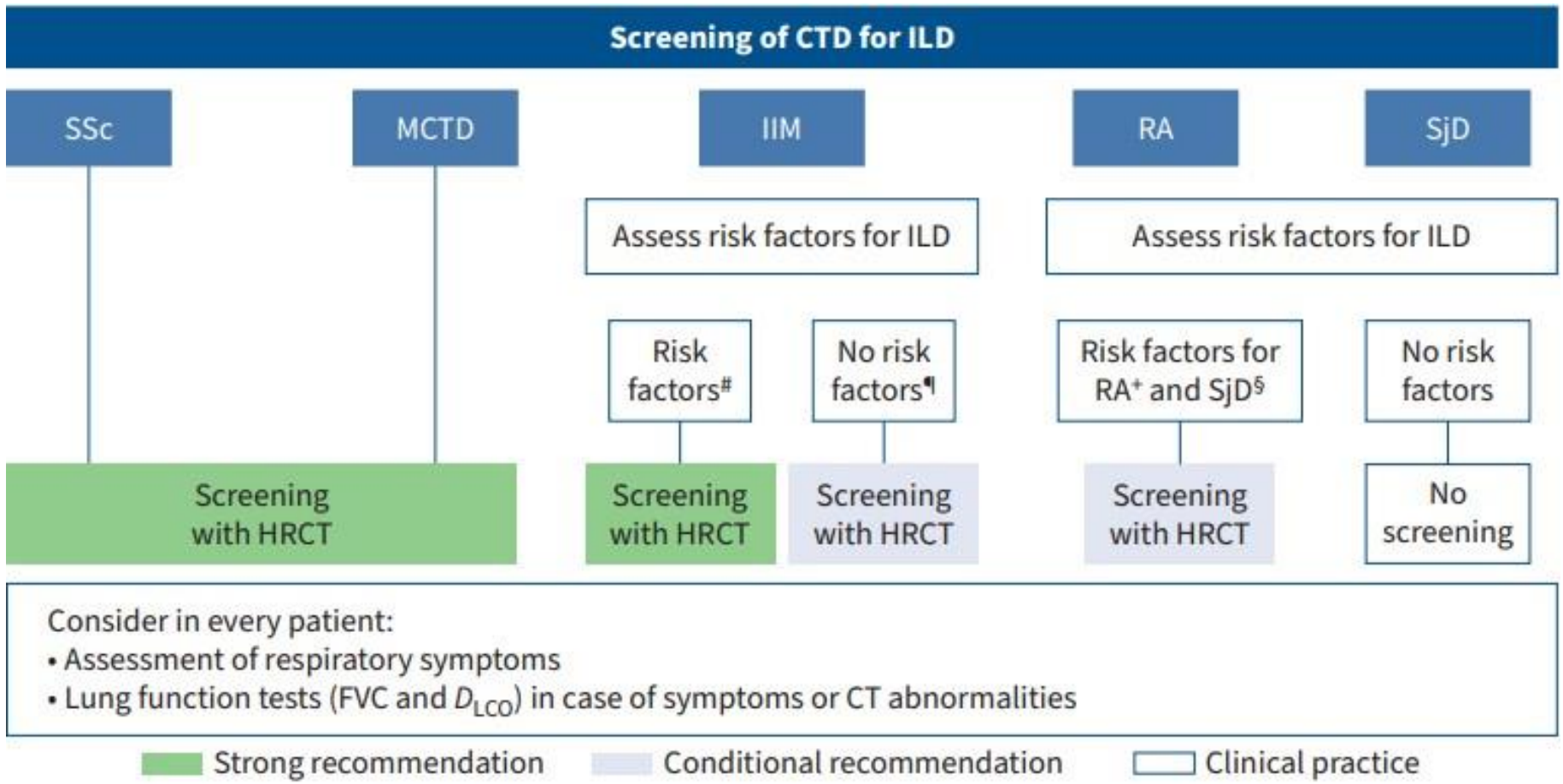
Jakob et al. Eur Respir J 2019

# ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease

Developed by the task force for connective tissue disease-associated interstitial lung disease of the European Respiratory Society (ERS) and the European Alliance of Associations for Rheumatology (EULAR)

Endorsed by the European Reference Network on rare respiratory diseases (ERN-LUNG)

Katerina M. Antoniou[1,36], Oliver Distler[2,36], Ana-Maria Gheorghiu[3], Catharina C. Moor[4], Jens Vikse[5,6,7],

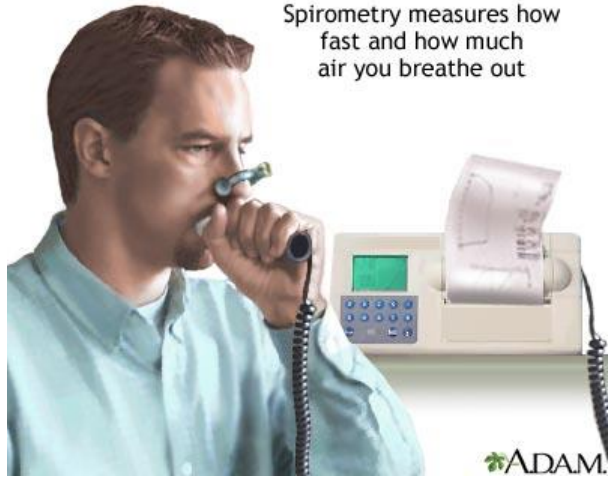


# Λειτουργικές αναπνευστικές δοκιμασίες

- **Σπιρομέτρηση**
- **FVC (βιαίως ζωτική χωρητικότητα): Μείωση της σημαίνει περιοριστική νόσο**

  φ.τ >80% της προβλεπόμενης

  κλινικά σημαντική μεταβολή >10%

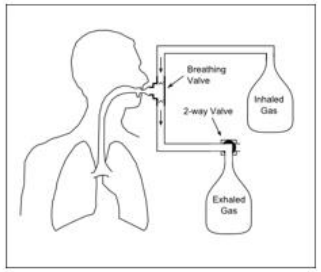


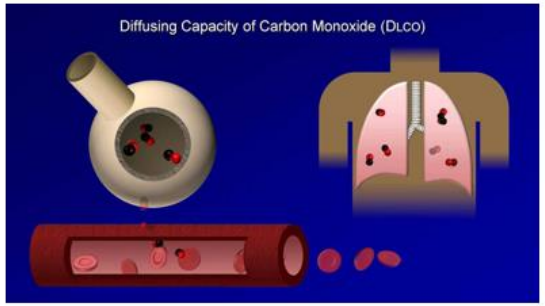

- DLCO (διαχυτική ικανότητα για CO): Η πιο ευαίσθητη και πρωιμότερα επηρεαζόμενη

  φ.τ>70% της προβλεπόμενης

  κλινικά σημαντική μεταβολή > 15%

- **Εξαρτάται τόσο από τη λειτουργία των κυψελίδων όσο και από αυτή των τριχοειδών**



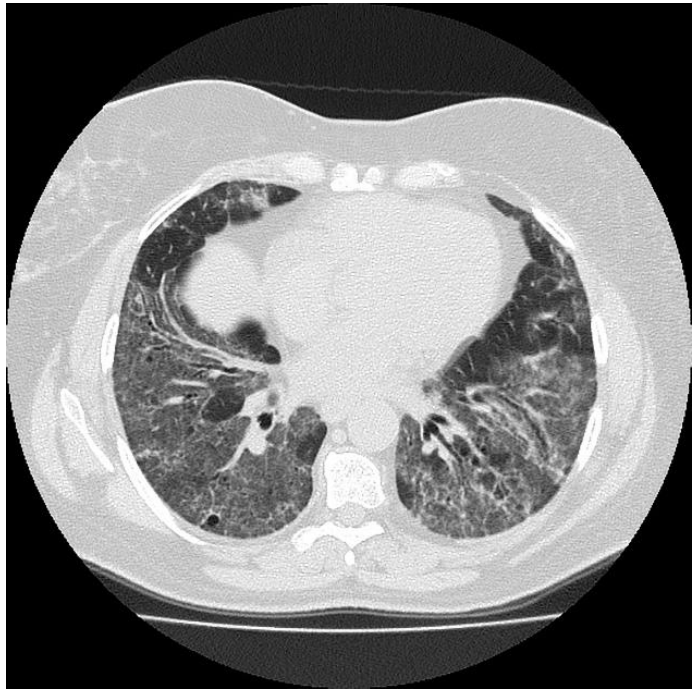

- **δυσανάλογα μεγάλη ή μεμονωμένη μείωση της DLCO σε σχέση με της FVC (FVC/DLCO>1.5) μπορεί να υποδηλώνει παρουσία πνευμονικής υπέρτασης**

# NSIP

- Το πιο συχνό πρότυπο, 65%
- **Εικονα θαμβής υάλου (ground glass)**
- αυξημένη κυτταρική συμμετοχή
- συνήθως ενεργός κυψελιδίτιδα (πάχυνση του τοιχώματος

των κυψελίδων)

- δυνητικά αντιμετωπίσιμη



# UIP

- Εμφανίζεται σε ποσοστό 25%
- **Εικονα μελισσοκυρήθρας (honeycombing) και βρογχιεκτασιων** εξ΄έλξεως
- ινοβλαστικές εστίες με μικρή ή μέτρια φλεγμονή
- Αντικατάσταση λειτουργικού παρεγχύματος από ινώδη ιστό
- στο μεγαλύτερο βαθμό μη αναστρέψιμη

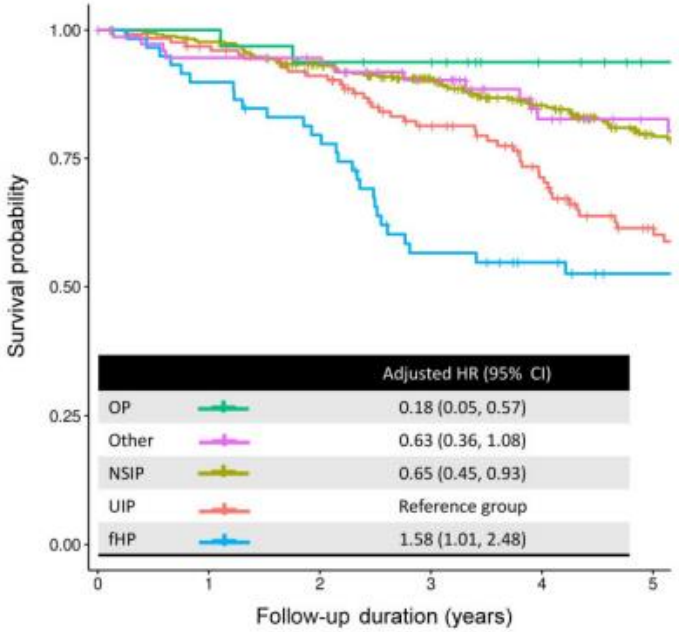
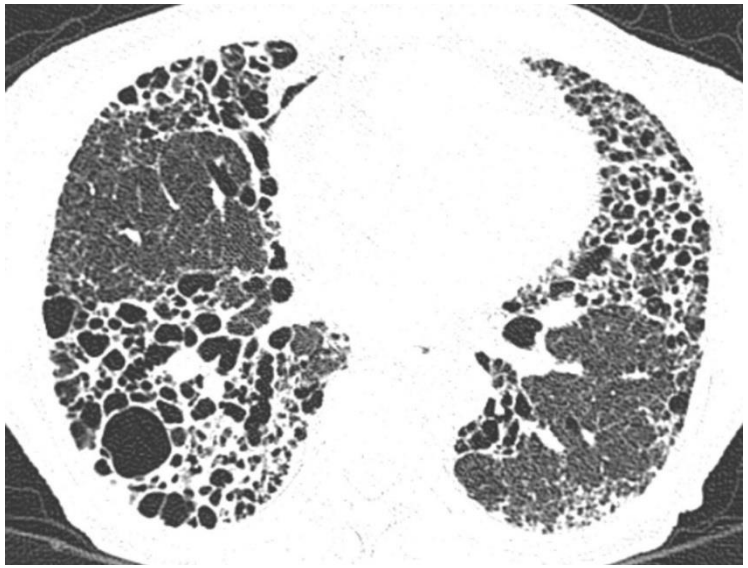



