Management of Systemic Sclerosis

Dinesh Khanna, M.D., M.S.

Frederick G. L Huetwell Professor of Rheumatology
Professor of Medicine
University of Michigan
khannad@umich.edu
Twitter: @sclerodermaUM

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  - CSL Behring
  - Genentech/Roche
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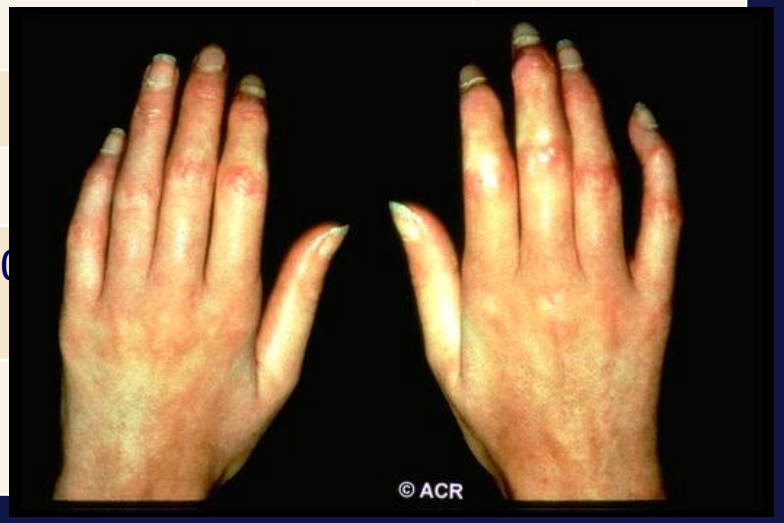
  - Pfizer
  - Prometheus
- Stocks
  - Eicos Sciences, Inc.
- No promotional talk

Evidence-Based Medicine

- Young A, Khanna D. Systemic sclerosis: commonly asked questions by rheumatologists. *J Clin Rheumatol* 2015.
- Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017.
- Roofeh D, Khanna D. Management of systemic sclerosis-the first five years. *Curr Opin Rheumatol* 2020.

2013 ACR/EULAR Classification Criteria For SSc

Criteria Domain	Sub-Criteria	Weight
Skin thickening of fingers (count higher of the 2)	Puffy fingers	2
	Whole finger, distal to MCP	4
Finger tip lesions (count higher of the 2)	Digital tip ulcers	2
	Pitting ulcers	3
Abnormal nailfold capillaries		2
Telangiectasia		
Lung involvement	PAH/ ILD	
Raynaud's phenomenon		
Scleroderma-associated antibodies	ACA, Anti-SCL-7(polymerase III	
TOTAL SCORE of 9 or more as classified as SSc		



Van den Hoogen F, Khanna D. *Arth Rheum.* 2013;65(11):2737-47.

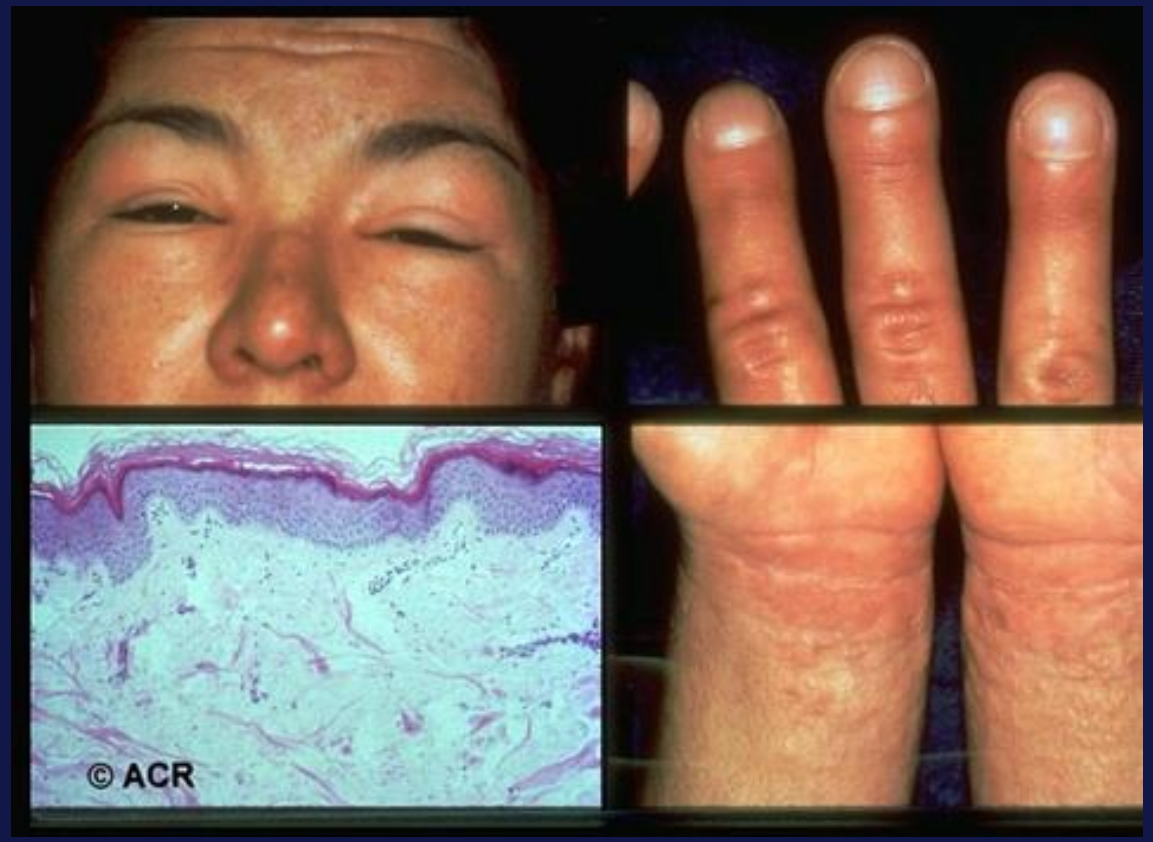
Signs and Symptoms Associated with SSc

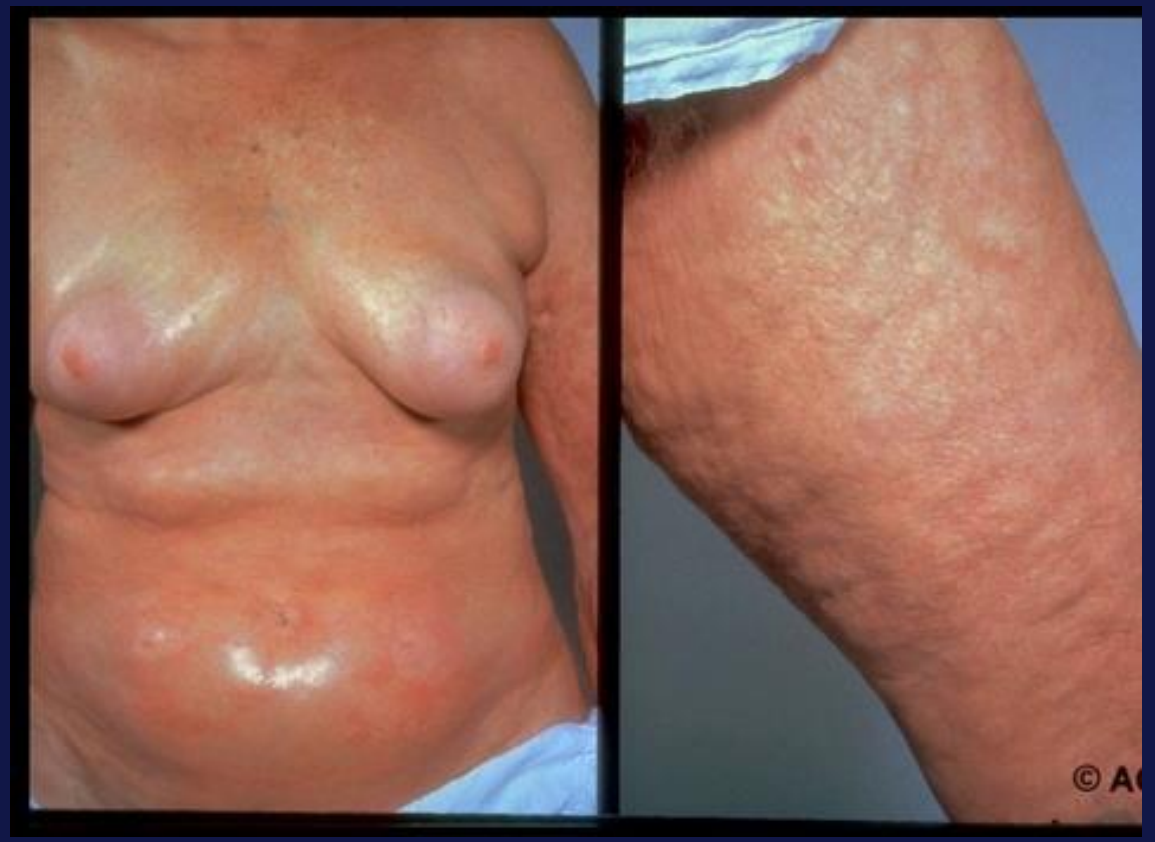
• Sclerodactyly	95%
• Raynaud's phenomenon	90%
• +ANA by IIF	95%

If absent, think of scleroderma-like skin disorder

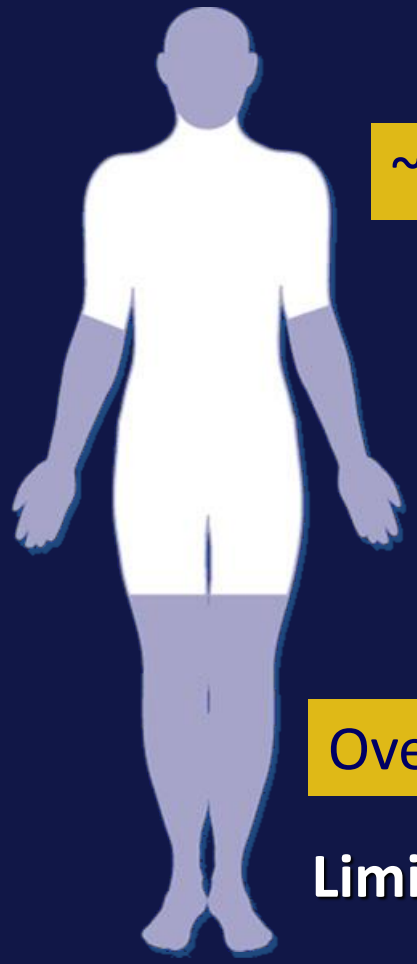
Clements P. *Baillieres Best Pract Res Clin Rheumatol.* 2000. Mar;14(1):1-16.

Scleroderma-like disorder





Classification Based on Skin Involvement Limited and Diffuse SSc



~55%

Overlap/ sine~10%

Limited

~35%

Diffuse

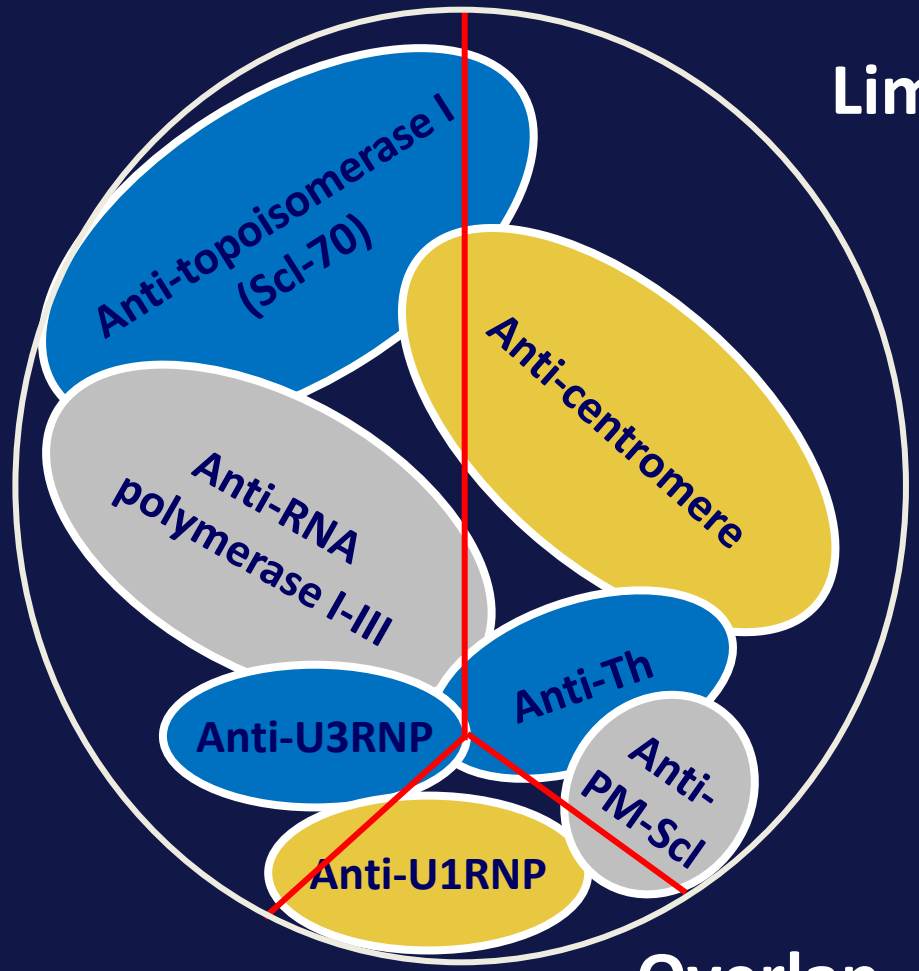
Clements PJ, Furst DE. Systemic sclerosis. Philadelphia, PA: Lippincott Williams &Wilkins; 2004.

Classification Based on Serological Subsets
Scleroderma Abs are Mutually Exclusive

Diffuse

50-60% have 3 common Ab
Anti-centromere, anti-SCL70, Anti-RNA pol III

Anti- Scl-70 = pulmonary fibrosis
Anti-Centromere = PAH
Anti-RNA pol III = renal crisis and malignancy
Anti-PM-Scl = SSc-myositis overlap
Anti-U3RNP and Anti-Th (nucleolar staining on ANA)=ILD and PAH

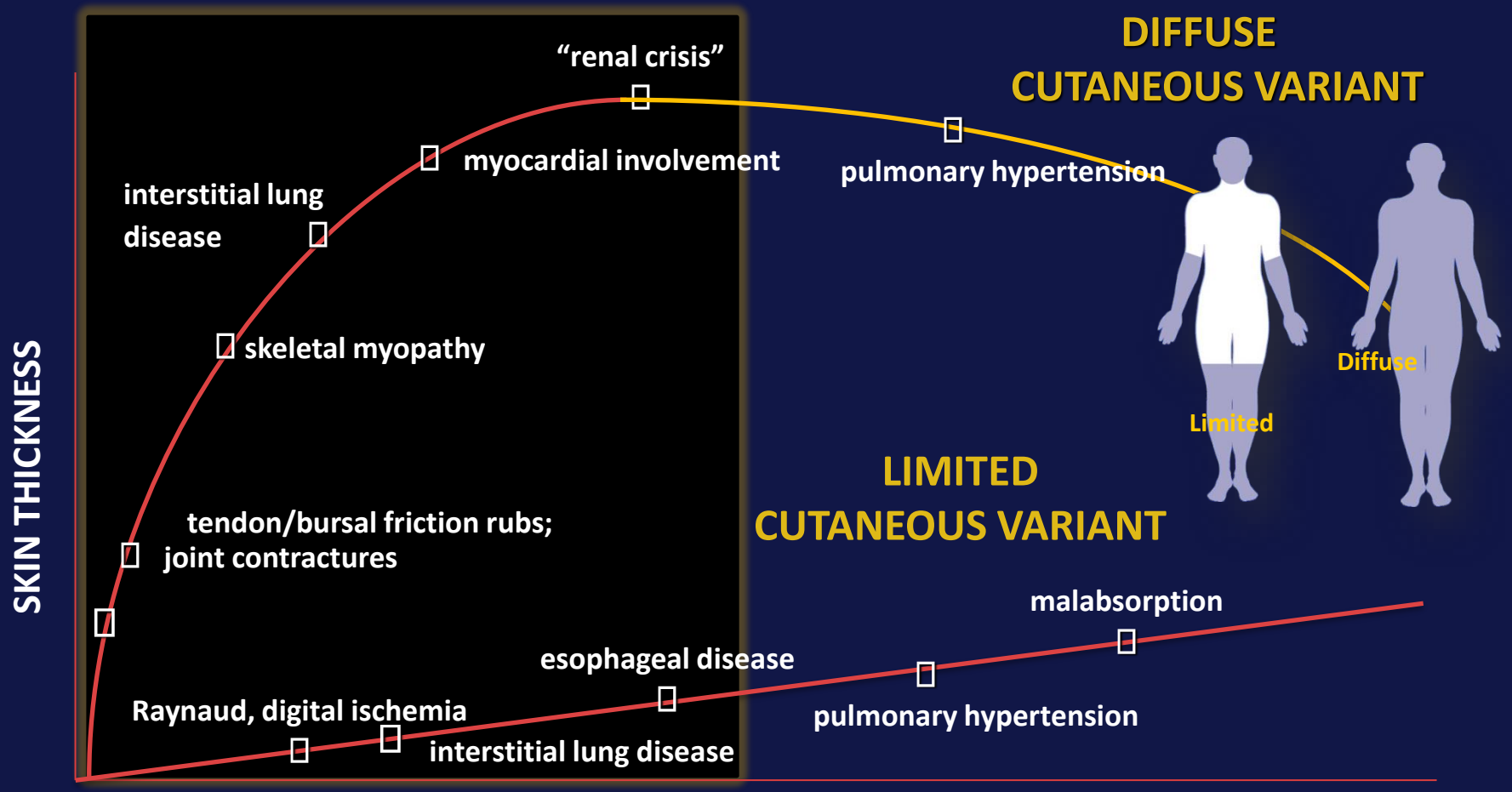


Clements PJ, Furst DE. *Systemic Sclerosis*; Lippincott, Williams & Wilkins, Baltimore, 2004.

Once the Diagnosis is Made……
Baseline Tests

- ANA by IIF
- SSc antibodies
  - Anti-centromere
  - Anti-SCL-70
  - Anti RNA Polymerase III
- EKG
- Echocardiogram with Doppler
- PFT with DLCO
- HRCT of lungs (non-contrast)

Usual Timing of Problems in Systemic Sclerosis



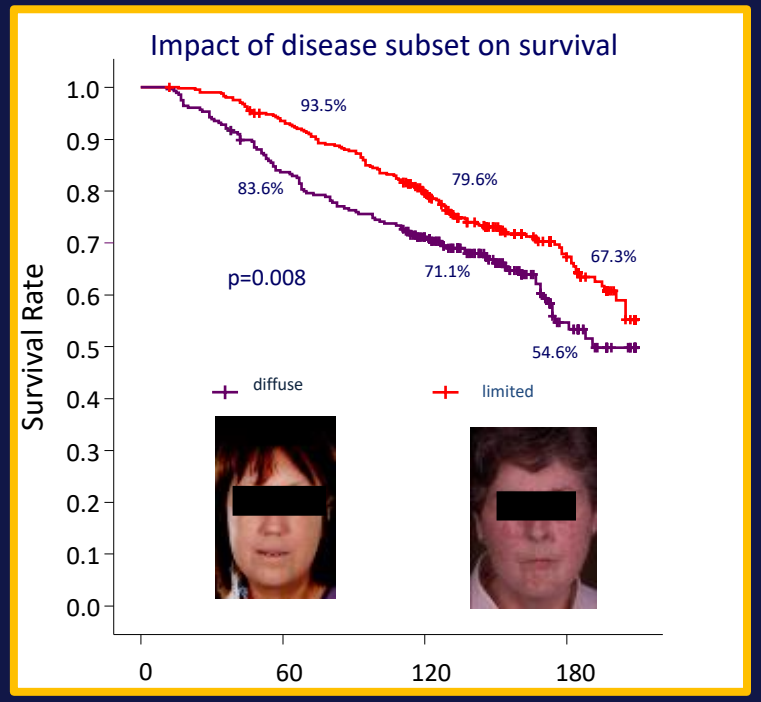
2-5 years after first non RP symptom/sign

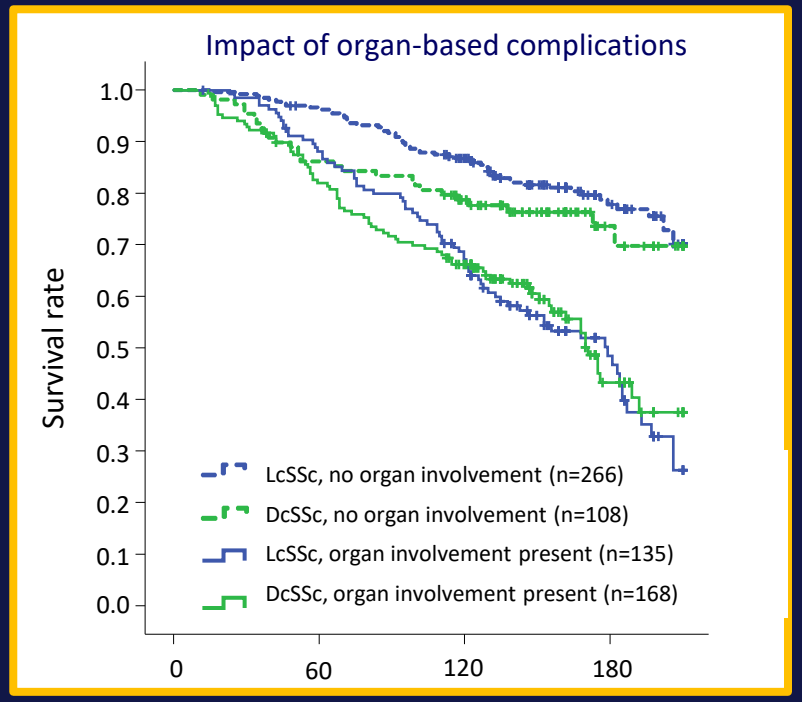
Provided by Thomas Medsger

Survival in Systemic Sclerosis is Determined by Subset and Organ-based Manifestations

1995 – 2003 incident SSc cohort at RFH (n=677)

Mortality is related to internal organ involvement and not skin involvement



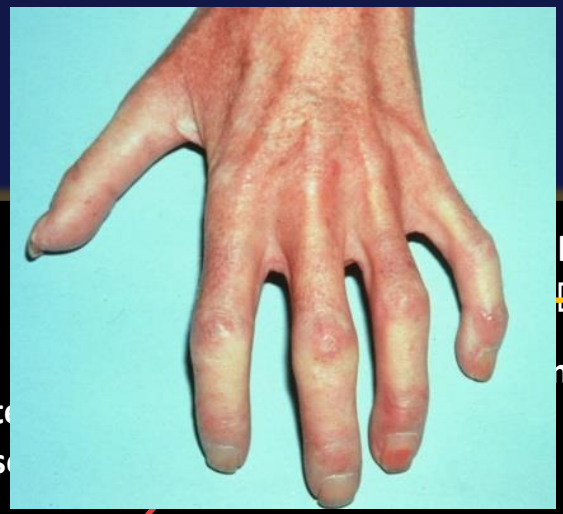


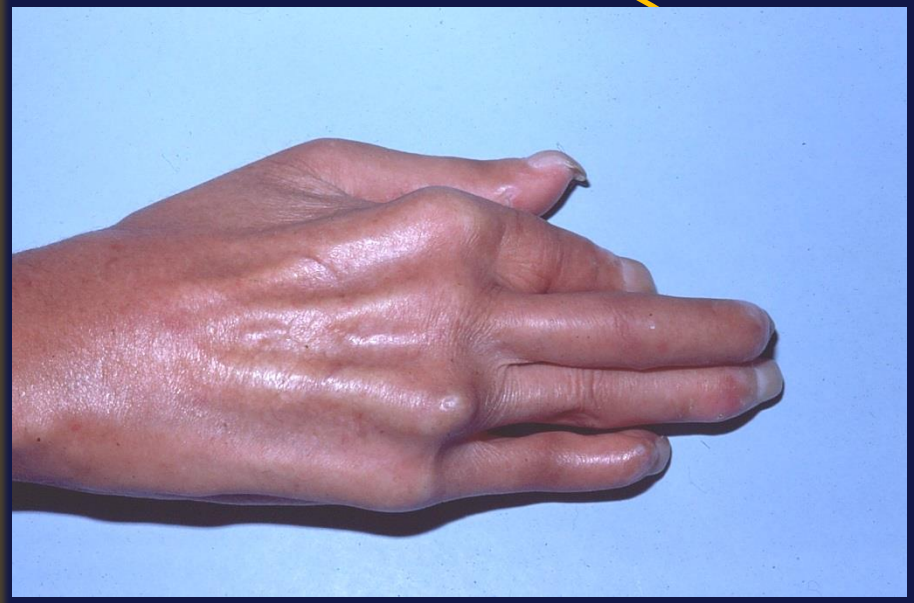
Complications: lung fibrosis, PH, SRC, cardiac – consensus definition for clinically important disease

Skin in Systemic Sclerosis

Who do you treat?

DIFFUSE CUTANEOUS VARIANT





2-5 years after first non RP symptom/sign

Associated with pain, stiffness, hand contractures, and disability

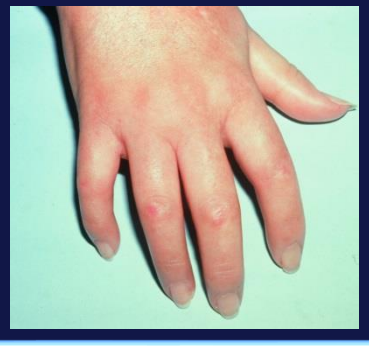
Provided by Thomas Medsger

Treatment of Skin Disease

- Traditional immunosuppressives
  - Methotrexate—Supported by 2 small clinical trials[1,2]
    - 15 mg/week oral for a year[1]
    - 15 mg/week subcutaneous for 24 weeks[2]
  - MMF-Supported by case series and post hoc analysis from the SLS-II
    - Mycophenolate mofetil at 3 grams/day[3]
  - Pulse CYC at 500 mg on monthly basis[4]
- IVIG[5]
- Abatacept S/Q week[6]
- Tocilizumab S/Q week[7]

1. Pope J et al *A&R.* 2001 Jun;44(6):1351-1358.
2. Van den Hoogen et al. *Br J Rheumatol.* 1996 Apr;35(4):364-72.
3. Namas R et al. *Arthritis Care Res (Hoboken). 2*018 Mar;70(3):439-444.
4. Valentini et al. *Scand J Rheumatol.* 2006 Jul;35:1,35-38.
5. Poelman et al. *J Rheumatol.* 2015 Feb;42(2):236-42.
6. Khanna D, et al. *Arthritis Rheumatol.* 2020 Jan;72(1):125-136.
7. Khanna D, et al *Lancet.* 2017 Oct;390(10103):1685-1699.