**Figure 3.** Mortality in CTD-ILD stratified by imaging pattern. Adjusted HR,

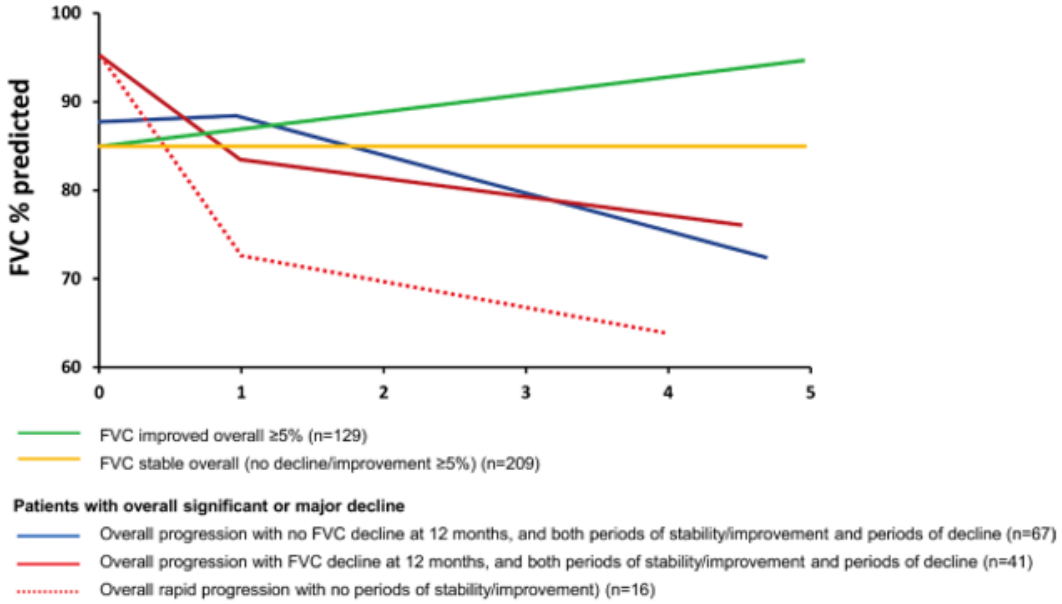


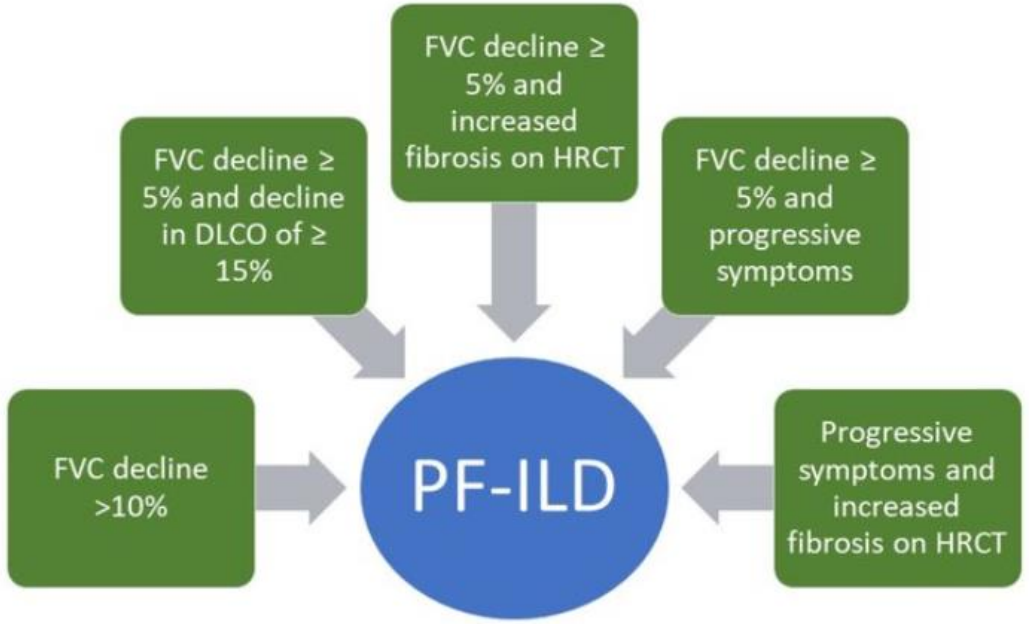
# Progression of CTD-ILD

826 patients with SSc-ILD.
Over 12±3 months, 219 (27%) showed progressive ILD

5-year follow-up.

- 58% had a pattern of slow lung function decline
- **8% showed rapid, continuously declining FVC**




Hoffmann-Vold A-M, et al. Ann Rheum Dis 2021;80:219–227
Flaherty et al. Eur Respir J 2022; 59: 2004538

# Predictors of ILD progression

**TABLE 4** Risk factors for poor outcome, defined as disease progression and death, in patients with connective tissue disease (CTD)-associated interstitial lung disease (ILD) and rheumatoid arthritis (RA)-associated ILD

| | SSc[#] | RA[#] | IIM[#,¶] |
|---|---|---|---|
| **Demographics** | • Older age<br>• Male sex<br>• African American ethnicity | • Older age at RA onset<br>• Male sex | |
| **Circulating markers** | • Elevated ESR, CRP<br>• ATA-I | • Anti-CCP, RF | • Elevated ferritin<br>• Anti-MDA-5, anti-synthetase |
| **Pulmonary function/markers** | • Baseline PFTs (FVC, $D_{LCO}$) | • Baseline PFTs (low FVC and/or $D_{LCO}$) | |
| **Imaging/histology** | • Higher extent of ILD on HRCT | • UIP and probable UIP HRCT/histological patterns<br>• Higher extent of ILD on HRCT | • Higher extent of ILD on HRCT and ILD pattern on HRCT |
| **Extrapulmonary involvement** | • Recent onset of SSc with rapid skin progression, more extensive skin fibrosis (mRSS) | • Higher articular disease activity | |

Antoniou et al. European Respiratory Journal 2026 67(1): 2402533

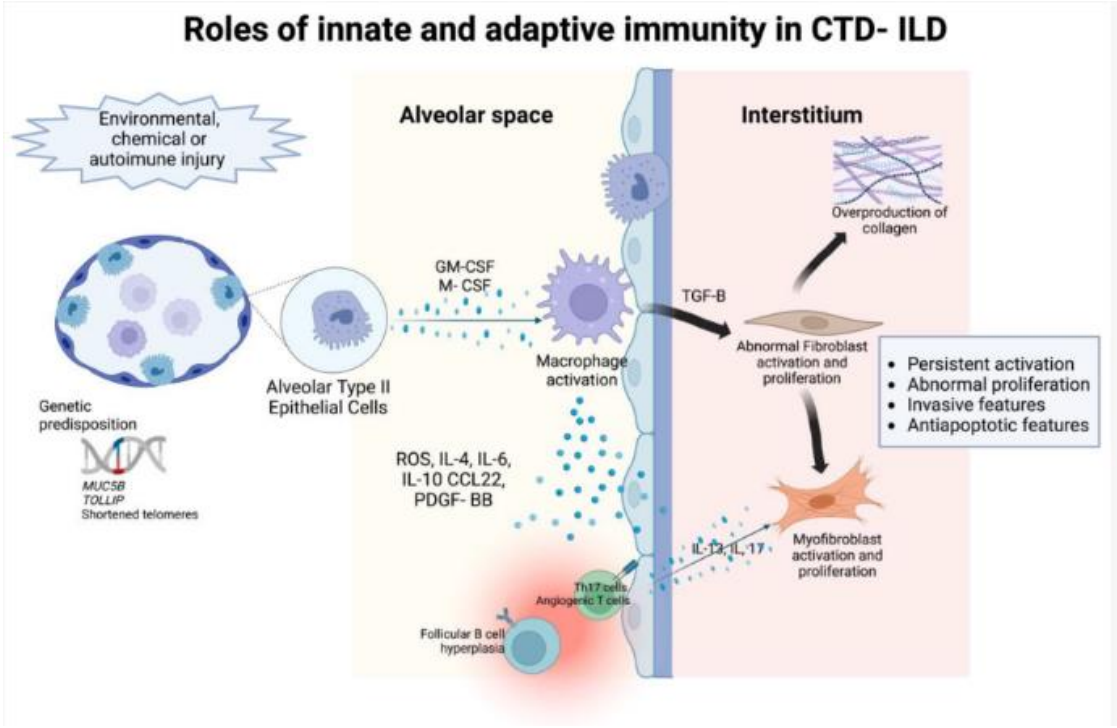
# Monitoring of SSc-ILD


Antoniou et al. European Respiratory Journal 2026 67(1): 2402533

# Available treatments for SSc-ILD

**Immunosuppressives**

- Cyclophosphamide - Scleroderma Lung Study I (SLS I)
- Mycophenolate – SLS II
- Tocilizumab – FocuSSced/FaSScinate
- Rituximab- Recital/Desires




**Antifibrotic**

- Nintedanib- Sencis
- Nerandomilast - Fibroneer

- Autologous Stem Cell Transplantation - SCOT, ASTIS (SSc)

- Cell Therapies

Contents lists available at ScienceDirect

Annals of the Rheumatic Diseases

journal homepage: https://www.sciencedirect.com/journal/annals-of-the-rheumatic-diseases

Systemic sclerosis

# Post hoc comparison of the effectiveness of tocilizumab, rituximab, mycophenolate mofetil, and cyclophosphamide in patients with SSc-ILD from the EUSTAR database

957 SSc pts
1 year follow-up

comparable efficacy of TCZ, RTX, MMF, and CYC on FVC change in SSc-ILD

Table 3

**Paired comparisons of tocilizumab, rituximab, mycophenolate mofetil, and cyclophosphamide effectiveness***

**Change in FVC% predicted from baseline to follow-up**

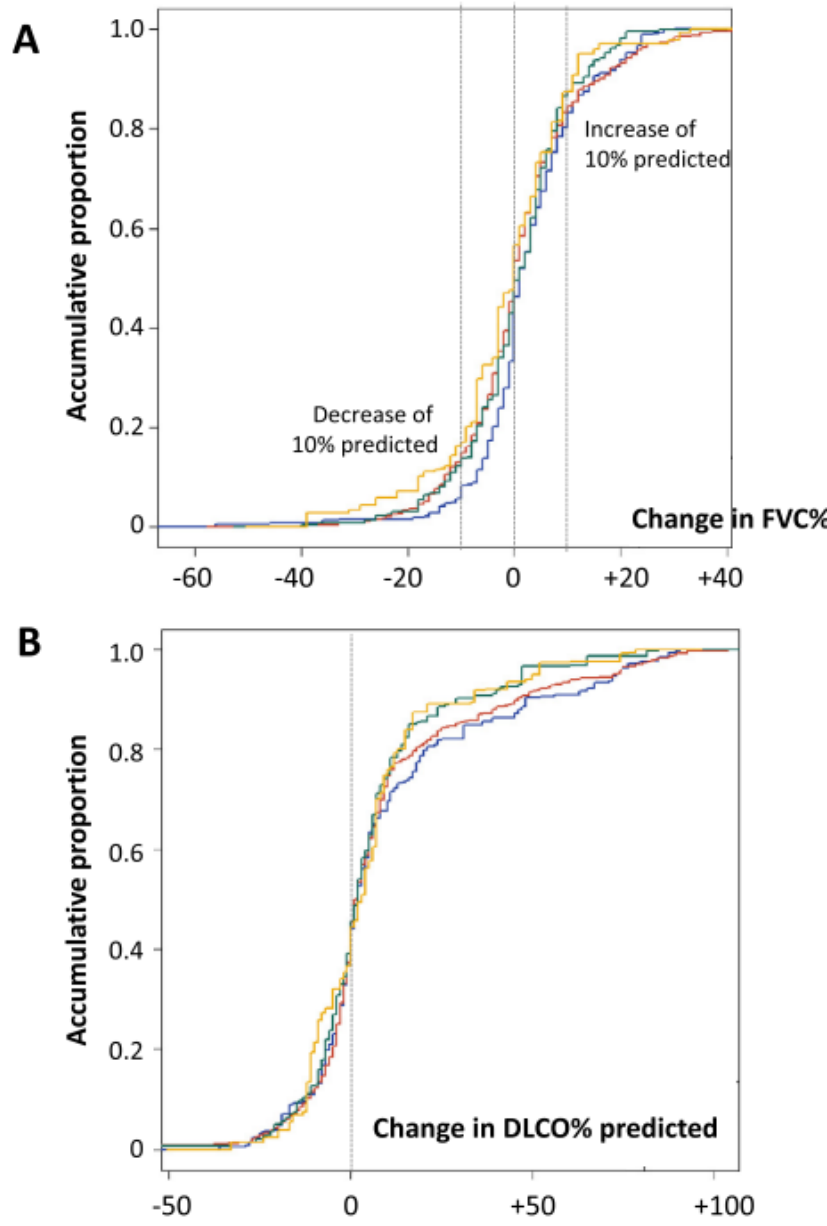
| | Estimate mean difference | SE | 95% CI | | | Adjusted *P* value† |
|---|---|---|---|---|---|---|
| MMF vs CYC | −1.46 | 0.92 | −3.27 | to | 0.36 | .462 |
| CYC vs TCZ | 3.94 | 1.81 | 0.40 | to | 7.48 | .116 |
| MMF vs TCZ | 2.49 | 1.73 | −0.91 | to | 5.89 | .606 |
| CYC vs RTX | 1.95 | 1.16 | −0.32 | to | 4.23 | .372 |
| MMF vs RTX | 0.49 | 1.05 | −1.56 | to | 2.55 | 1.000 |
| TCZ vs RTX | −2.00 | 1.87 | −5.66 | to | 1.67 | 1.000 |

**Change in DLCO% predicted from baseline to follow-up**

| | Estimate mean difference | SE | 95% CI | | | Adjusted *P* value |
|---|---|---|---|---|---|---|
| MMF vs CYC | −1.63 | 2.32 | −6.17 | to | 2.91 | 1.000 |
| CYC vs TCZ | 4.86 | 3.07 | −1.17 | to | 10.88 | .458 |
| MMF vs TCZ | 3.23 | 2.59 | −1.86 | to | 8.31 | .856 |
| CYC vs RTX | 5.07 | 3.03 | −0.87 | to | 11.00 | .378 |
| MMF vs RTX | 3.44 | 2.54 | −1.54 | to | 8.42 | .705 |
| TCZ vs RTX | 0.21 | 3.24 | −6.15 | to | 6.57 | 1.000 |

**Change in mRSS from baseline to follow-up**

| | Estimate mean difference | SE | 95% CI | | | Adjusted *P* value |
|---|---|---|---|---|---|---|
| MMF vs CYC | −0.87 | 0.61 | −2.07 | to | 0.32 | .602 |
| CYC vs TCZ | 1.90 | 1.01 | −0.08 | to | 3.87 | .241 |
| MMF vs TCZ | 1.02 | 0.95 | −0.84 | to | 2.88 | 1.000 |
| CYC vs RTX | −0.16 | 0.79 | −1.71 | to | 1.38 | 1.000 |
| MMF vs RTX | −1.04 | 0.71 | −2.44 | to | 0.36 | .583 |
| TCZ vs RTX | −2.06 | 1.07 | −4.17 | to | 0.05 | .222 |