Treatment of Skin Disease

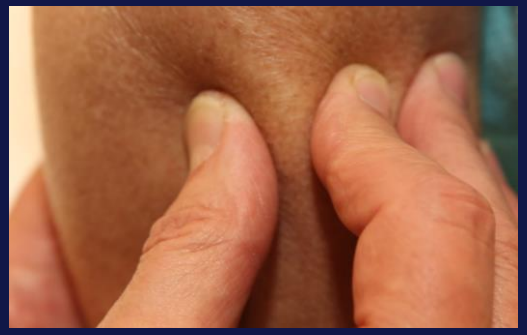


Very early < 1-2 years

Puffy Fingers

Anti-SCL-70/RNA Polymerase 3; +TFR

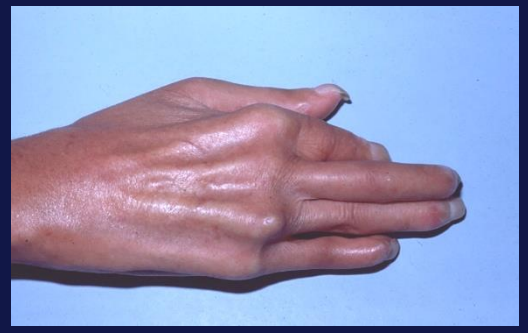
Treat with immunosuppressive therapy



Up to 4 years

Progressive skin fibrosis

Treat with immunosuppressive therapy



Late > 4 years

ONLY IF Progressive skin fibrosis

VERY RARELY happens

Treat with immunosuppressive therapy

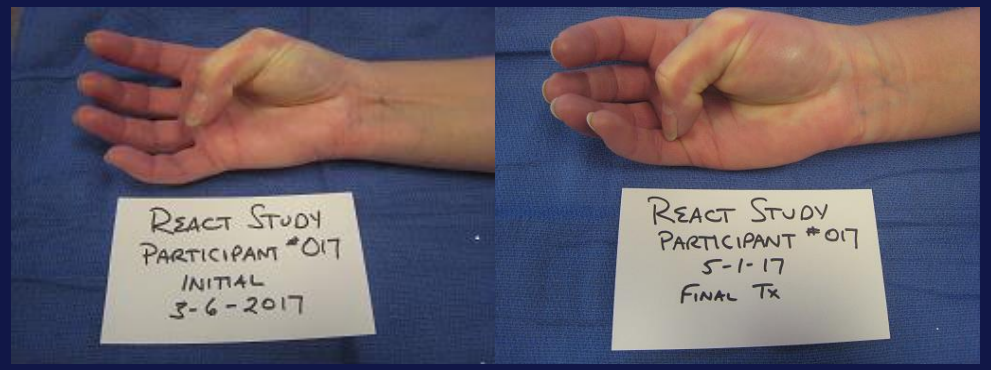
Management for Early Scleroderma Disorders

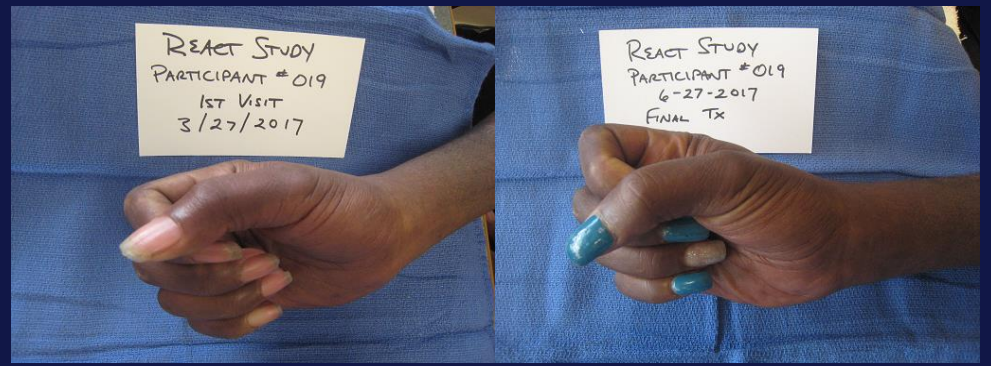
Arthritis Care & Research
Vol. 70, No. 11, November 2018, pp 1653–1660
DOI 10.1002/acr.23522

ORIGINAL ARTICLE

Occupational Therapy Treatment to Improve Upper Extremity Function in Individuals with Early Systemic Sclerosis: A Pilot Study

SUSAN L. MURPHY,[1] MARY WHITEHOUSE BARBER,[2] KATE HOMER,[3] CAROLE DODGE,[2] GARY R. CUTTER,[4] AND DINESH KHANNA[5]





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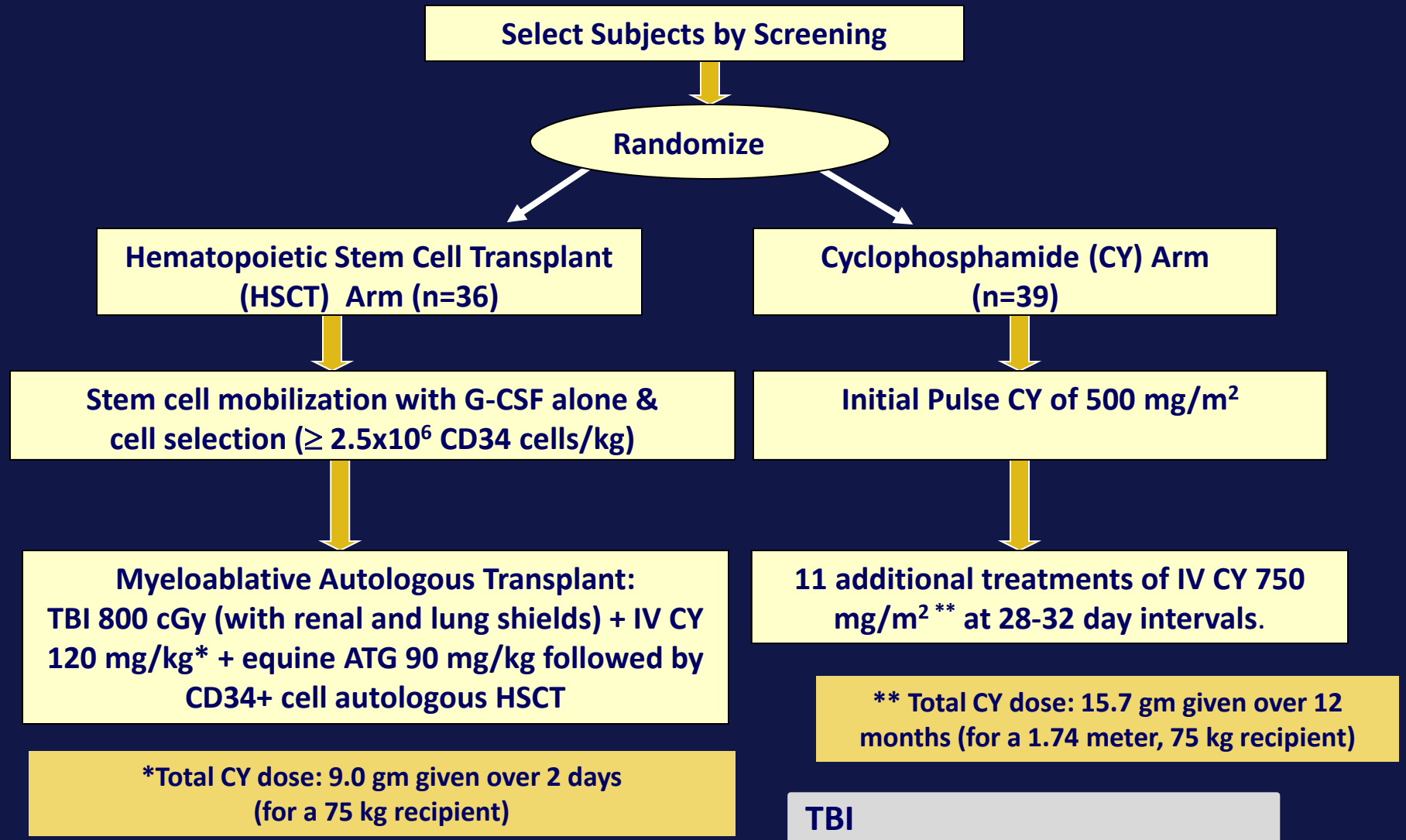
Treating Early Moderate-to-Severe Disease

Resetting the immune system

SCOT Trial Study Design



TBI

1. Highly immunosuppressive
2. Kills non-cycling cells

Key Eligibility Criteria for SCOT

- Age 18-69 years
- Diffuse SSc with poor prognosis
- Extensive skin involvement
- Disease duration < 5 years
- Early internal organ involvement with either:
  - Pulmonary disease (DLCO *or* FVC <70%)
  - Prior scleroderma renal crisis

- Want active disease
- Want reversible disease
- Want disease with PREDICTIBLY POOR PROGNOSIS

Abbreviations:
DLCO - diffusion capacity lung for carbon monoxide
FVC - forced vital capacity

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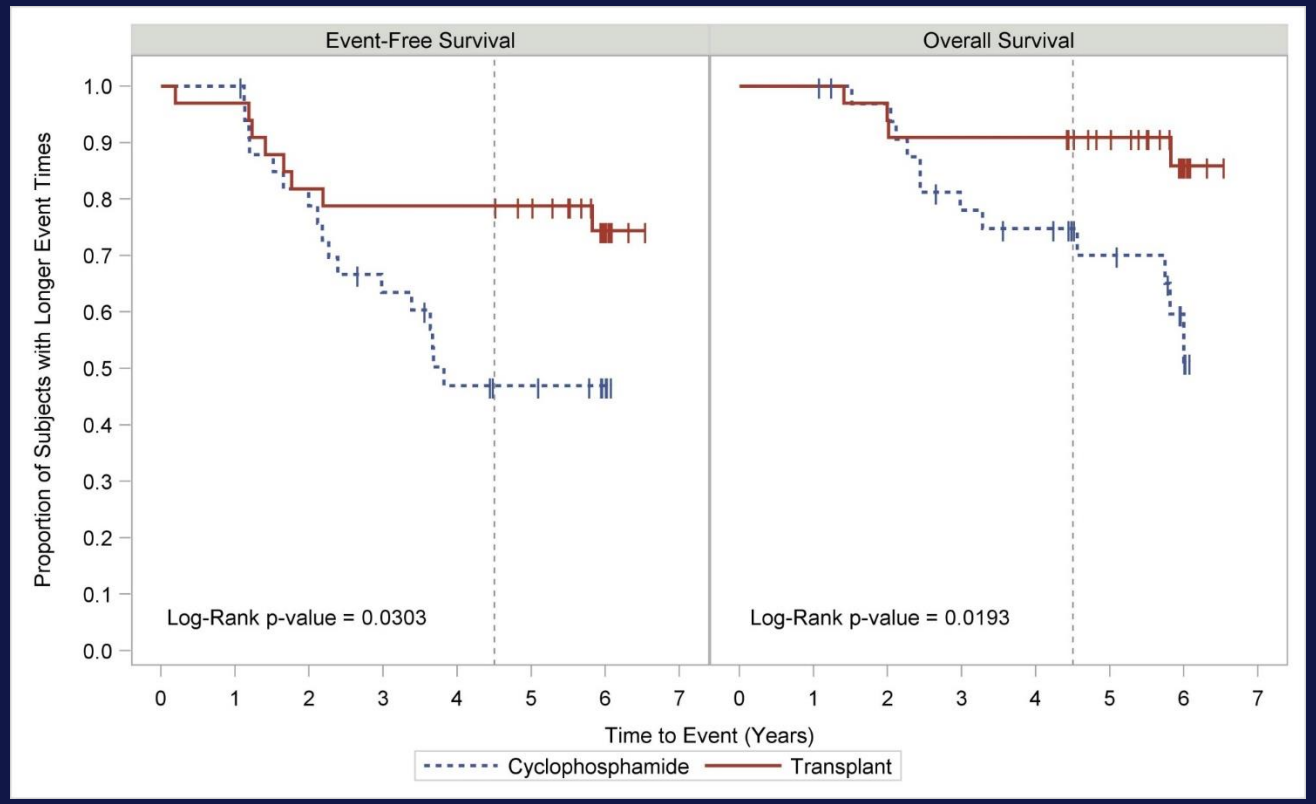
ORIGINAL ARTICLE

Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma

K.M. Sullivan, E.A. Goldmuntz, L. Keyes-Elstein, P.A. McSweeney, A. Pinckney, B. Welch, M.D. Mayes, R.A. Nash, L.J. Crofford, B. Eggleston, S. Castina, L.M. Griffith, J.S. Goldstein, D. Wallace, O. Craciunescu, D. Khanna, R.J. Folz, J. Goldin, E.W. St. Clair, J.R. Seibold, K. Phillips, S. Mineishi, R.W. Simms, K. Ballen, M.H. Wener, G.E. Georges, S. Heimfeld, C. Hosing, S. Forman, S. Kafaja, R.M. Silver, L. Griffing, J. Storek, S. LeClercq, R. Brasington, M.E. Csuka, C. Bredeson, C. Keever-Taylor, R.T. Domsic, M.B. Kahaleh, T. Medsger, and D.E. Furst, for the SCOT Study Investigators*

	Transplant (N=36)	CYC (N=39)
Age, years (mean)	44.9	46.9
Female, %	52.8	74.4
Scleroderma duration, months (mean)	**25.1**	**29.0**
Lung involvement, %	**100**	**95**
FVC% predicted, mean (SD)	**74.5 (14.8)**	**73.8 (17.0)**
DLCO% predicted, mean (SD)	53.9 (7.6)	52.7 (8.2)
MRSS, mean (SD)	28.5 (8.7)	30.8 (10.5)

Kaplan-Meier Survival Estimates:
(Treated Population)



Abbreviations: EFS, Event-free Survival; PP, Per Protocol (Treated) Population

Secondary Disease Progression Events (Month 54 in the Treated Population)

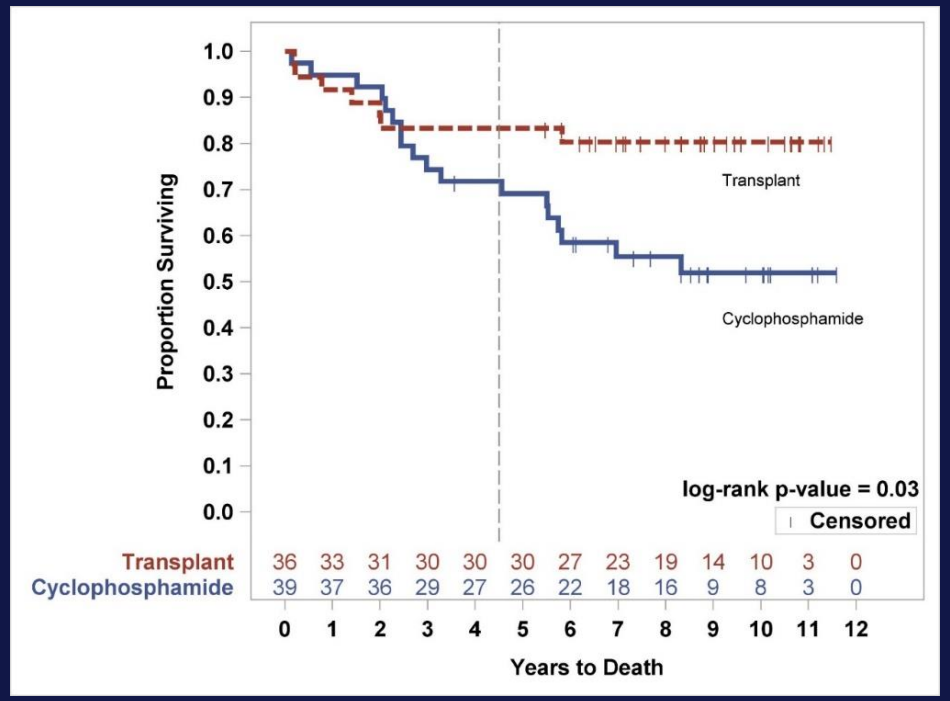
	HSCT (N=33)	CY (N=34)	P - value
Initiated DMARDs, n	3 (9%)	15 (44%)	0.001
Pulmonary artery hypertension, n	0	5 (15%)	0.022
Congestive heart failure*, n	0	4 (12%)	0.042

Abbreviations: CY, cyclophosphamide; DMARDS, Disease Modifying Anti-Rheumatic Drugs; HSCT, Hematopoietic Stem Cell Transplant

* Requiring Treatment

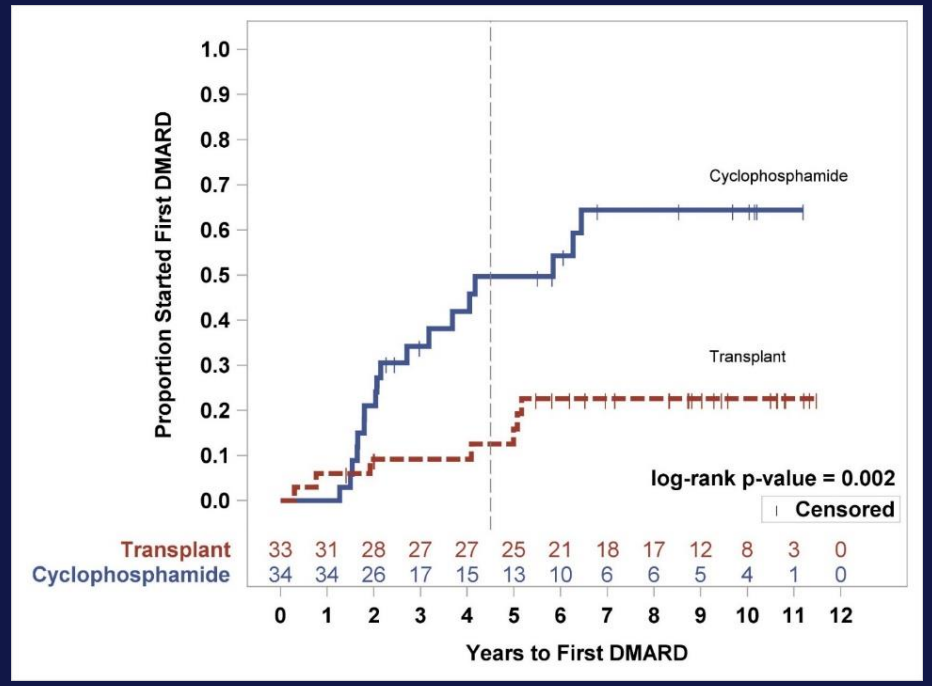
Overall Survival and Relapse Over 11 Years

Intention to Treat Population



Relapse or Progression of Disease

(Time to first DMARD use in the per protocol treated population)



Sullivan K. *ACR* 2018 [Plenary session]

Referral Criteria for HSCT Evaluation (Changing Clinical Practice)

- Diffuse SSc
- <65 years old
- < 5 years of disease duration
- < 6 months of prior cyclophosphamide
- Normal cardiac function and no PAH
- Early pulmonary involvement with:
  - FVC or DLCO of 80%-45% predicted
  - Serial PFTs not improving on DMARDS

Sullivan et al. *Arthritis Rheumatol*. 2016 Oct;68(10):2361-71.

- Diffuse cutaneous SSc
  - < 5 years of onset with mild-to-moderate internal organ involvement, esp ILD (*severe internal organ involvement will make patients ineligible due to risks associated with HSCT*)
- Limited cutaneous SSc
  - < 5 years with progressive internal organ involvement, esp ILD

Khanna D, et al. *JAMA* 2014 Nov;312(17):1805.

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Renal Involvement

Renal crisis

SSc patient	+	New onset ↑ BP	Rising + creatinine	Renal = crisis

Acute rise in BP defined as any of the following:

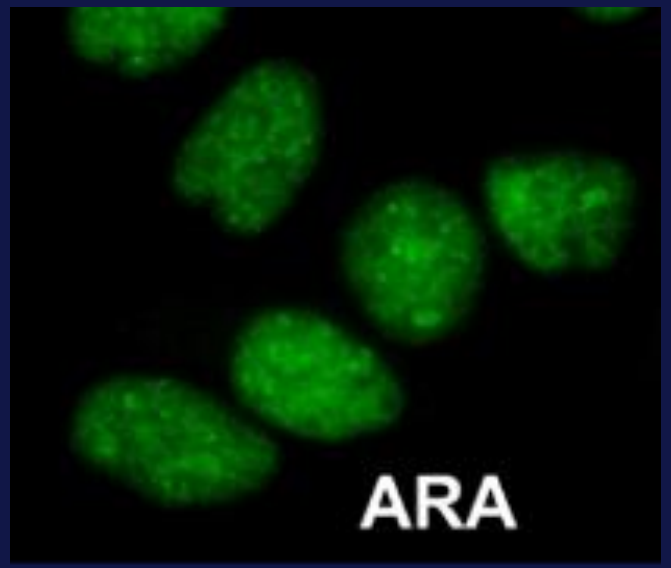
- **SBP ≥ 140 mmHg**
- **DBP ≥ 90mmHg**
- **A rise in SBP ≥ 30 mmHg**
- **A rise in DBP ≥ 20 mmHg**

BP is very resistant to treatment

ACE-inhibitors are the drugs of choice

Features Predictive of Renal Crisis

- 20% diffuse SSc have SRC
- 90% SRC occur in diffuse SSc
- <1% in classic limited SSc
- Early disease - 80% with < 4 years symptoms
- Rapidly progressive skin thickening
- New cardiac events
  - —CHF
  - —Pericardial effusion - before and during SRC
- Autoantibodies - anti-RNA polymerase III - 24-33% SRC (also severe skin), anti-topo predicts diffuse SSc but not SRC



Provided by Virginia Steen

Major Clinical Features of Renal Crisis

- Blood pressure - Severely increased, > 180/130
- Very resistant BP and difficult to control on outpatient basis
- Renal function
  - —Creatinine increases daily, even after BP controlled
  - —New onset proteinuria or hematuria
- Hematologic
  - —Microangiopathic hemolytic anemia
  - —Thrombocytopenia in 40%
- Cardiac
  - —Congestive heart failure
  - —Pericardial effusions

Renal Crisis Management

- Admit to the hospital in a monitored bed
- Begin ACE-inhibitor:
  - Captopril 25 mg every 6-8 hours
    - Push dose to 50-100 mg every 6-8 hours.
  - Lisinopril 5-10 mg every 12 hours
    - Push dose to 20-40 mg daily.
  - Goal is to normalize blood pressure within 72 hours
    - Risk not the same with long standing hypertension
  - Expect Cr to continue to ↑
    - don't stop ACE, even on dialysis
  - Only contraindication- Resistant K+ ↑

Renal Crisis Management

- If inadequate result:
  - Add calcium-channel blocker, i/v furosemide, i/v nitroprusside and other therapies
  - Role of continuous low dose I/V prostanoids
  - Dialyze as needed

Longer Term Therapy

- Transition to long acting ACE inhibitors
  - Example: enalapril or ramipril
  - Life long use
- If on dialysis, use lower dose on day of dialysis or on days not on dialysis due to lowering of BP
- Limit nephrotoxic agents
- Await 18 months before considering renal transplant.

Penn et al. *QJM.* 2013 Sep; 106(9):839-48.

Frequency of Steroids in the 6 Months Prior to SRC in Matched Cases and Controls

	Cases	Controls	Odds Ratio
New high dose (>15mg) steroid use	36%	12%	2.9*
Low dose (<15mg) steroid use	16%	10%	1.46
Any steroid use	59%	31%	2.86*

*p<0.05

Steen V. *Arthritis Rheum.* 1998 Sep;41:1613-9.

Role of Corticosteroids in SRC

- Glucocorticoids are prescribed for early progressive SSc
  - Management of inflammatory arthritis
  - Management of tendon friction rubs
  - Concomitant myopathy
- Relationship with SRC
  - Fluid retention
  - Confounding by indication

Who to Screen?

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Diffuse SSc

Early disease

RNA Poly 3++

S
a

-Check B
-Advice
to do

Limited SSc

Early disease

Discussion that complication exists

Late disease

No recs on BP monitoring

g /day in early SSc
c
+
n rubs
usion

SCLERODERMA RENAL CRISIS PREVENTION

Endorsed by Scleroderma Foundation/Tri-State Chapter Medical Advisory Board

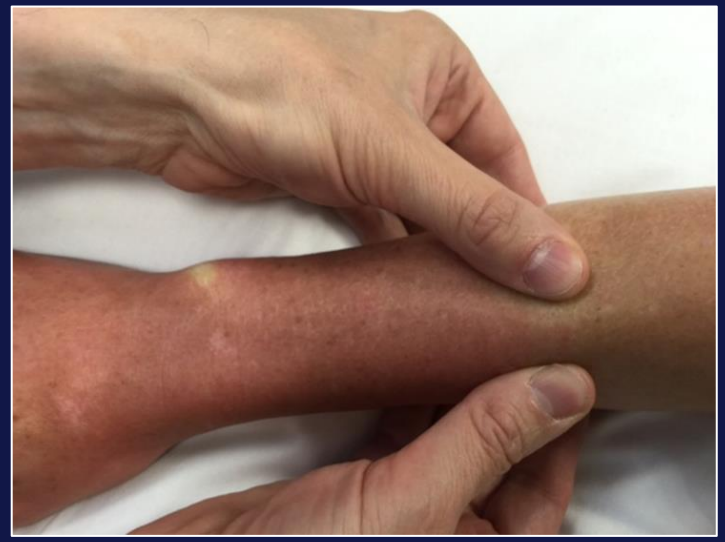
You have been identified as a person at risk of RENAL CRISIS, a preventable problem. **Know the warning signs:** New onset headaches, blurred vision, shortness of breath, confusion, abrupt elevation of blood pressure. **Monitor your blood pressure** and know **your usual readings**: _____/_____

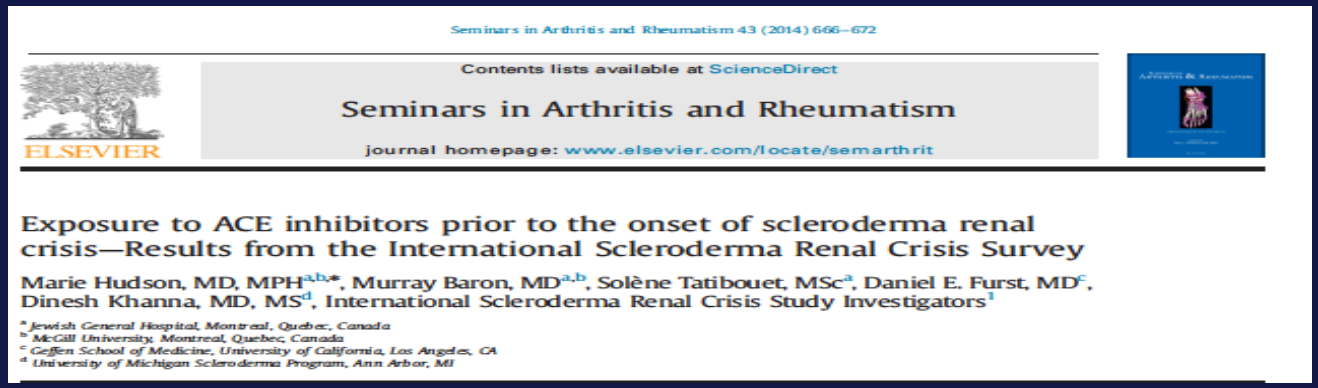
Call Dr. _____, if **BP is greater than** _____/_____ or **seek urgent care.**

Show any treating physician this card.

41 year old woman

- New consultation
- BP 114/82
- RNA polymerase 3+ with progressive skin thickening
- + tendon friction rubs
- Should she be treated with prophylactic ACE inhibitor?