# Nerandomilast for progressive pulmonary fibrosis

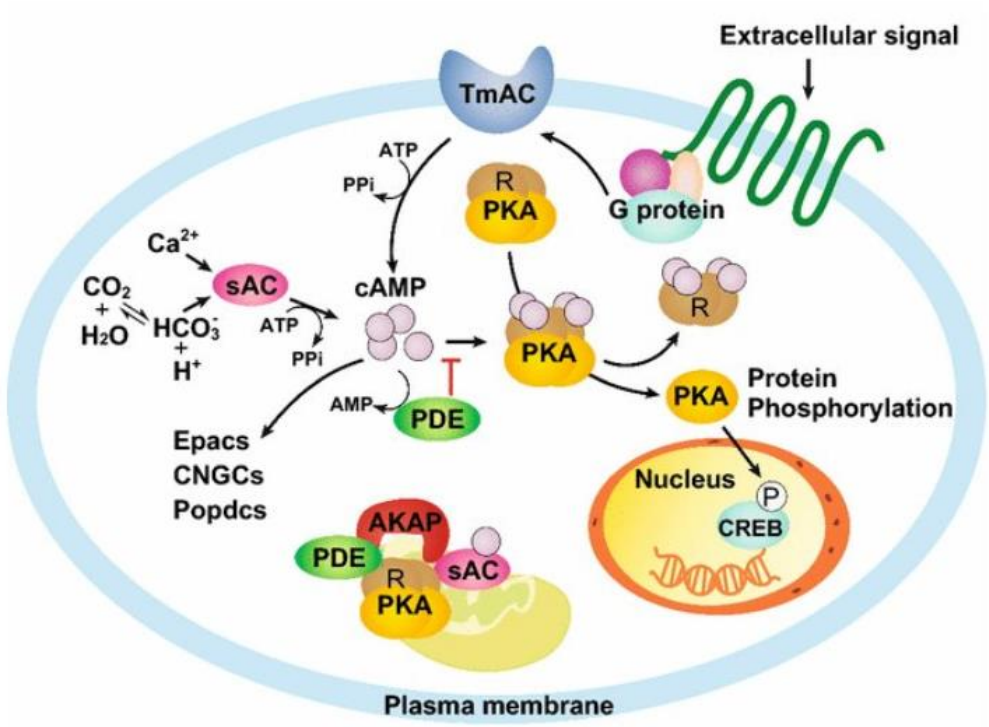
- oral, selective inhibitor of phosphodiesterase 4B (PDE4B)

~9 times higher selectivity for PDE4B vs. PDE4D, ~24.8 times higher vs. PDE4A and ~870 times higher vs. PDE4C

Less AEs compared to pan-inhibition of PDE4

- antifibrotic and immunomodulatory properties

- In lung fibroblasts from patients with IPF, addition of Nintedanib to nerandomilast, showed an approximately 10-fold synergistic inhibitory effect on the proliferation of fibroblasts and the expression of collagen A1



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Nerandomilast in Patients with Progressive Pulmonary Fibrosis

Toby M. Maher, M.D.,[1,2] Shervin Assassi, M.D.,[3] Arata Azuma, M.D.,[4,5]

- 1176 patients with PPF
- 43.5% on background nintedanib therapy
- 30% CTD-ILD

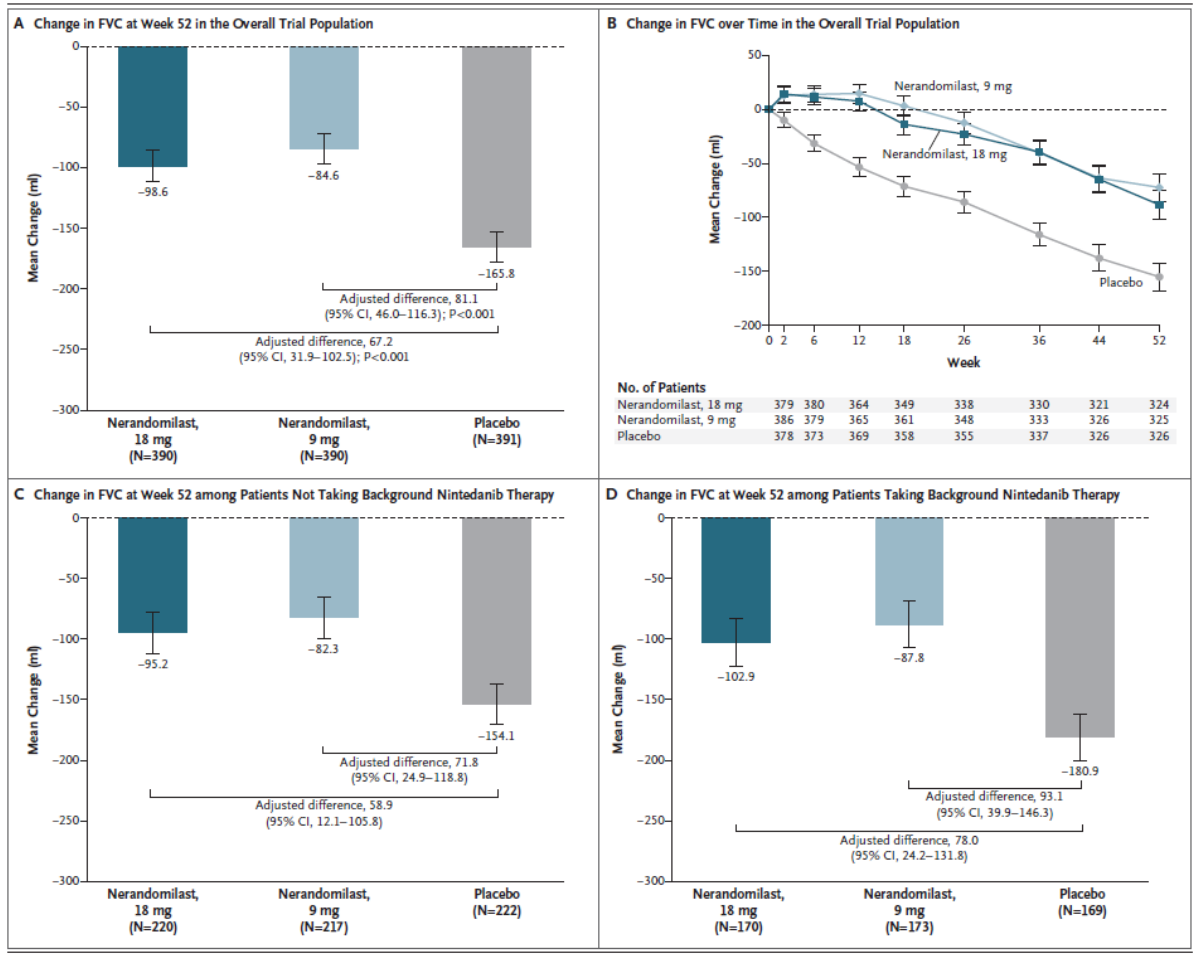
primary end point

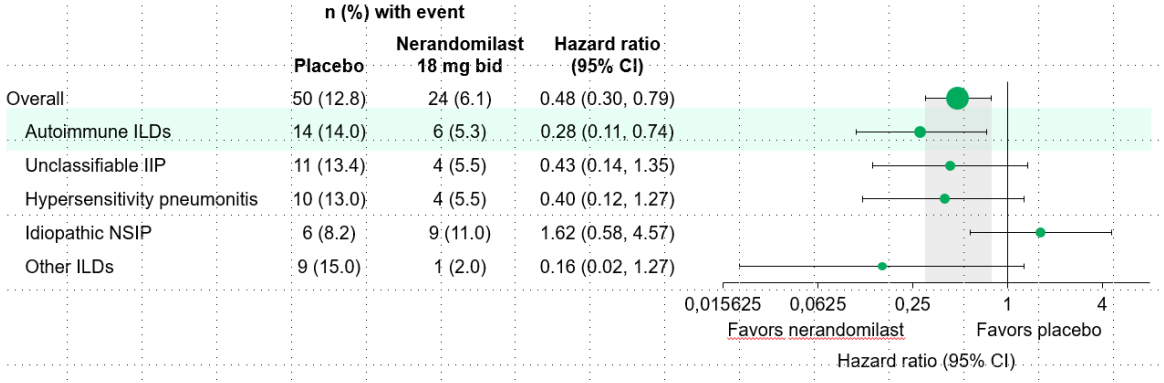
- absolute change from baseline in FVC at week 52

Secondary endpoints

- major event (first acute exacerbation, hospitalization for a respiratory cause, or death).

**Significant less decline (45-50%) in absolute FVC for active drug in either group receiving background or not therapy**




Nerandomilast 18 mg bid, had a nominally significant effect on the risk of death in patients with autoimmune ILDs

Original Investigation

June 25, 2014

# Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis

## A Randomized Clinical Trial

Jacob M. van Laar, MD, PhD[1]; Dominique Farge, MD, PhD[2]; Jacob K. Sont, PhD[5]; et al

- Ένδειξη μόνο σε ασθενείς με πρώιμη, πολύ σοβαρή/εξελισσόμενη νόσο καθώς η διαδικασία σχετίζεται με υψηλή νοσηρότητα-θνητότητα. Μακροχρόνια, αυξάνεται η επιβίωση



Table 2. Treatment Responses in Clinical Outcome Variables, Change in the Area Under the Time Response Curve From Baseline to 2 Years' Follow-up

| Variable | AUC, Mean (SD) HSCT Group (n = 67)[a] | AUC, Mean (SD) Control Group (n = 64)[a] | Difference (95% CI) | P Value |
|---|---|---|---|---|
| Weight, kg | -0.7 (9.5) | -0.8 (9.6) | -0.2 (-3.5 to 3.1) | .91 |
| Modified Rodnan skin score | -19.9 (10.2) | -8.8 (12.0) | 11.1 (7.3 to 15.0) | <.001 |
| Creatinine clearance, mL/min[b] | -12.1 (29.7) | -1.2 (24.1) | 10.9 (1.5 to 20.3) | .02 |
| LVEF, % by cardiac echocardiography | -2.2 (14.7) | -1.9 (13.8) | 0.3 (-4.7 to 5.2) | .91 |
| Forced vital capacity, % predicted | 6.3 (18.3) | -2.8 (17.2) | -9.1 (-14.7 to -2.5) | .004 |
| Total lung capacity, % predicted | 5.1 (17.5) | -1.3 (13.9) | -6.4 (-11.9 to -0.9) | .02 |
| Residual volume, % predicted | -4.8 (33.7) | -2.1 (26.9) | 2.7 (-7.9 to 13.2) | .62 |
| DLCO, % predicted | -4.7 (13.7) | -4.1 (17.6) | 0.6 (-4.9 to 6.0) | .84 |
| HAQ-DI | -0.58 (1.14) | -0.19 (0.79) | 0.39 (0.51 to 0.73) | .02 |
| SF-36 score | | | | |
| Physical component | 10.1 (15.8) | 4.0 (11.2) | -6.1 (-10.9 to -1.4) | .01 |
| Mental component | 3.1 (16.0) | 3.4 (17.1) | 0.3 (-5.41 to 6.07) | .91 |
| EQ-5D | | | | |
| Index-based utility score | 0.31 (0.50) | 0.03 (0.44) | -0.29 (-0.45 to -0.12) | <.001 |
| VAS score | 16.9 (44.5) | 10.2 (39.7) | -6.7 (-21.33 to 7.87) | .36 |

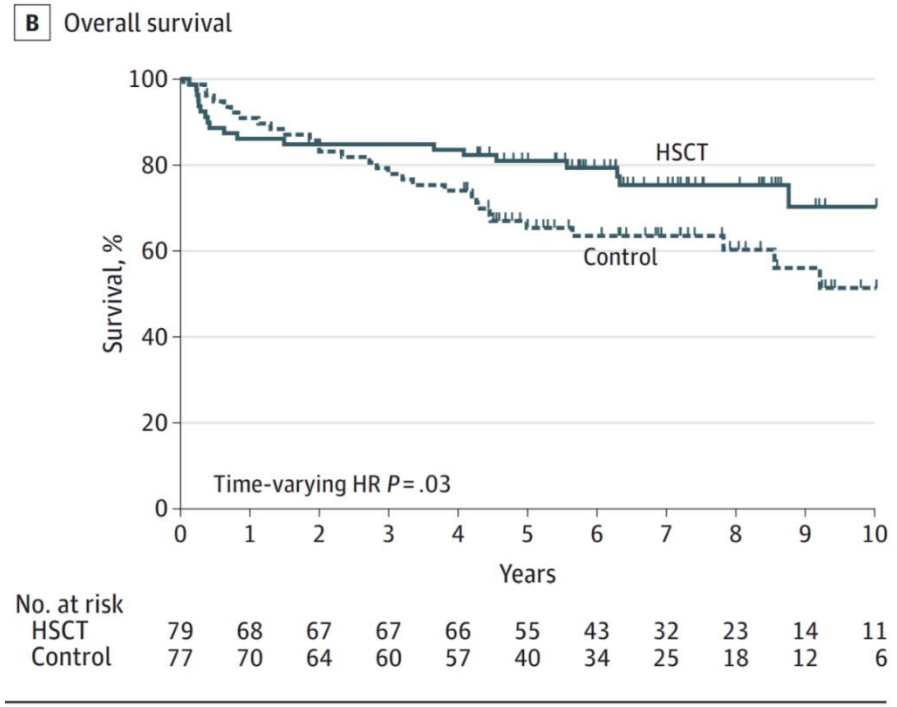
- Αυστηρά κριτήρια επιλογής
- διάχυτη μορφή
- πρώιμη νόσος (συνήθως <5 έτη από έναρξη)
- ταχεία εξέλιξη / επιθετική νόσος
- απουσία βαριάς οργανικής προσβολής

FVC<45–50%DLCO <40%

LVEF<45-5-%

Πνευμονική υπέρταση

ενεργή νεφρική κρίση / νεφρική ανεπάρκεια



Recommendation

OPEN ACCESS

# EULAR recommendations for the treatment of systemic sclerosis: 2023 update

Francesco Del Galdo [1,2] Alain Lescoat [3] Philip G Conaghan [1,2]

| | |
|---|---|
| ILD | MMF (1A), cyclophosphamide (1A) or rituximab (1A) should be considered for the treatment of SSc-ILD* |
| | Nintedanib should be considered alone or in combination with MMF for the treatment of SSc-ILD* |
| | Tocilizumab should be considered for the treatment of SSc-ILD* |

EUROPEAN RESPIRATORY JOURNAL
ERS OFFICIAL DOCUMENTS
K.M. ANTONIOU ET AL.

# ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease

Developed by the task force for connective tissue disease-associated interstitial lung disease of the European Respiratory Society (ERS) and the European Alliance of Associations for Rheumatology (EULAR)

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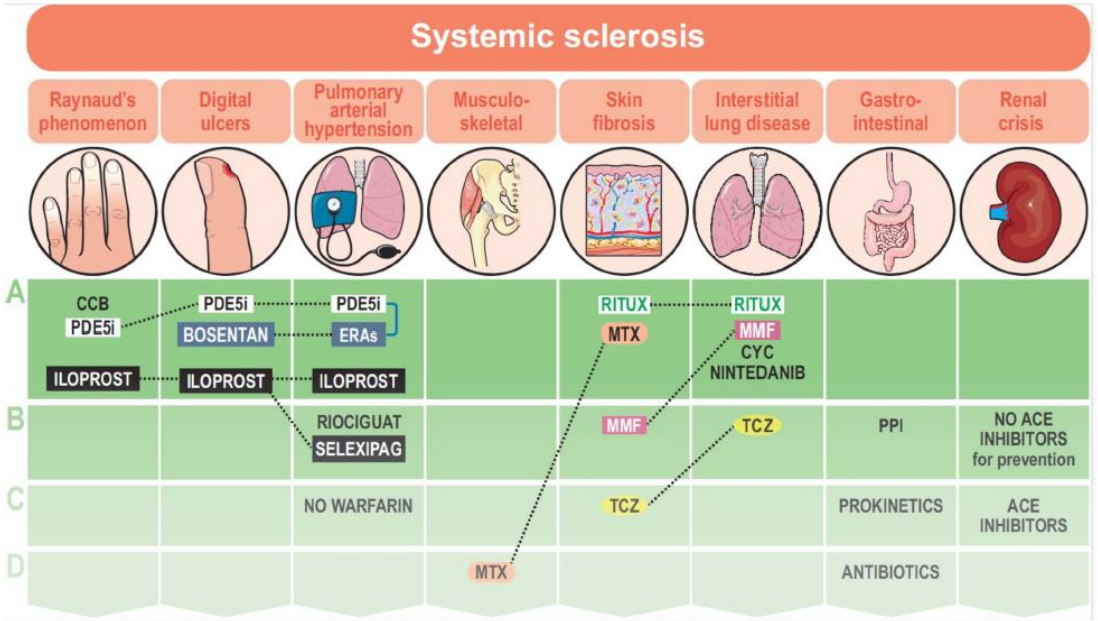
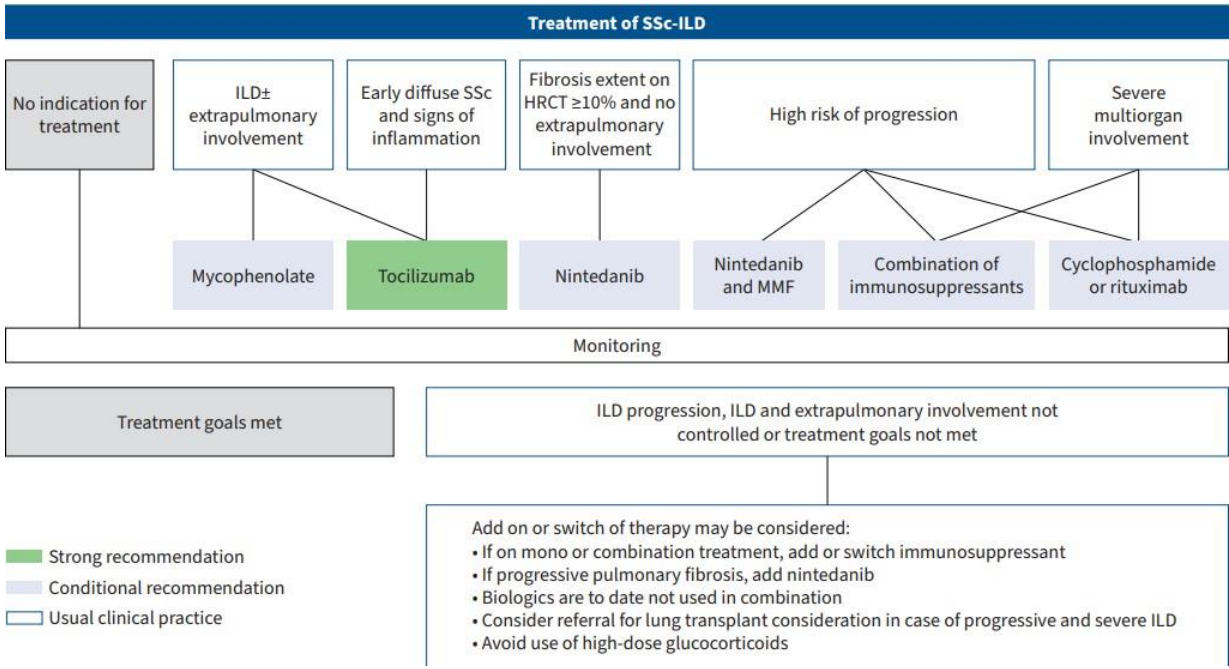
Recommendation




Del Galdo et al.Ann Rheum Dis. 2024

*Rheumatology*, 2024, **63**, 1534–1538
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Advance access publication 6 September 2023
**Concise Report**

British Society for Rheumatology RHEUMATOLOGY OXFORD

Clinical science

# Outcomes in progressive systemic sclerosis treated with autologous hematopoietic stem cell transplantation compared with combination therapy

**Shiri Keret [1,‡], Israel Henig[2,‡], Tsila Zuckerman[2], Lisa Kaly [1], Aniela Shouval[1], Abid Awisat[1],**

16 with AHSCT vs. 21 SSc patients with combination therapy (RTX+MMF+NTD)

significant and comparable increase in FVC

The hazard ratio for EFS at 24 months favored the combination group (HR: 0.09, p: 0.04)

more AEs (46vs 25) and SAEs (21 vs 3) in the AHSCT group compared to the combination group
Treatment-related mortality after AHSCT was 3/16 (18.7%)

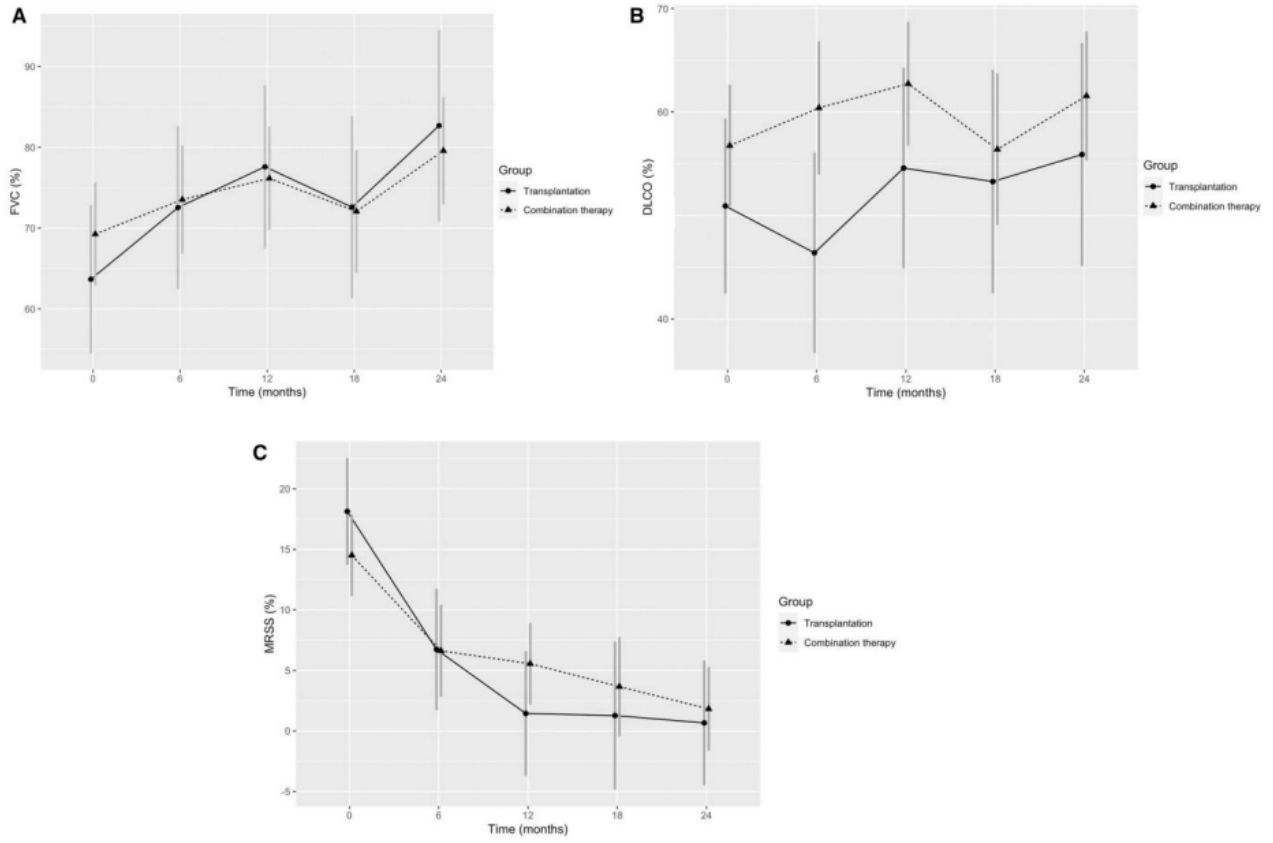
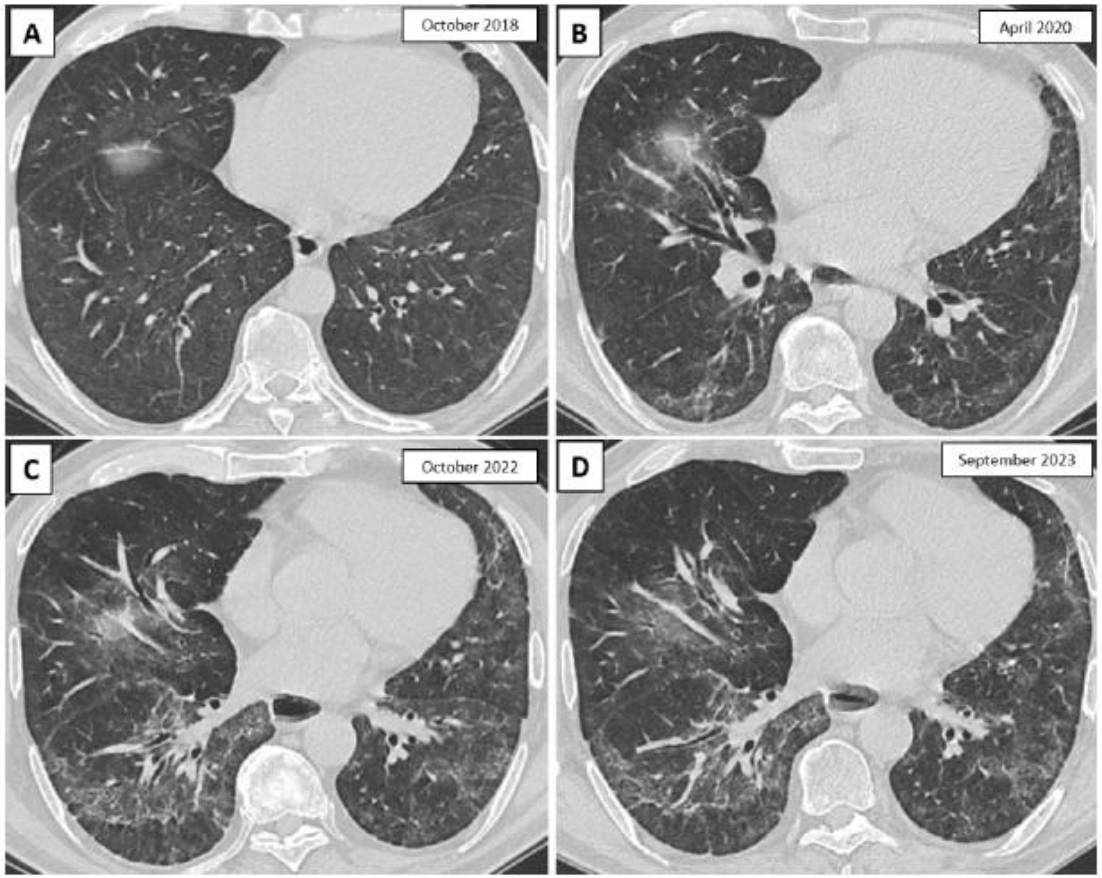
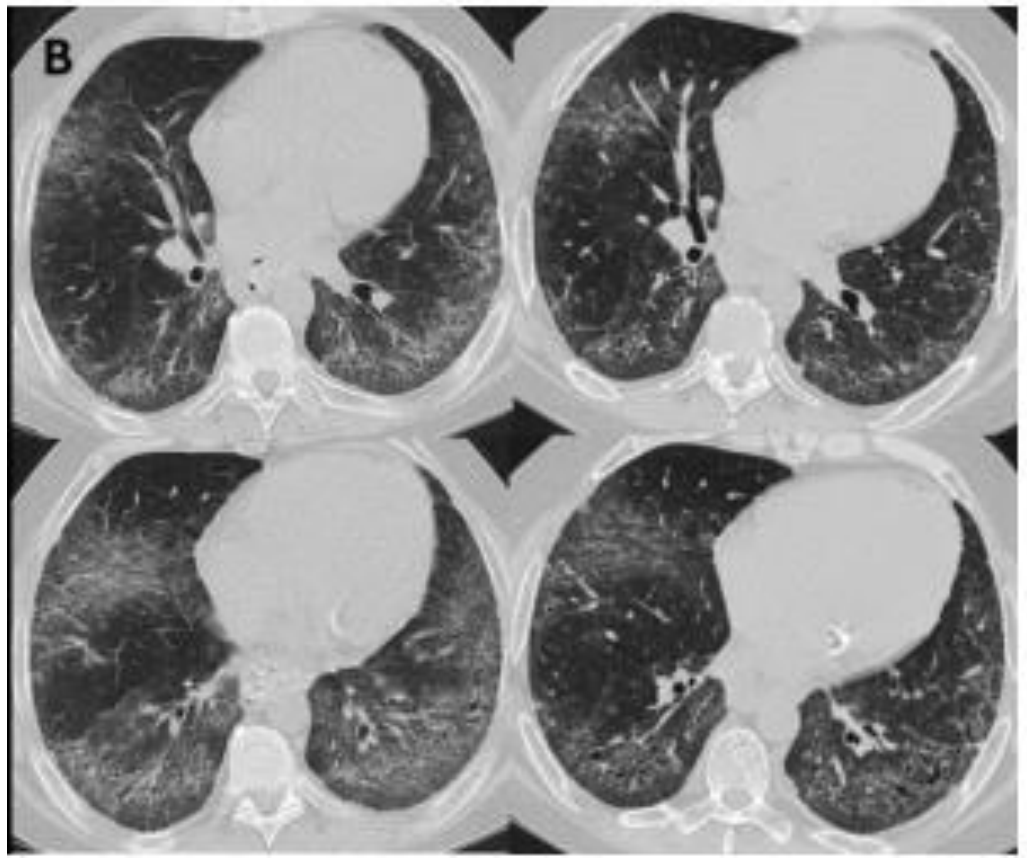



**Figure 1.** A linear mixed model of the forced vital capacity (FVC) (**A**), diffusing capacity of the lung for carbon monoxide (DLCO) (**B**), and modified Rodnan Skin Score (mRSS) (**C**) values at follow-up in the two groups




Panopoulos et al. Rheumatol Int. 2024;44:1959-1966.