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journal homepage: www.elsevier.com/locate/semarthrit

Exposure to ACE inhibitors prior to the onset of scleroderma renal crisis—Results from the International Scleroderma Renal Crisis Survey

Marie Hudson, MD, MPH[a,b,*], Murray Baron, MD[a,b], Solène Tatibouet, MSc[a], Daniel E. Furst, MD[c], Dinesh Khanna, MD, MS[d], International Scleroderma Renal Crisis Study Investigators[1]

[a] Jewish General Hospital, Montreal, Quebec, Canada
[b] McGill University, Montreal, Quebec, Canada
[c] Geffen School of Medicine, University of California, Los Angeles, CA
[d] University of Michigan Scleroderma Program, Ann Arbor, MI

Mean (SD) age, years	52.5 (12)
Disease subsets, N(%)	
Diffuse	56 (75%)
Limited	16 (21%)
Sine scleroderma	3 (4%)
Disease duration (since first non-Raynaud's symptom)	
Median, years (IQR)	1.5 (0.9, 3.7)
Hypertensive SRC, N (%)	70 (93%)
Normotensive SRC, N (%)	5 (7%)

Adjusted	ACE inhibitor prior to SRC	2.42	[1.02; 5.75]	**0.0460**
	Prednisone (mg/d)	1.04	[1.02; 1.07]	**0.0023**

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Pulmonary Hypertension

What is Pulmonary Hypertension?

- Pulmonary hypertension: elevated pulmonary pressure with multiple etiologies
- Hemodynamic observation and should lead to identify underlying cause
- Pulmonary arterial hypertension (PAH) results from restricted flow through pulmonary arterial circulation
  - Leads to ↑ pulmonary vascular resistance (PVR), ultimate right heart failure
  - Predominant cause - loss of vascular luminal volume from vascular remodeling, excessive cell proliferation, ↓ apoptosis

6th World Symposium Classification of PH

1. Pulmonary Arterial Hypertension

1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4 PAH associated with:
- 1.4.1 Connective tissue disease
- 1.4.2 HIV infection
- 1.4.3 Portal hypertension
- 1.4.4 Congenital heart diseases
- 1.4.5 Schistosomiasis

1.5 PAH long-term responders to CCBs
1.6 PAH with overt features of venous/ capillaries involvement
1.7 Persistent PH of the newborn syndrome

2. PH Due to Left Heart Disease

2.1 PH due to HF with preserved LVEF
2.2 PH due to HF with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3. PH Due to Lung Diseases and/or Hypoxia

3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/ obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders

4. PH Due to Pulmonary Artery Obstructions

4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions

5. PH With Unclear and/or Multifactorial Mechanisms

5.1 Hematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

Simonneau G, et al. *Eur Resp J.* 2019;53:1801913

New Hemodynamic Definition of PH/PAH

PH

Mean PAP ≥20 mm Hg

PAH

Mean PAP >20 mm Hg *plus*

PCWP/LVEDP ≤15 mm Hg

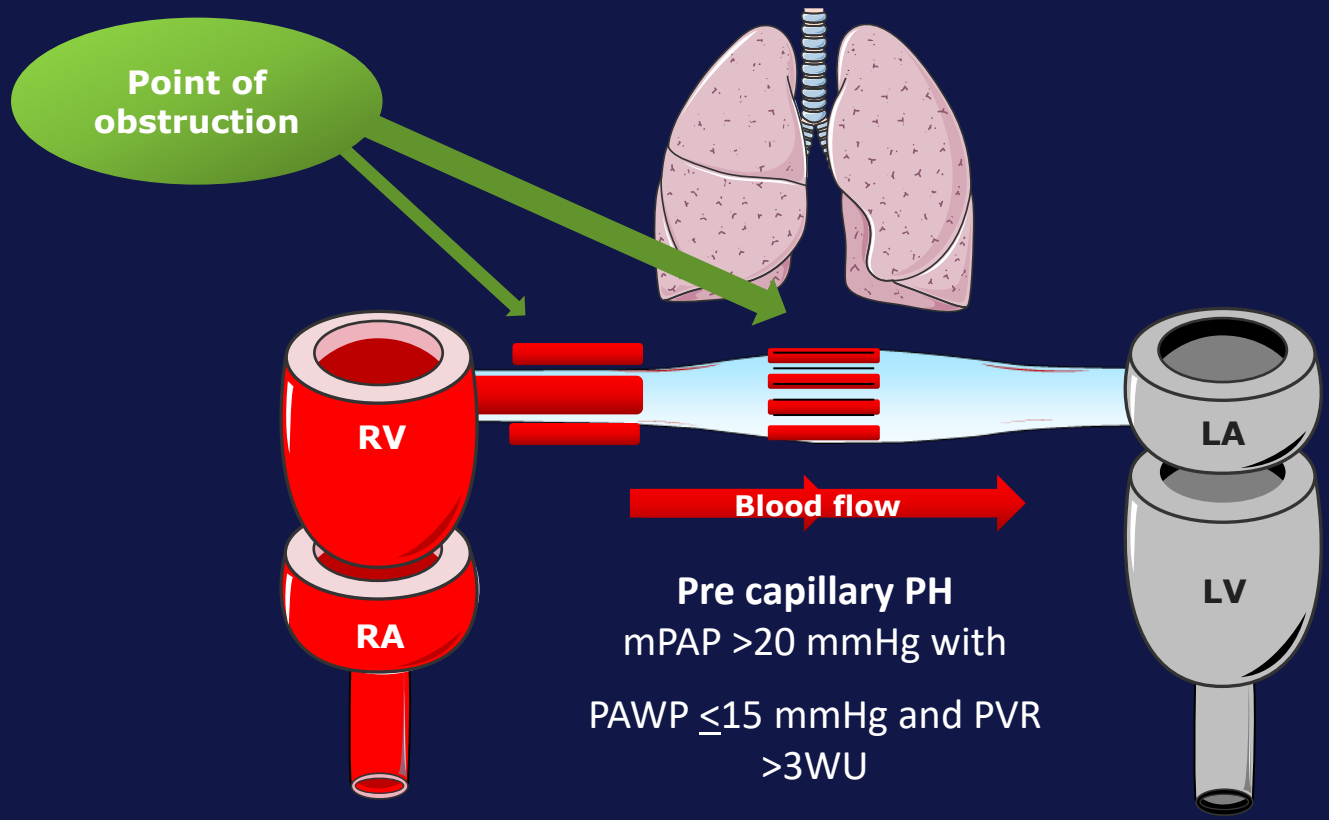
+

PVR > 3 Wood Units

Badesch D et al. *J Am Coll Cardiol.* 2009;54(1 Suppl):S55-66.
Galiè et al. *Eur Respir J.* 2019;53(1):1802148.

Attaining a differential diagnosis of PAH in SSc patients can be challenging:

Group 1



Pre capillary PH

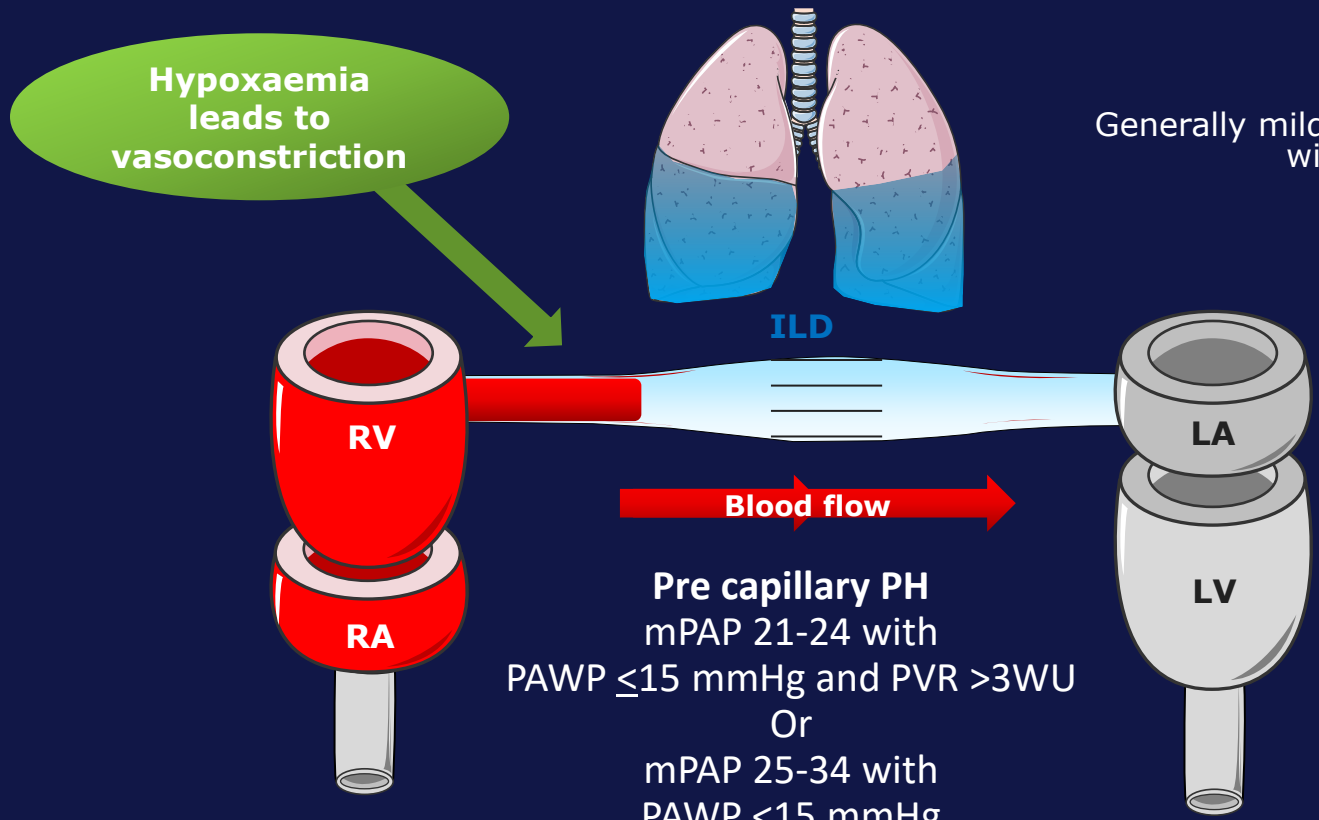
mPAP >20 mmHg with

PAWP ≤15 mmHg and PVR >3WU

Take Home Message #3

Provided by Eric Hachulla

Attaining a differential diagnosis of PAH in SSc patients can be challenging: Group 3, PH related to ILD



Generally mild PH = mPAP <35 mmHg with normal CI

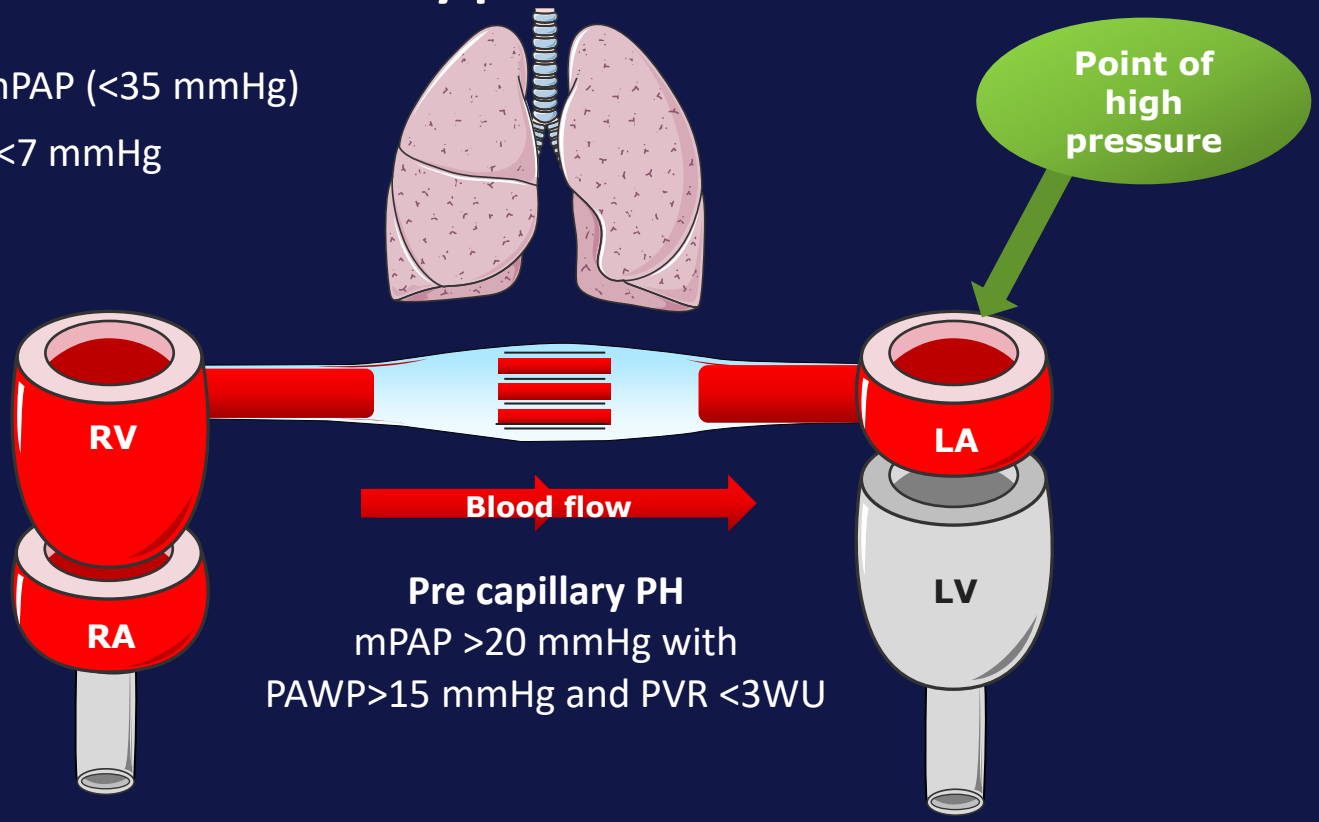
Pre capillary PH
mPAP 21-24 with
PAWP ≤15 mmHg and PVR >3WU
Or
mPAP 25-34 with
PAWP ≤15 mmHg

ILD, interstitial lung disease

Provided by Eric Hachulla

Attaining a differential diagnosis of PAH in SSc patients can be challenging: Group 2, Pulmonary Venous Hypertension

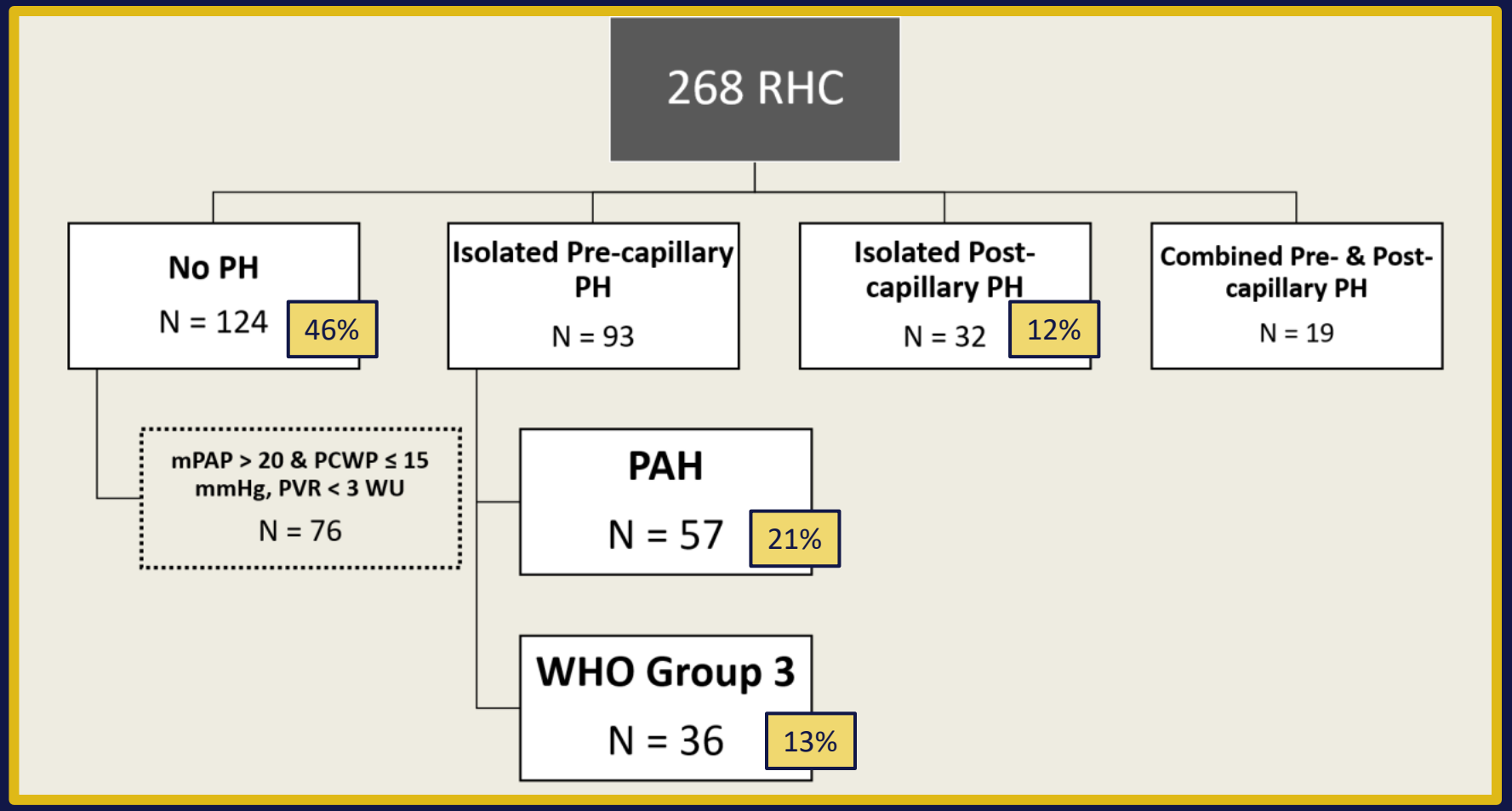
- Mild increase of mPAP (<35 mmHg)
- DG = dPAP - PWP <7 mmHg



WU, Wood unit;
PWP, pulmonary wedge pressure

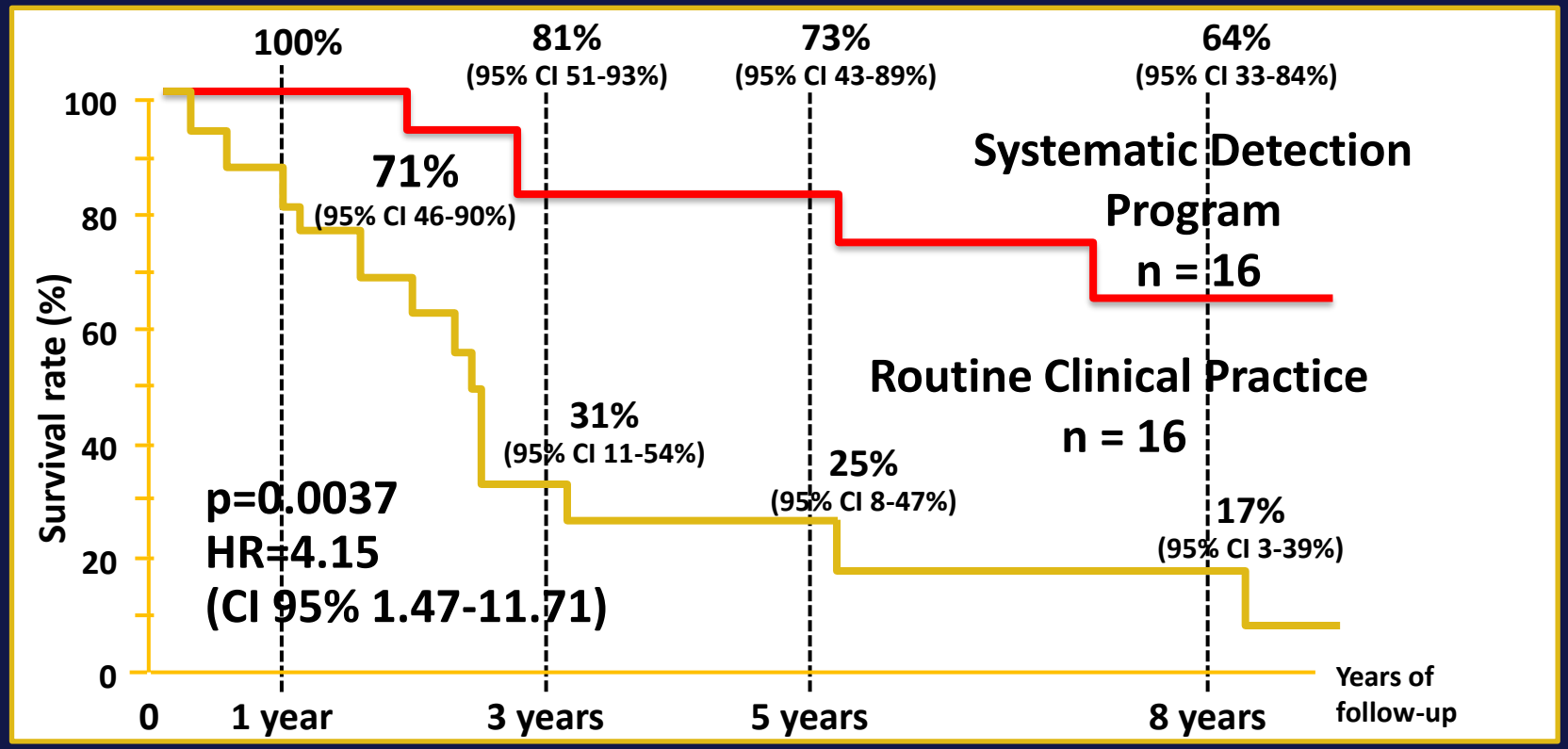
Provided by Eric Hachulla

UM Experience 2005-March 2019



Jaafar S et al. *Eur Respir J.* 2019 Aug;54(2):1900586.

Active Screening Reveals Patients Earlier Who Live Longer



Values at each time point are the survival rate with 95% confidence interval (95% CI), HR = hazard ratio

Humbert M et al. *Arthritis Rheum.* 2011 Nov;63(11)3522-30.

Recent Guidelines Support Screening for PAH in SSc

Recommendations for Screening and Detection of PAH-CTD[1]:

Every patient with SSc should be screened annually for PAH due to the high prevalence of PAH in SSc

Recommendations from 5th and 6th WSPH[2,3]:

Annual screening for PAH is recommended in (cardiopulmonary) asymptomatic patients with the SSc spectrum of diseases

Recommendations from 2015 ESC/ERS guidelines[4,5]:

Recommendations
Resting echocardiography is recommended as a screening test in asymptomatic patients with SSc, followed by annual screening with echocardiography, DLCO and biomarkers

*The DETECT algorithm is not yet validated in patients with DLCO > 60%

DLCO: diffusing capacity of the lung for carbon monoxide; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; SSc: systemic sclerosis. [a]Class of recommendation [b]Level of evidence.

1. Khanna D, et al. *Arthritis Rheum.* 2013 Dec;65(12):3194-201.
2. Hoeper M, et al. *J Am Coll Cardiol.* 2013 Dec;62(25 Suppl):D42-D50.
3. Frost A, et al Eur Respir J. 2019 Jan;53(1):1801904.
4. Galiè N, et al. *Eur Respir J* 2015 Oct;46(4):903-75.
5. Galiè N, et al. *Eur Heart J* 2016 Aug;48(2):311-4.

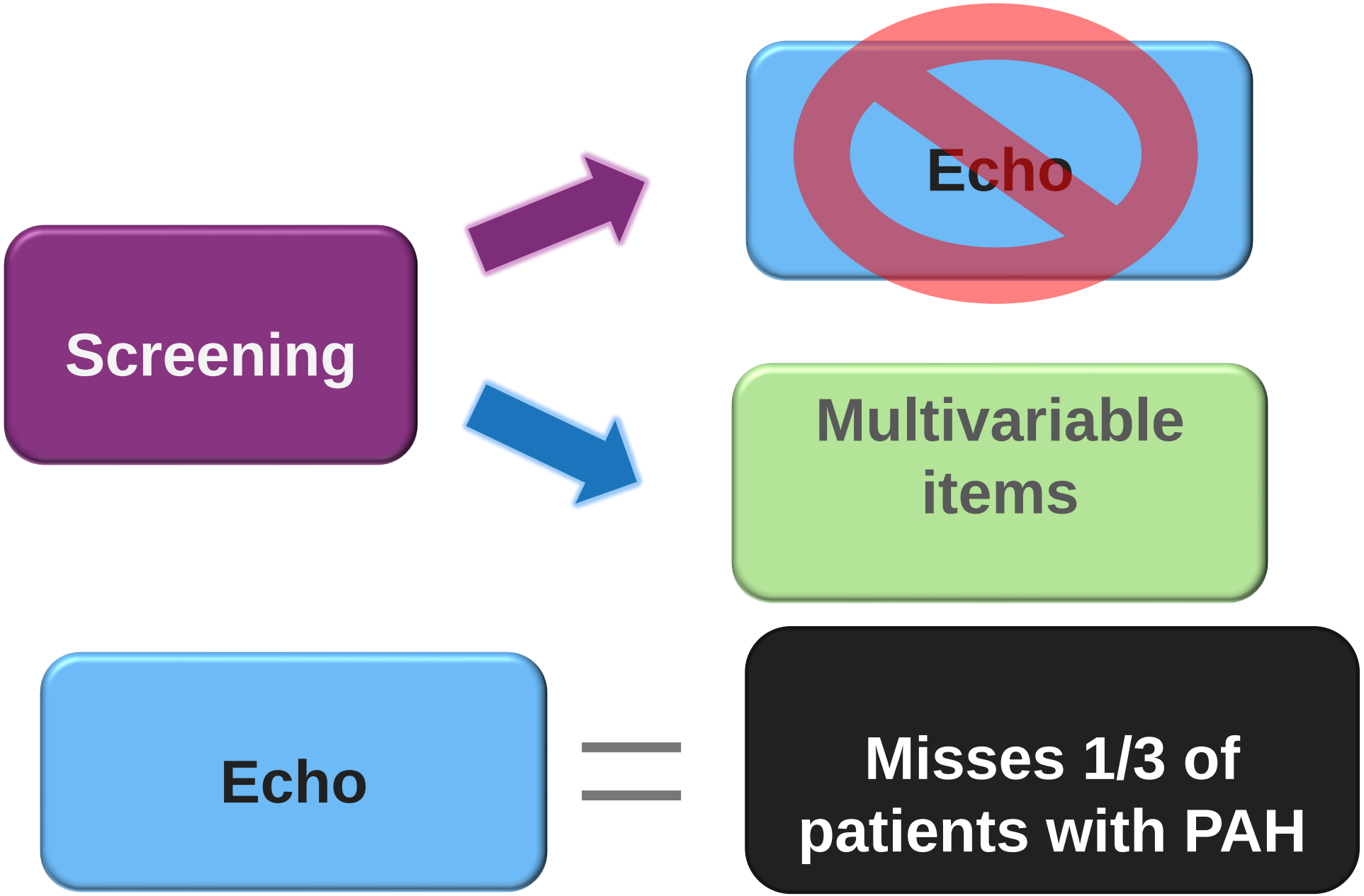
False Negativity Associated with Echocardiographic in DETECT Study (N=303)