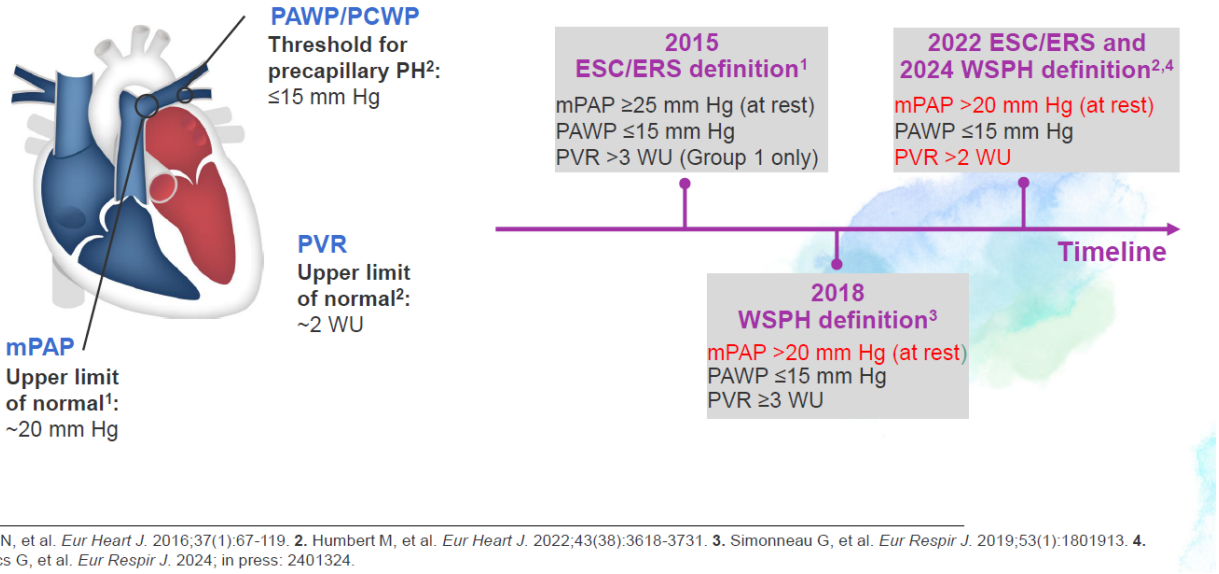
# Key points for SSc-ILD

- HRCT and LFTs in all patients at diagnosis
- Risk stratification
- Annual monitoring during the first 5 years after onset

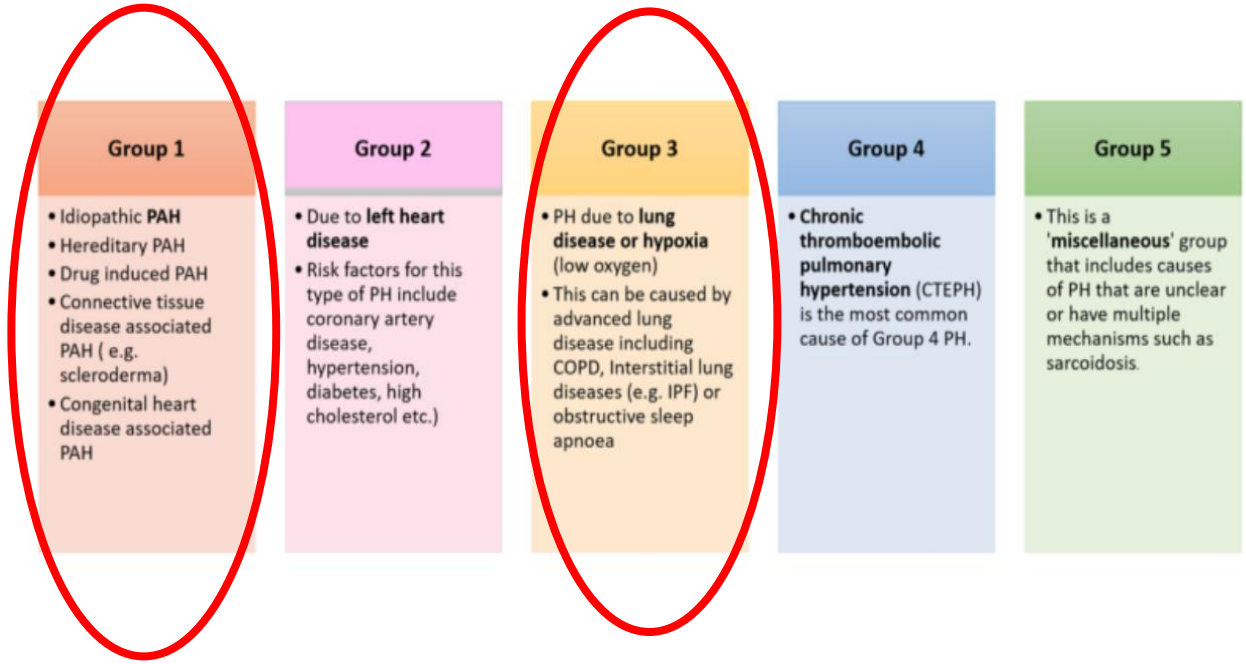
- MMF first choise (RTX, CYC alternatives)
- TCZ if inflammatory phenotype
- Nintedanib if fibrotic phenotype
- Combination treatment in refractory or high risk cases

# Πνευμονική Υπέρταση

## The Hemodynamic Definition of Precapillary PH Has Changed Over Time




Galiè N, et al. *Eur Heart J.* 2016;37(1):67-119. **2.** Humbert M, et al. *Eur Heart J.* 2022;43(38):3618-3731. **3.** Simonneau G, et al. *Eur Respir J.* 2019;53(1):1801913. **4.** Kovacs G, et al. *Eur Respir J.* 2024; in press: 2401324.




Στη Συστηματική Σκλήρυνση:
Τύπος 1: Πνευμονική αρτηριακή υπέρταση (πρωτοπάθής, λόγω αγγειοπάθειας πνευμονικών αγγείων)
Τύπος 3: 2παθής πνευμονική υπέρταση λόγω πνευμονικής ίνωσης

**Table 3** Survival according to three bands of mean pulmonary artery pressure (mPAP in mm Hg) in SSc cohort

| mPAP (mm Hg) | 1 Year survival (%) | 2 Year survival (%) | 3 Year survival (%) |
|---|---|---|---|
| Overall (n = 148) | 81 | 63 | 56 |
| <32 (n = 47) | 93 | 78 | 75 |
| 32–44 (n = 48) | 91 | 72 | 61 |
| >45 (n = 53) | 61 | 39 | 33 |

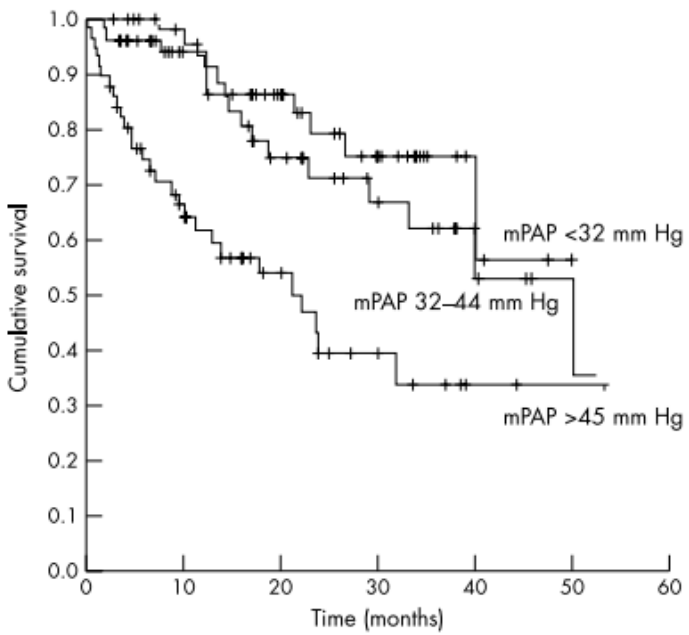



**Figure 2** Kaplan-Meier survival curves for 148 patients with SScPAH divided into tertiles—47 with mPAP <32 mm Hg, 48 with mPAP = 32–44 mm Hg, and 53 with mPAP >45 mm Hg. There was a significant

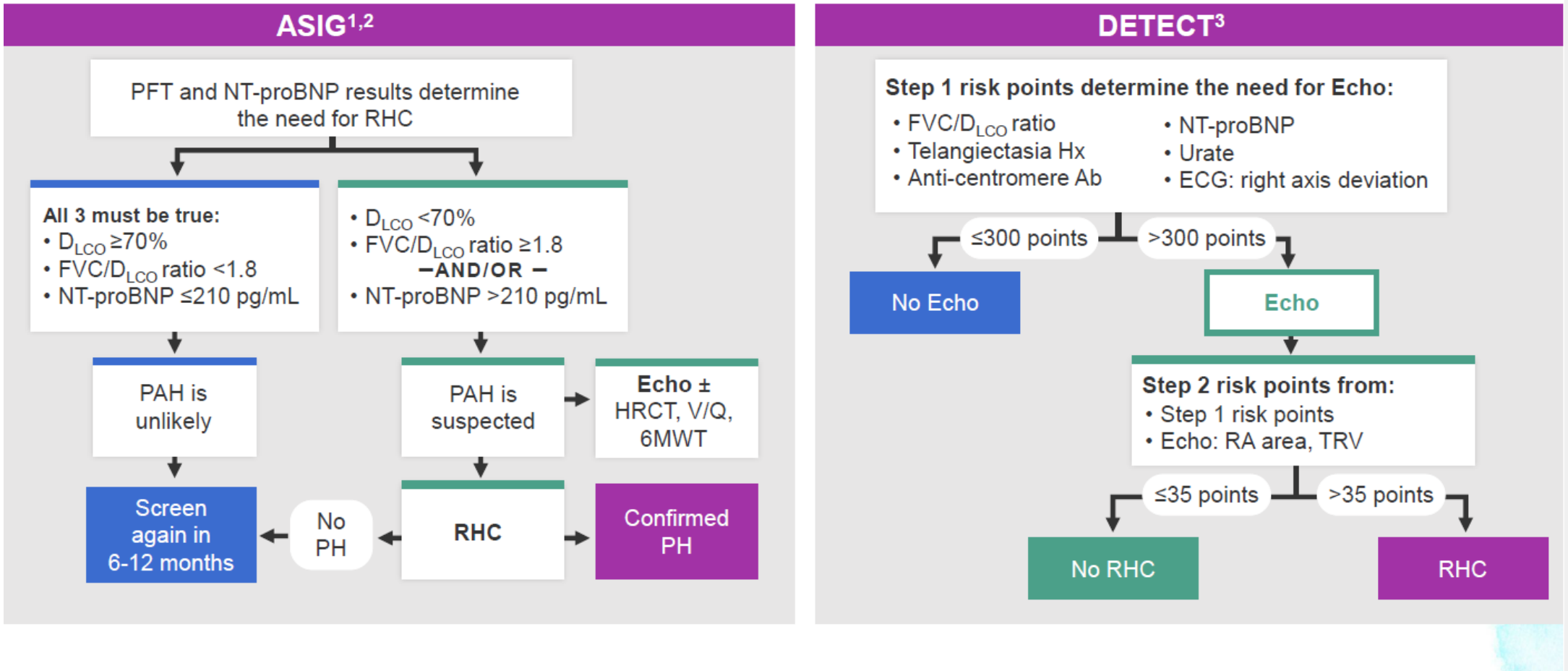
## SSc-spectrum disorders*

### Annual PH screening for all patients is recommended[1,2]

Due to the prevalence and impact of PAH on survival, the WSPH and ESC/ERS recommend that **all patients with SSc-spectrum disorders (ie, those with no PH symptoms or disease manifestations)** receive annual screening