SSc
DLCO < 60%
Disease duration > 3 years

PAH suspicion threshold (TR velocity/eRVSP)	Percentage of PAH patients
< 2.5 m/s; 30 mmHg	20%
≤ 2.8 m/s; 36 mmHg	36%
≤ 3.4 m/s; 50 mmHg	63%

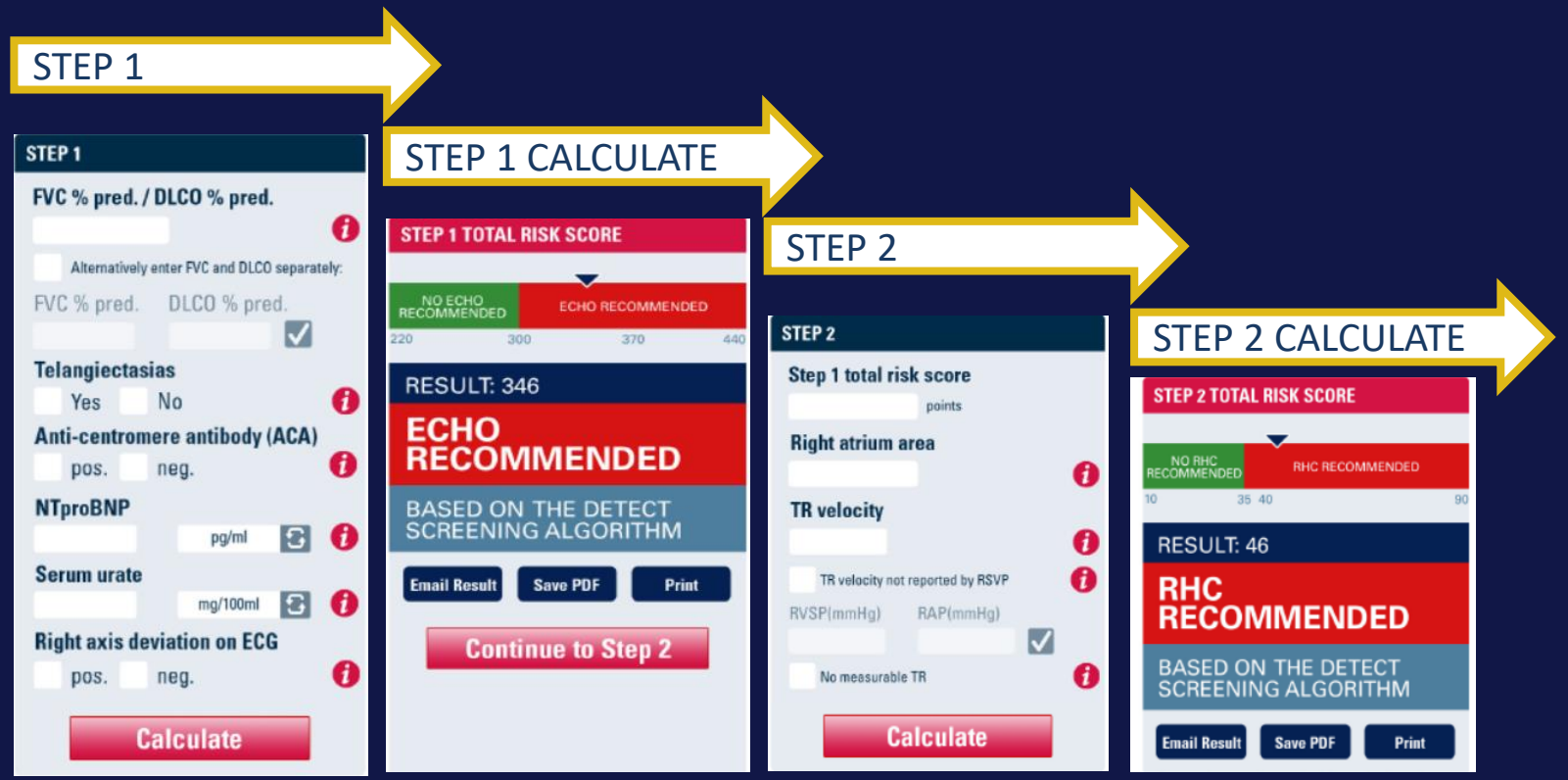
- eRVSP = 4 (TR velocity)^2 + RAP (assumed 5 mmHg)
- The use of TR velocity thresholds alone for detecting PAH is associated with a high rate of missed PAH diagnoses
- eRVSP: estimated right ventricular systolic pressure

Coghlan JG, et al. *Ann Rheum Dis.* 2014 Jul;73(7):1340-9.


Screening
Echo
Multivariable items
Echo
Misses 1/3 of patients with PAH

DETECT Two-step Decision Tree for Screening Ssc Patients

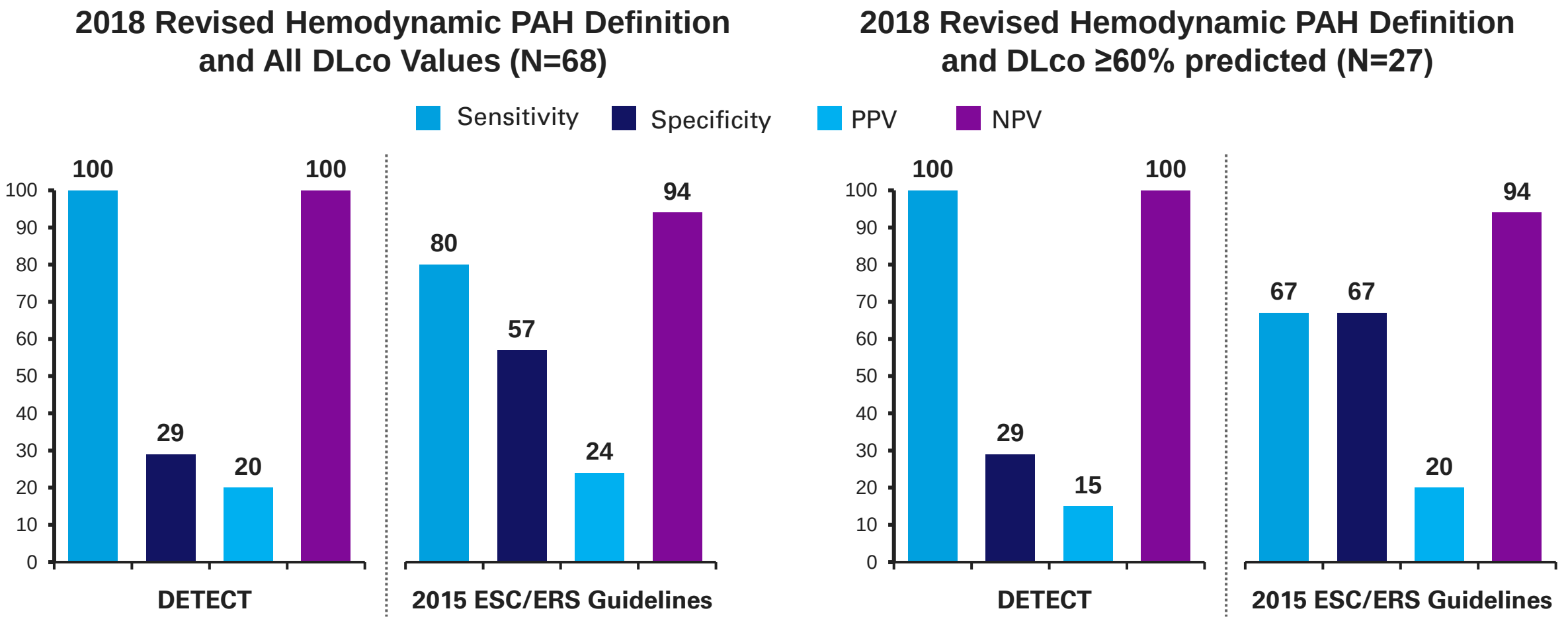
- DETECT v2.0 was released in January 2019



Coghlan JG, et al. *Ann Rheum Dis.* 2014 Jul;73(7):1340-9.

U-M Experience in SSc

Predictive Accuracies of the DETECT Algorithm and 2015 ESC/ERS Guidelines



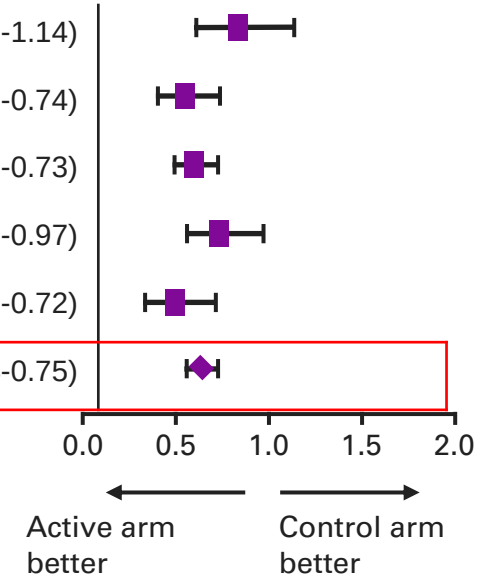
*Patients were screened using scheduled echocardiographic assessment.

Young A M, et al. *Arthritis Rheum*. 2021 [Epub ahead of print]

Risk of a Clinical Event by Drug Treatment and PAH Etiology

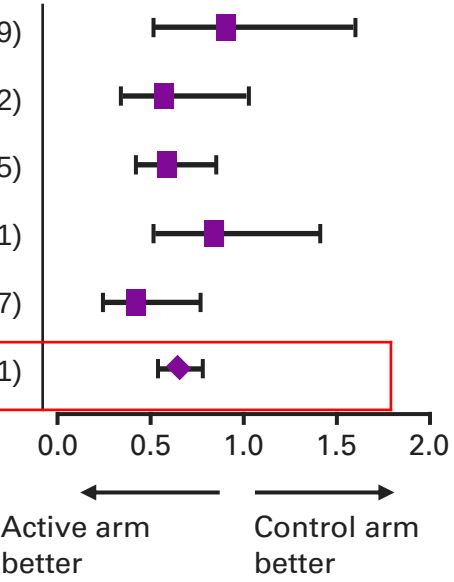
Overall PAH population
36% reduction in risk of a clinical event
HR=0.64 (95% CI, 0.54–0.75; *P*<0.001):

Study name	Active arm (n)	Control arm (n)	HR (95% CI)
COMPASS-2	159	175	0.83 (0.61-1.14)
SERAPHIN	242	250	0.55 (0.41-0.74)
GRIPHON	574	582	0.60 (0.49-0.73)
FREEDOM-EV	346	344	0.74 (0.56-0.97)
AMBITION	253	247	0.50 (0.35-0.72)
Overall			0.64 (0.54-0.75)



CTD-PAH population
36% reduction in risk of a clinical event
HR=0.64 (95% CI, 0.51–0.81; *P*<0.001)

Study name	Active arm (n)	Control arm (n)	HR (95% CI)
COMPASS-2	43	45	0.90 (0.51-1.59)
SERAPHIN	73	81	0.58 (0.33-1.02)
GRIPHON	167	167	0.59 (0.41-0.85)
FREEDOM-EV	94	84	0.84 (0.50-1.41)
AMBITION	103	84	0.43 (0.24-0.77)
Overall			0.64 (0.51-0.81)



Five randomized controlled trials (N=3172; n=941 with CTD-PAH [30%]) reported HRs for a morbidity or mortality event by drug treatment and PAH etiology. Clinical event definitions varied between trials but generally included death, worsening of PAH, hospitalization due to PAH, and treatment escalation.

Khanna D, et al. *Arthritis Rheumatol*. 2021 [Epub ahead of print].

PAH-Specific FDA-Approved Therapies

Endothelin Receptor Antagonists	NO-cGMP Pathway	Prostanoids – Prostacyclin Analogs	Prostacyclin Agonists
Bosentan (PO) FDA Approved: 2001	**Sildenafil (PO)** FDA Approved: June 2005	**Epoprostenol (IV)** Flolan FDA Approved: September 1995 Veletri FDA Approved: June 2008	**Selexipag (PO)** FDA Approved: December 2015
Ambrisentan (PO) FDA Approved: June 2007	**Tadalafil (PO)** FDA Approved: May 2009	**Treprostinil (IV, SC, PO, and inhaled)** First (SC formulation) FDA Approved: July 2002	
Macitentan (PO) FDA Approved: October 2013	**Riociguat (PO)** FDA Approved: October 2013	**Iloprost (inhaled)** FDA Approved: December 2004	

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed April 1, 2016.