Mukerjee et al.Ann Rheum Dis 2003;62:1088–1093

# Validated Screening Algorithms for SSc-PAH




Brown et al.Jour int Med2024 Sep;54:1561-1566
Coghlan et al. Ann Rheum Dis.2014 Jul;73:1340-9

# PASP (in heart u/s) = $4 \times (TRV)^2$ + $R_{(ight)}A_{(atrial)}P_{(ressure)}$

## A Thorough Evaluation of the Right Heart Is Necessary When Using Echo to Screen for PH

**TRV is used in conjunction with other Echo signs of PH to determine ESC/ERS probability of PH**

| Low probability | Intermediate probability | High probability |
|---|---|---|
| TRV ≤2.8 m/s or unmeasurable, Echo signs of PH from ≤1 category | TRV 2.9-3.4 m/s, Echo signs of PH from ≤1 category **OR** TRV ≤2.8 m/s **plus** signs from >1 Echo category | TRV >3.4 m/s **OR** TRV 2.9-3.4 m/s **plus** signs from >1 Echo category |

**Probability of PH: Echo signs by category**

| Ventricles | Pulmonary artery | IVC and RA |
|---|---|---|
| • RV/LV diameter/area ratio >1.0<br>• TAPSE/sPAP ratio <0.55 mm/mm Hg<br>• Septal flattening (LVEI >1.1 in systole and/or diastole) | • RVOT AT <105 ms and/or mid-systolic notching<br>• PA diameter >AR diameter<br>• PA diameter >25 mm<br>• Early diastolic pulmonary regurgitation velocity >2.2 m/s | • RA area (end-systole) >18 $cm^2$<br>• IVC diameter >21 mm with decreased inspiratory collapse* |

- Πίεση πνευμονικής αρτηρίας (PAP)

φ.τ meanPAP<20 mmHg

- Πίεση ενσφήνωσης (PWP)

Αν < 15 mmHg προτριχοειδική PH (group 1,3,4)

Αν> 15 mmHg μετατριχοειδική (group 2)

- Πνευμονικές αγγειακές αντιστάσεις (PVR)

φ.τ < 2 wood units ( 160 dynesxs/cm5)

Καρδιακή παροχή (cardiac output)

φ.τ > 4 lt/min

## ΔΕΞΙΟΣ ΚΑΘΕΤΗΡΙΑΣΜΟΣ

Ημερομηνία εξέτασης: 21/12/2021

ΗΛΙΚΙΑ. 79 ΒΑΡΟΣ: 56 kg ΥΨΟΣ: 155 cm ΕΠΙΦ. ΣΩΜΑΤΟΣ: 1,55 $m^2$ Hb : 11,2 %

Ένδειξη καθετηριασμού :
Πνευμονική υπέρταση.

Σύντομο κλινικό ιστορικό :
Πνευμονική υπέρταση - σκληρόδερμα.

ΤΕΧΝΙΚΗ

| | |
|---|---|
| Οδός προσπέλασης: | RBV |
| Τύπος καθετήρων: | SG |
| Σκιαγραφικό διάλυμα: | Μη ιοντικό |

| | |
|---|---|
| Καρδιακός ρυθμός: | Φλεβοκομβικός ρυθμός |
| Καρδιακή συχνότητα: | 65 / min |

| ΠΙΕΣΕΙΣ | ΠΡΙΝ ΤΗΝ ΑΓΓΕΙΟΓΡΑΦΙΑ |
|---|---|
| Δεξιός κόλπος mmHg: | 5 |
| Δεξιά κοιλία mmHg: | 42/7 |
| Πνευμονική αρτηρία mmHg: | 43/9/28 |
| Ενσφήνωση πνευμ. τριχοειδών mmHg: | 14 |
| Αορτή mmHg: | 169/73/109 |

| ΟΞΥΜΕΤΡΙΑ | ΚΟΡΕΣΜΟΣ ΟΞΥΓ (%) |
|---|---|
| Αριστερή κοιλία: | 95 |
| Πνευμονική αρτηρία: | 71,1 |

| ΠΑΡΟΧΕΣ – ΑΝΤΙΣΤΑΣΕΙΣ – ΟΓΚΟΙ – ΣΤΟΜΙΑ | |
|---|---|
| Καρδιακή παροχή (l/min): | 5,23 |
| Καρδιακός δείκτης (l/min.m2): | 3,38 |
| Αρτηρ. πνευμονικές αντιστάσεις: | 2,68 |
| Συστηματικές αρτηριακές αντιστάσεις: | 19,68 |

Recommendation

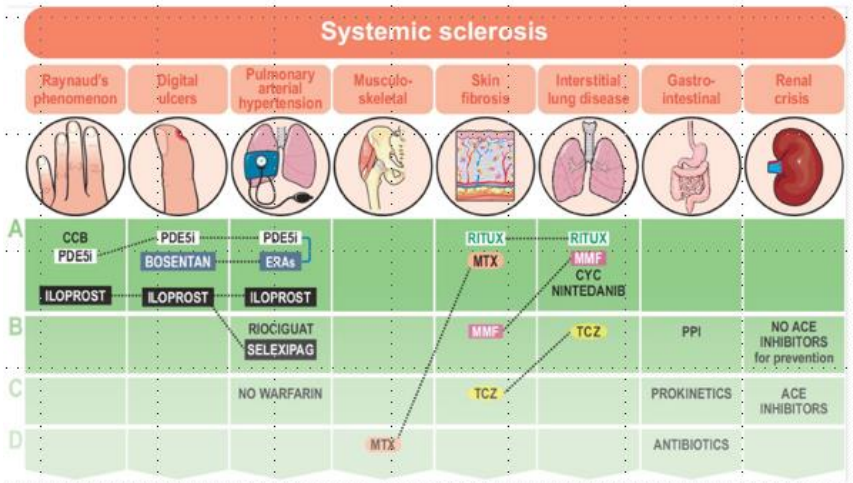
OPEN ACCESS

# EULAR recommendations for the treatment of systemic sclerosis: 2023 update

Francesco Del Galdo ,[1,2] Alain Lescoat ,[3] Philip G Conaghan ,[1,2]

| | |
|---|---|
| LD | MMF (1A), cyclophosphamide (1A) or rituximab (1A) should be considered for the treatment of SSc-ILD* |
| | Nintedanib should be considered alone or in combination with MMF for the treatment of SSc-ILD* |
| | Tocilizumab should be considered for the treatment of SSc-ILD* |

Recommendation



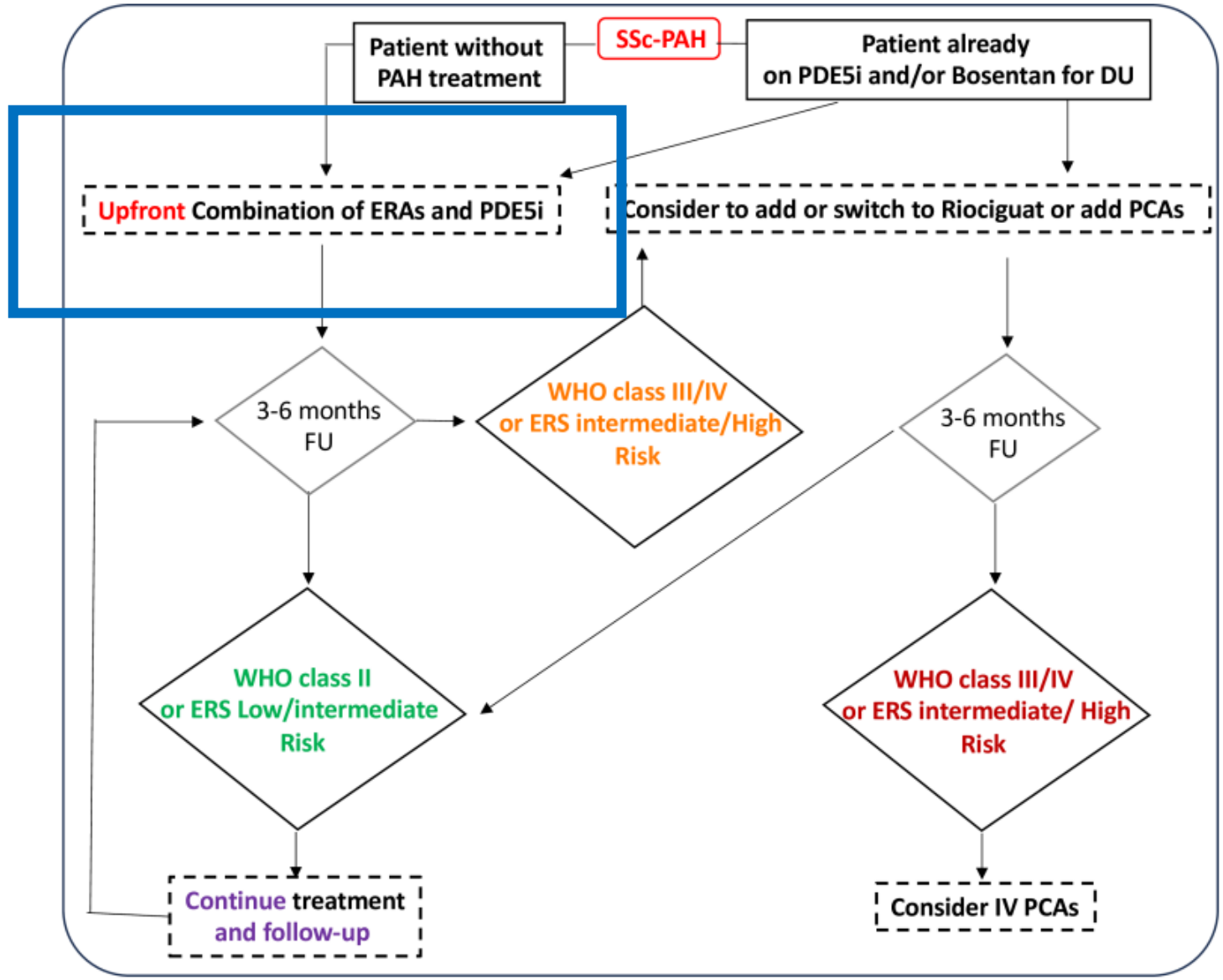
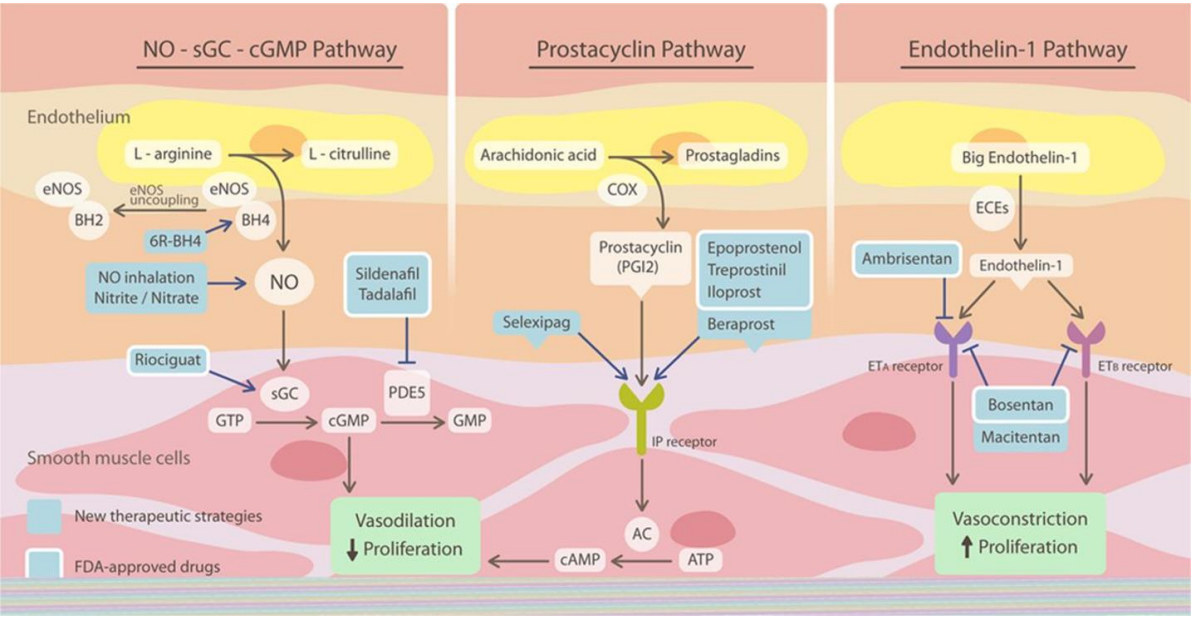
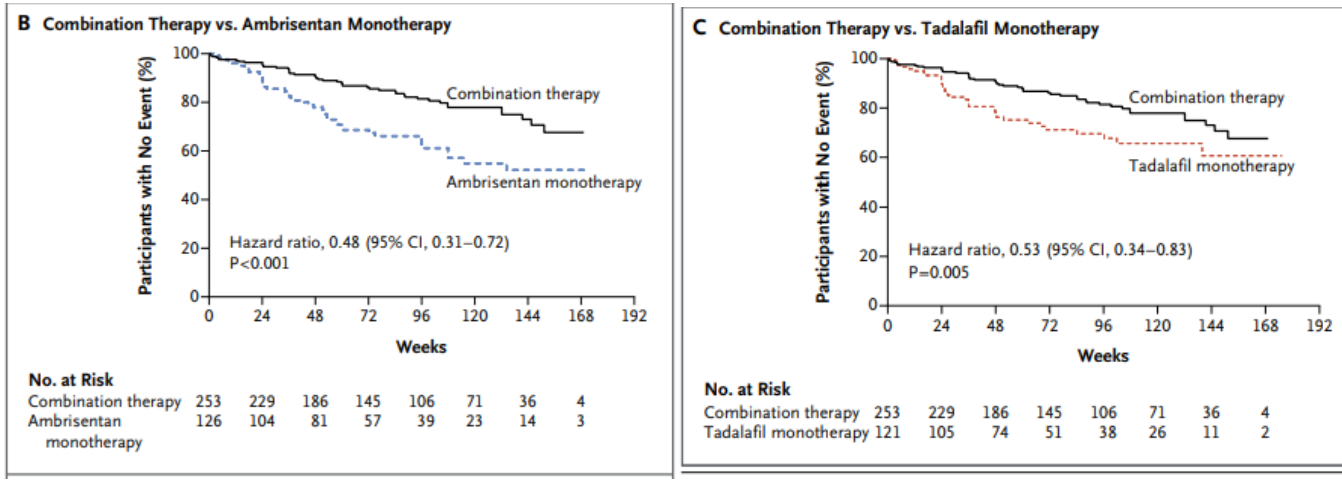



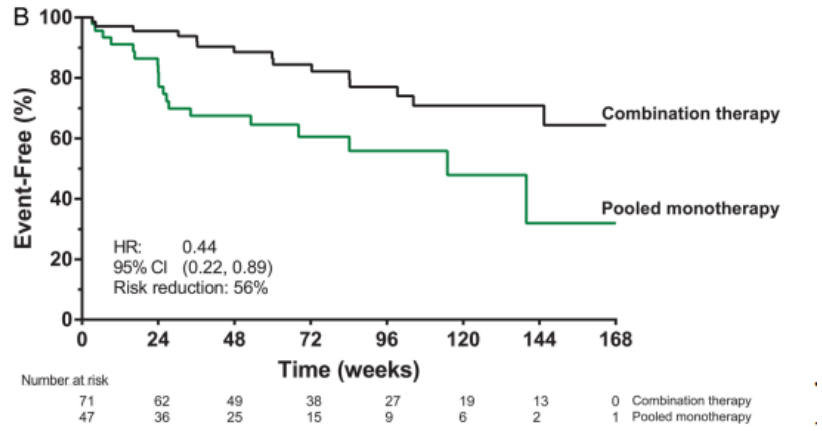

Figure 3 Treatment flow chart for the evidence informing the recommendations for treatment of SSc pulmonary artery hypertension (PAH). DU, digital ulcer; ERAs, endothelin receptor antagonists; ERS, European Respiratory Society; IV, intravenous; PCA, prostacyclin agonists.

# Management of Pulmonary arterial Hypertension in SSc



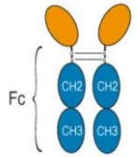

**The AMBITION trial**



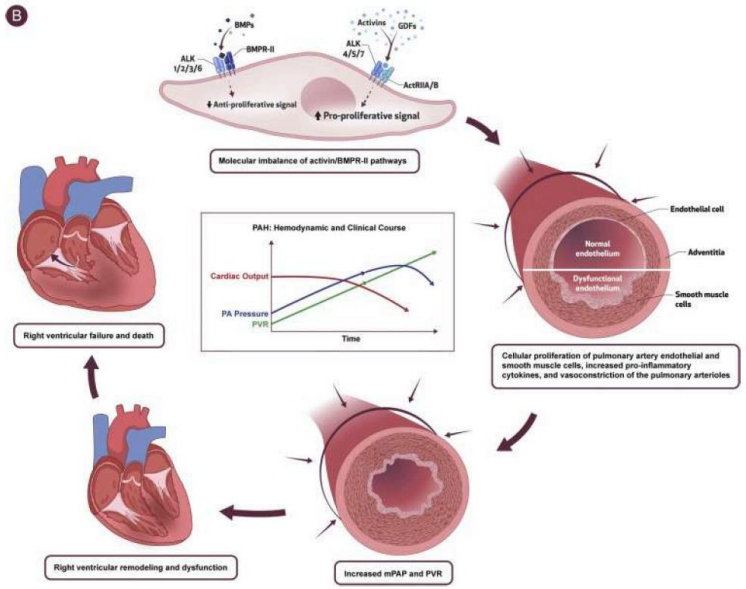

Galie et al. N Engl J Med 2015;373:834-844

# Sotatercept




first-in-class fusion protein composed of the extracellular domain of the human activin receptor type IIA fused to the Fc domain of human IgG1.
sotatercept acts as a ligand trap for members of the TGF-β superfamily

0.3mg and 0.7mg subcutaneous injection every 21 days.



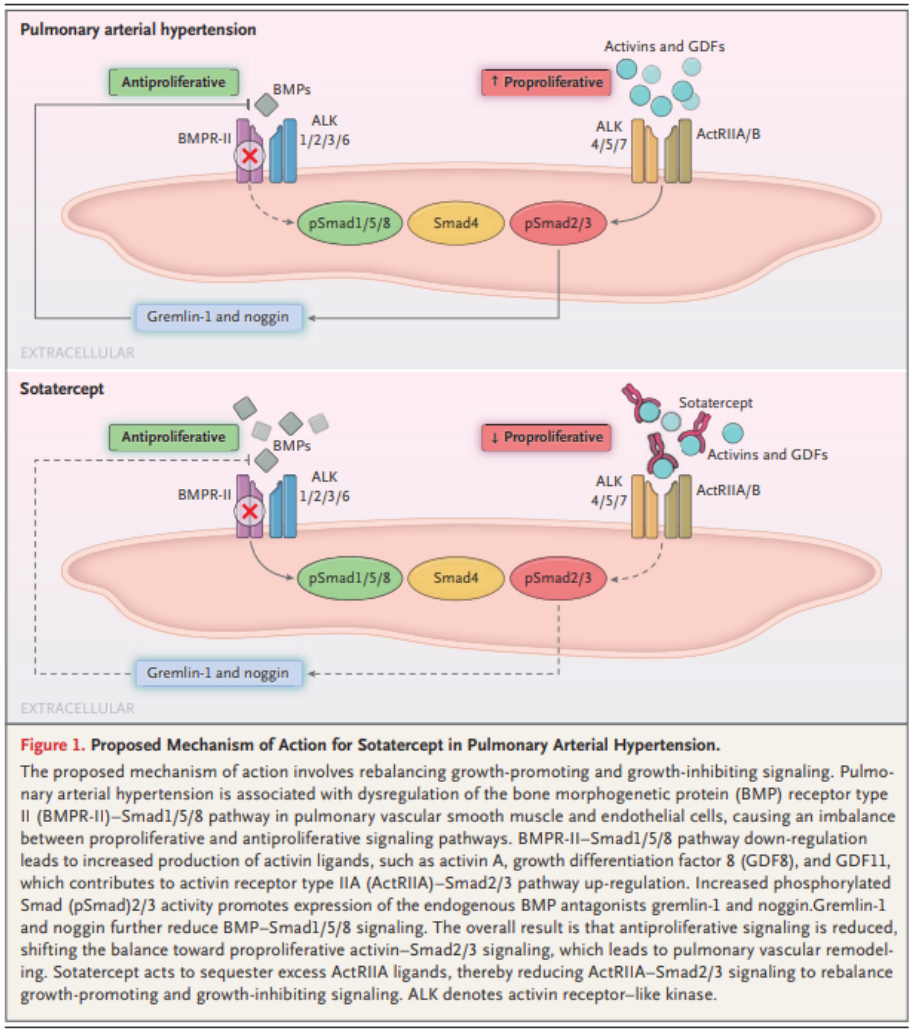




**Figure 1. Proposed Mechanism of Action for Sotatercept in Pulmonary Arterial Hypertension.**

The proposed mechanism of action involves rebalancing growth-promoting and growth-inhibiting signaling. Pulmonary arterial hypertension is associated with dysregulation of the bone morphogenetic protein (BMP) receptor type II (BMPR-II)–Smad1/5/8 pathway in pulmonary vascular smooth muscle and endothelial cells, causing an imbalance between proproliferative and antiproliferative signaling pathways. BMPR-II–Smad1/5/8 pathway down-regulation leads to increased production of activin ligands, such as activin A, growth differentiation factor 8 (GDF8), and GDF11, which contributes to activin receptor type IIA (ActRIIA)–Smad2/3 pathway up-regulation. Increased phosphorylated Smad (pSmad)2/3 activity promotes expression of the endogenous BMP antagonists gremlin-1 and noggin.Gremlin-1 and noggin further reduce BMP–Smad1/5/8 signaling. The overall result is that antiproliferative signaling is reduced, shifting the balance toward proproliferative activin–Smad2/3 signaling, which leads to pulmonary vascular remodeling. Sotatercept acts to sequester excess ActRIIA ligands, thereby reducing ActRIIA–Smad2/3 signaling to rebalance growth-promoting and growth-inhibiting signaling. ALK denotes activin receptor–like kinase.

# PULSAR STUDY

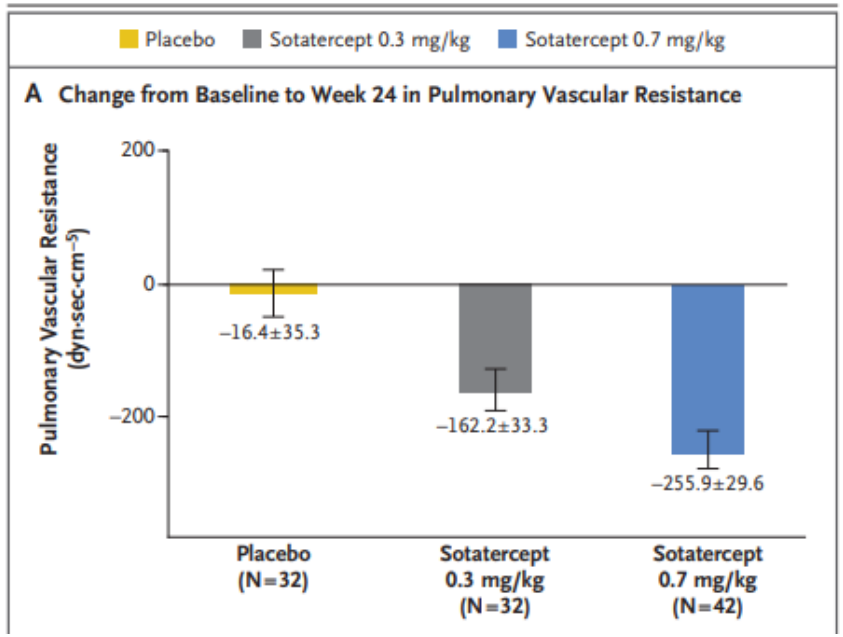
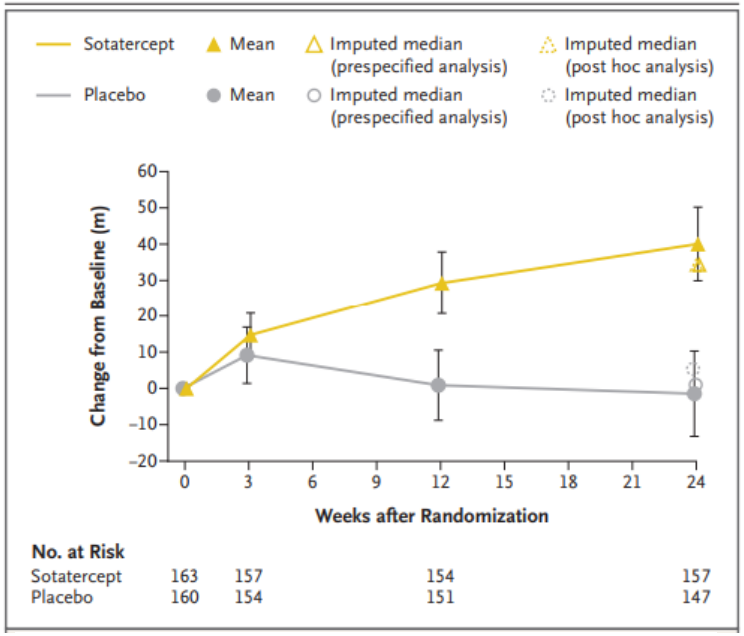
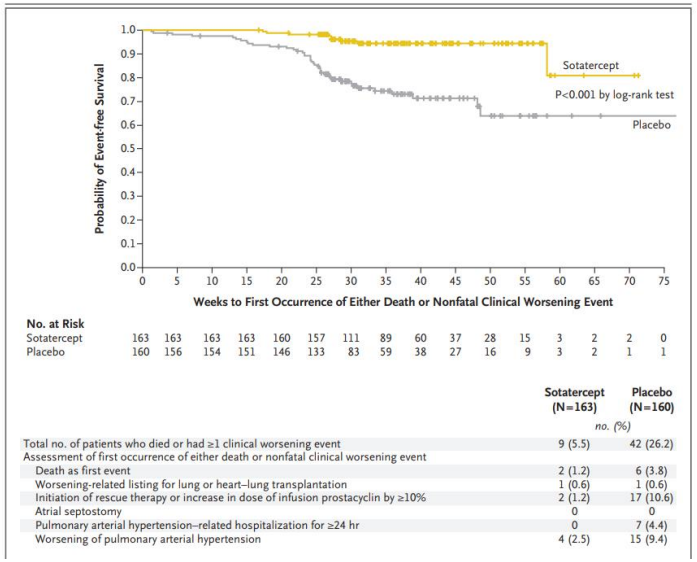



**Table 2. Primary and Secondary Efficacy End Points.***

| End Point | Placebo (N=32) | Sotatercept 0.3 mg/kg (N=32) | Sotatercept 0.7 mg/kg (N=42) | Both Sotatercept Dose Groups (N=74) |
|---|---|---|---|---|
| **Primary End Point** | | | | |
| Pulmonary vascular resistance — dyn·sec·cm$^{-5}$ | | | | |
| Least-squares mean change ±SE from baseline at week 24 | −16.4±35.3 | −162.2±33.3 | −255.9±29.6 | −215.2±22.4 |
| Least-squares mean difference as compared with placebo (95% CI) | | −145.8 (−241.0 to −50.6) | −239.5 (−329.3 to −149.7) | −198.9 (−281.5 to −116.3) |
| **Secondary End Points** | | | | |
| 6-Minute walk distance — m | | | | |
| Least-squares mean change ±SE from baseline at week 24 | 28.7±9.3 | 58.1±9.2 | 50.1±8.2 | 53.5±6.1 |
| Least-squares mean difference as compared with placebo (95% CI) | | 29.4 (3.8 to 55.0) | 21.4 (−2.8 to 45.7) | 24.9 (3.1 to 46.6) |
| NT-proBNP — pg/ml | | | | |
| Least-squares mean change ±SE from baseline at week 24 | 310.4±151.3 | −621.1±150.6 | −340.6±139.4 | −462.4±101.4 |
| Least-squares mean difference as compared with placebo (95% CI) | | −931.5 (−1353.2 to −509.7) | −651.0 (−1043.3 to −258.7) | −772.1 (−1125.2 to −419.1) |
| Systolic excursion from the tricuspid annular plane — cm | | | | |
| Least-squares mean change ±SE from baseline at week 24 | 0.0±0.05 | −0.0±0.05 | −0.1±0.05 | −0.0±0.04 |
| Least-squares mean difference as compared with placebo (95% CI) | | 0.0 (−0.15 to 0.15) | −0.1 (−0.2 to 0.08) | −0.0 (−0.16 to 0.09) |
| WHO functional class | | | | |
| Patients with improvement of at least once class — no. (%) | 4 (12) | 10 (31) | 7 (17) | 17 (23) |
| Clinical worsening | | | | |
| Patients with a clinical worsening event — no. (%)† | 2 (6) | 0 | 1 (2) | 1 (1) |

# STELLAR STUDY




| | Sotatercept (N=163) | Placebo (N=160) |
|---|---|---|
| | *no. (%)* | |
| Total no. of patients who died or had ≥1 clinical worsening event | 9 (5.5) | 42 (26.2) |
| Assessment of first occurrence of either death or nonfatal clinical worsening event | | |
| Death as first event | 2 (1.2) | 6 (3.8) |
| Worsening-related listing for lung or heart–lung transplantation | 1 (0.6) | 1 (0.6) |
| Initiation of rescue therapy or increase in dose of infusion prostacyclin by ≥10% | 2 (1.2) | 17 (10.6) |
| Atrial septostomy | 0 | 0 |
| Pulmonary arterial hypertension–related hospitalization for ≥24 hr | 0 | 7 (4.4) |
| Worsening of pulmonary arterial hypertension | 4 (2.5) | 15 (9.4) |

**Table 3. Adverse Events through Week 24 (Safety Population).***

| Variable | Sotatercept (N=163) | Placebo (N=160) | Difference† |
|---|---|---|---|
| | *number (percent)* | | *percentage points* |
| Adverse events | | | |
| Any | 138 (84.7) | 140 (87.5) | −2.8 (−10.5 to 4.8) |
| Related to sotatercept or placebo‡ | 67 (41.1) | 41 (25.6) | 15.5 (5.2 to 25.5) |
| Leading to discontinuation of sotatercept or placebo | 3 (1.8) | 10 (6.2) | −4.4 (−9.5 to −0.1) |
| Leading to withdrawal from the trial | 3 (1.8) | 5 (3.1) | −1.3 (−5.5 to 2.5) |
| Leading to death | 0 | 6 (3.8) | −3.8 (−7.9 to −1.4) |
| Severe adverse event§ | 13 (8.0) | 21 (13.1) | −5.1 (−12.2 to 1.6) |
| Serious adverse events¶ | | | |
| Any | 23 (14.1) | 36 (22.5) | −8.4 (−16.9 to 0.1) |
| Related to sotatercept or placebo‡ | 2 (1.2) | 2 (1.2) | −0.0 (NR) |
| Leading to discontinuation of sotatercept or placebo | 1 (0.6) | 8 (5.0) | −4.4 (−9.0 to −1.0) |
| Leading to withdrawal from the trial | 1 (0.6) | 5 (3.1) | −2.5 (−6.6 to 0.6) |
| Adverse events of interest or special interest‖ | | | |
| Increased hemoglobin level: increased hematocrit or increased red-cell count | 9 (5.5) | 0 | 5.5 (2.9 to 10.2) |
| Thrombocytopenia | 10 (6.1) | 4 (2.5) | 3.6 (−0.9 to 8.8) |
| Bleeding events | 35 (21.5) | 20 (12.5) | 9.0 (0.8 to 17.2) |
| Increased blood pressure | 6 (3.7) | 1 (0.6) | 3.1 (−0.2 to 7.3) |
| Telangiectasia | 17 (10.4) | 5 (3.1) | 7.3 (2.0 to 13.3) |
| Adverse events reported in ≥10% of patients in either group | 138 (84.7) | 140 (87.5) | −2.8 (−10.5 to 4.8) |
| Headache | 33 (20.2) | 24 (15.0) | 5.2 (−3.1 to 13.6) |
| Covid-19 | 24 (14.7) | 21 (13.1) | 1.6 (−6.1 to 9.3) |
| Nausea | 16 (9.8) | 18 (11.2) | −1.4 (−8.4 to 5.4) |
| Diarrhea | 20 (12.3) | 12 (7.5) | 4.8 (−1.8 to 11.6) |
| Fatigue | 17 (10.4) | 12 (7.5) | 2.9 (−3.5 to 9.5) |
| Epistaxis | 20 (12.3) | 3 (1.9) | 10.4 (5.2 to 16.6) |
| Telangiectasia | 17 (10.4) | 5 (3.1) | 7.3 (2.0 to 13.3) |
| Dizziness | 17 (10.4) | 3 (1.9) | 8.6 (3.6 to 14.4) |

# Key points for SSc-PAH

- Insidious onset
- Annual screening with heart u/s

- Dyspnoea not explained due to ILD, indicative of PAH
- Disportionate low DLCO to FVC (FVC/DLCO>1.5) indicative of PAH
- Tricuspid velocity > 2.9 m/s indicative of PAH

- Upfront combination treatment improves outcomes
- Sotatercept may alter the natural course of the disease

# Pleural effusion in SSc

- 7-10% of SSc patients
- more frequent in the diffuse subtype
- most effusions are small and asymptomatic
- poor prognostic factor, especially when associated with interstitial lung disease (ILD), as it is linked to a five-fold increase in mortality
- in several cases elevated serum CA-125

Thompson AE, Pope JE. Br J Rheumatol 1998; 37: 1320–1323.Kimura K,et al. J Dermatol 1995; 22: 28–31. Highland KB et al. Curr Opin Pulm Med 10: 390-396.

# Differential and Treatment

## ➢Transudative effusions

- Heart failure  (pulmonary hypertension, myocardial involvement)
- Hypoalbuminemia (malnutrition, renal loss)

## ➢ Exudative effusions

- Infections
- (autoimmune) scleroderma-related pleuritis
- malignancy lung cancer, metastases / recurrent, unilateral, large effusion, weight loss
- pulmonary embolism (small to moderate/bilateral effusions)
- Uremia (renal crisis)
- pericarditis-related effusion

## ➢Management

NSAIDS

Glucocorticoids (small to moderate doses)

Cs/b DMARDS ( mtx, mycophenolate, tocilizumab, rituximab)

# Aspiration pneumonia

- GERD common in SSc, >50–90% of patients
- caused due to esophageal dysmotility and incompetent lower esophageal sphincter
- mild cases may asymptomatic
- Severe cases: cough, coughing up sputum and sometimes fever, recurrent pneumonia.

mortality 30-50%

- may cause or deteriorate interstitial lung disease

direct correlation has been shown between reflux severity and PF severity

➢ **Management**

- antireflux treatment (PPIs, Antacids)
- prokinetics (Domperidone, Buspirone)
- elevating the head of the bed and not eating near bedtime.
- hospitalization (antibiotics, oxygen supply)

SK Ntoumazios et al. Semin Arthritis Rheum 2006; 36: 173–181
I Marie et al. Arthritis Rheum 2001; 45: 346–354.
Hant FN, et al. Clin Chest Med 31: 433-449.
Johnson DA,et al. Arch Intern Med 149: 589-593

**Lung cancer risk in Systemic Sclerosis: data from an inception cohort and meta-analysis of published studies**

Anastasios Makris[1], Vassiliki Poulia[1], Vasiliki K. Bournia[1], Kalliopi Fragkiadaki[1], Maria G. Tektonidou[1], Petros P. Sfikakis[1], Stylianos Panopoulos[1]

180 inception SSc patients (2,110 person-years follow-up)

12 cases of lung Ca
Most cases non-small cell adenocarcinoma

According to GLOBOCAN data
SIR of lung cancer in the entire SSc inception cohort was 5.1[95% (CI) 4.7-5.4]
- for males SIR was 3.8 (95% C.I3.5-4.1)
- for females SIR was 9.5 (95% C.I8.7-10.3)

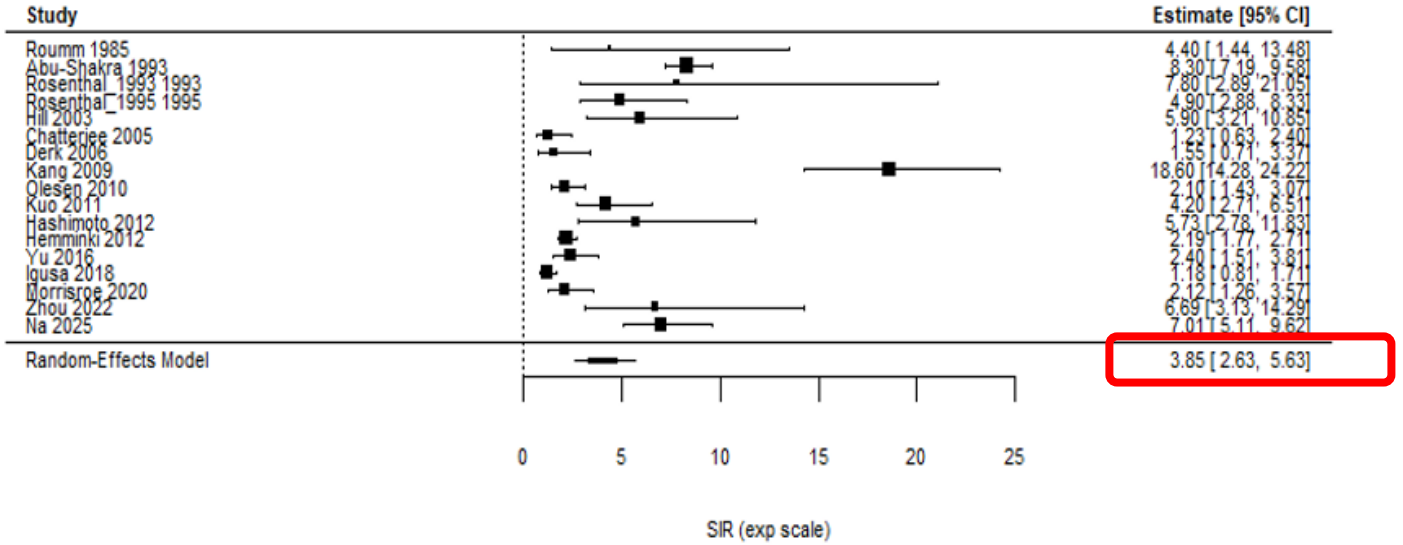



**Figure 3.** Forest plot showing individual and pooled lung cancer standardized incidence ratios (SIR) with 95% confidence intervals (CI) in Systemic Sclerosis

# Lung Cancer in SSc

- Risk factors: female gender, increased age and diffuse systemic sclerosis, smoking, immunosuppression
- Pathogenesis: chronic inflammation-mediated DNA damage, impaired tissue repair, abnormal epithelial-to-mesenchymal transition, immunosuppressive agents, environmental exposures like silica.
- Non-small cell adenocarcinoma is the most frequent type
- SSc, patients should be monitored for lung Ca, especially if prognostic factors or symptoms are present

# Rare lung manifestations in SSc

- **Alveolar hemorrhage**

very rare, only sporadic cases reported

D Peniccilamine-induced ANCA vasculitis with DAH

Pneumo-renal syndrome in renal crisis

high dose steroids and CYC

- **Respiratory muscle weakness**

rare cause of hypercapnic respiratory failure

often  overlap syndrome with polymyositis or mixed connective tissue disease.

restrictive pattern, characterized by reductions in FVC, TLC and in maximum inspiratory and expiratory pressures

- **Spontaneous pneumothorax**

usually occurs in patients with ILD due to rupture of a subpleural bleb

acute onset of symptoms (eg, shortness of breath, pleuritic chest pain)

diagnosis is made by a chest radiograph.

Yamada T, et al.(2003) Ryumachi 43: 690-695.
Chaer RA, et al. Med Sci Monit 7: 1013-1015.
Defendenti C,et al. Recenti Prog Med 100: 361-364
Teixeira Moreira et al.. Rheumatol Int 27: 675-677
Pugazhenthi M, et al. J Clin Rheumatol 9: 43-46.

# Συμπεράσματα

- Η πνευμονική ίνωση και η πνευμονική αρτηριακή υπέρταση είναι οι 2 πιο συχνές πνευμονικές επιπλοκές στη συστηματική σκλήρυνση με σημαντική νοσηρότητα και θνητότητα

- Όλα τα DMARDs έχουν συγκρίσιμη αποτελεσματικότητα στην θεραπεία της διάμεσης πνευμονοπάθειας. Το μυκοφαινολικό αποτελέι συνήθως την πρώτη επιλογή. Επί παρουσίας ινωτικού προτύπου χορήγηση αντιινωτικής θεραπείας

- Οι συνδυαστικές θεραπείες βελτιώνουν την έκβαση της νόσου και έχουν καλό προφίλ ασφάλειας

- Η λήψη μέτρων για τον περιορισμό της ΓΟΠ είναι απαραίτητη για την αποφυγή λοιμώξεων και εμφάνισης/προόδου πνευμονικής ίνωσης

- Οι ασθενείς με ΣΣ έχουν αυξημένο κίνδυνο για εμφάνιση νεοπλασίας πνεύμονα και θα πρέπει να υπάρχει επαγρύπνηση για την έγκαιρη διάγνωση της.

# Σας ευχαριστώ πολύ για τη προσοχή