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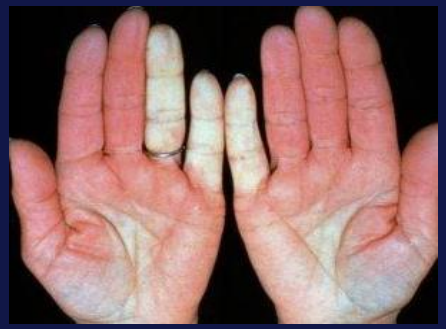
Raynaud's Phenomenon

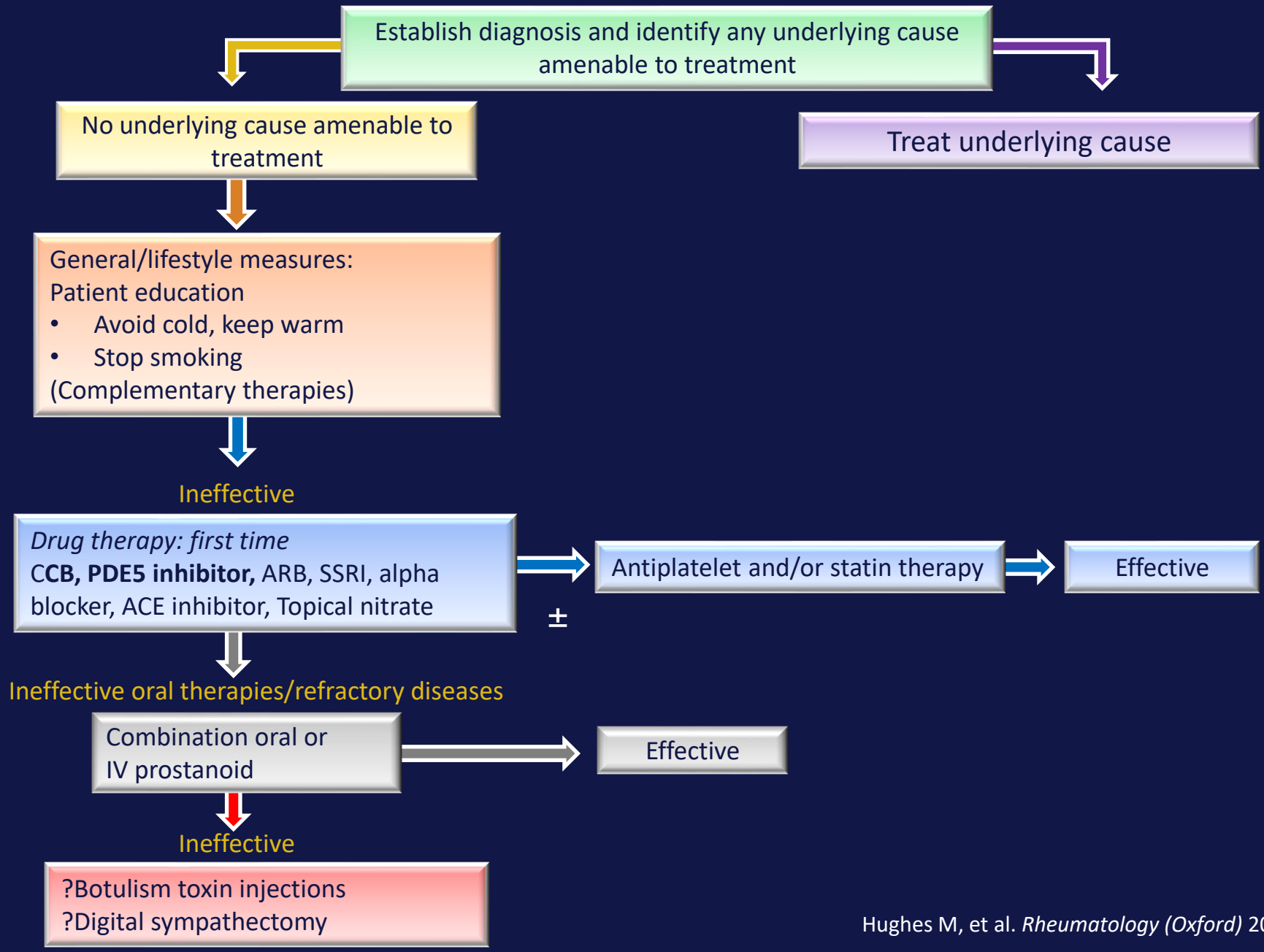
Raynaud's Phenomenon in SSc[1]

- 95% of patients with SSc
- Part of the 2013 ACR EULAR Classification criteria[2]
- Mainly affects digits; can affect ears, nose, etc.
- Triphasic color change
  - Pallor– cold-induced digital artery vasospasm and venous spasm
  - Cyanosis— Vasodilation of venous system
  - Rubor– dilatation of Atrial Venous Anastomosis with influx of oxygenated blood
- Clinical diagnosis
  - Ask the following screening questions[1]:
    - Are your fingers unusually sensitive to cold?
    - Do your fingers change color when exposed to cold temperatures?
    - Do they turn white, blue, or both?



1. Wigley and Flavahan. *N Engl J Med* 2016;375(6):556-565.
2. Van den Hoogen, et al. *Arthritis Rheum* 2013 Nov;65(11):2737-47.

Management of Raynaud's Phenomenon



Hughes M, et al. *Rheumatology (Oxford)* 2015 Nov;54(11):2015-24.

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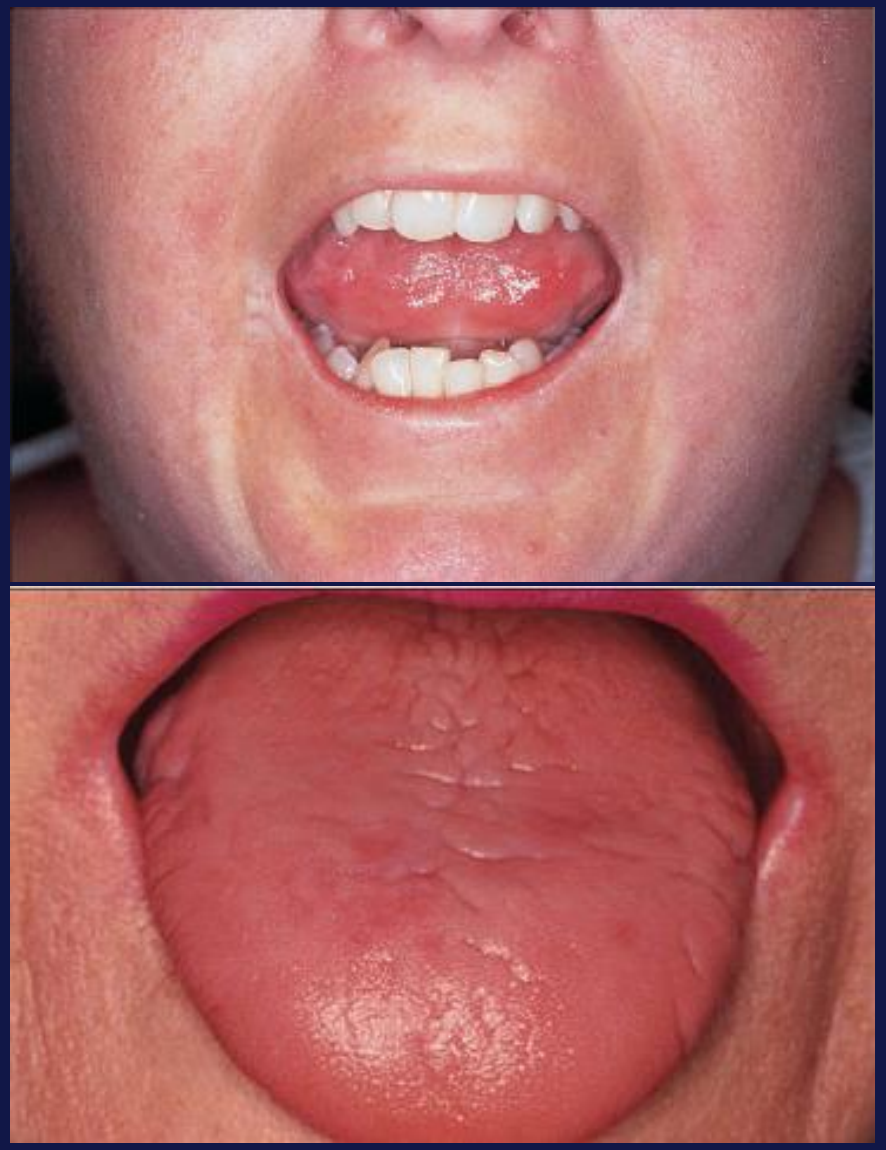
Gastrointestinal Symptoms

Oropharyngeal Manifestations

- Facial involvement interferes with mastication
- 20% Sjogren's syndrome

TREATMENT

- Liberal fluid intake
- Regular dental appointments
- Sugar free gums
- Trial of pilocarpine and cevimeline therapy

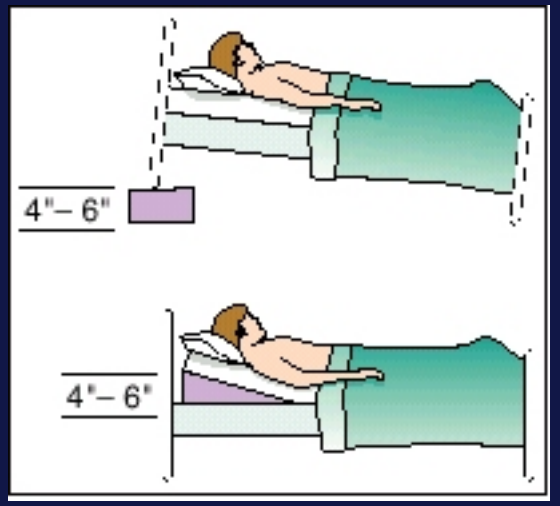


Oral Moistures & Protection

- Xylitol containing products
- Caphsol- super saturated calcium phosphate
- Fluoride based products
- Calcium phosphate paste

Anti-Reflux Measures

- Head of the bed elevated (i.e. wedge pillow, blocks under head of bed, electric bed.) NOT extra pillows
- Biggest meal at noon, small meals otherwise
- Do not eat late (after 6pm); do not drink fluids late (after 8pm)
- Frequent small meals (5-6 per day)
- No tight garments around waist



How to use PPI?

- PPI blockers 30 to 60 minutes before each meal
  - May require higher dose
- Start PPI agent once a day
- Increase to twice a day*
- Add H2 blocker at bedtime*
- Continuing symptoms– refer to GI for w/u.
  - R/O stricture
  - R/O candida esophagitis
  - Further studies such as manometry and ph impedance (can tell about both acidic and non-acidic reflux)

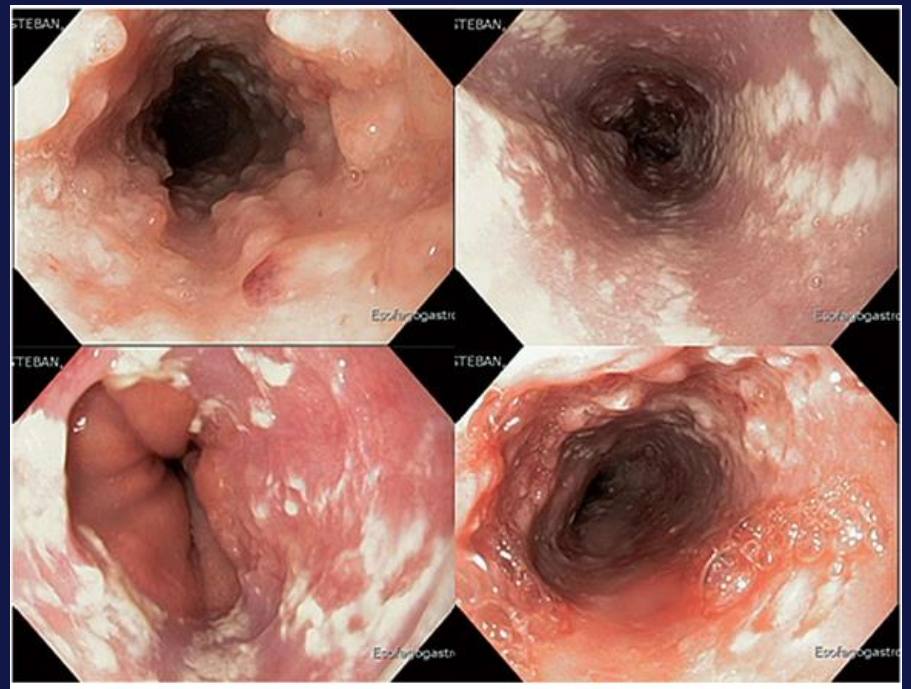


Figure 1. Initial upper endoscopy.

** If the heartburn or other symptoms continue for 2 weeks*

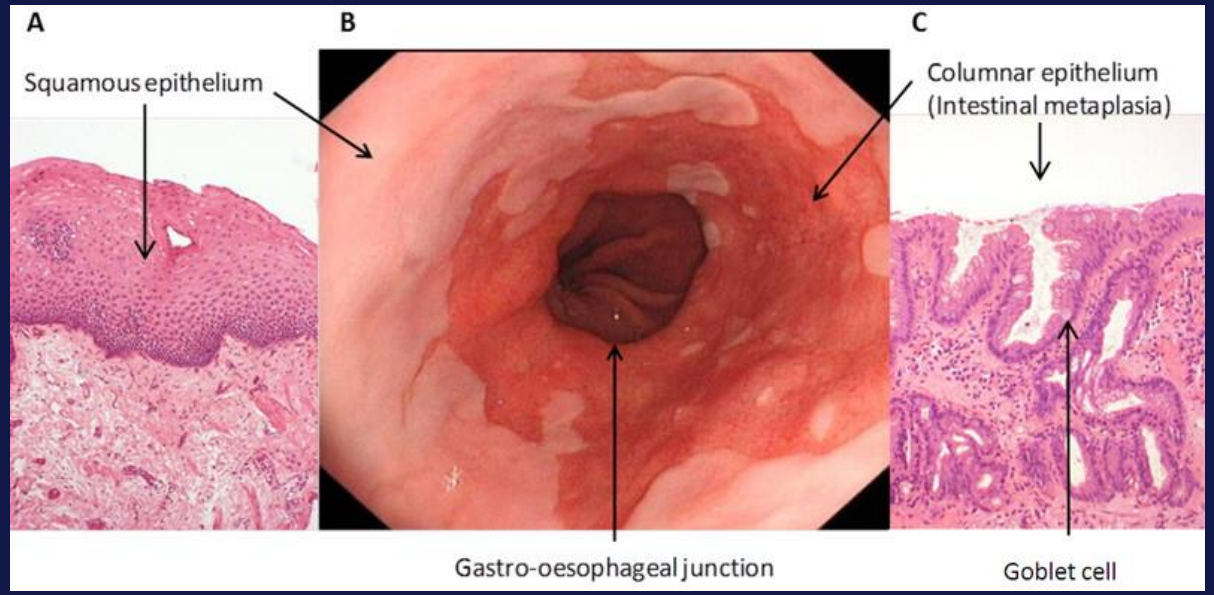
Failure of the PPI

- RCT in SSc patients who had ongoing GERD despite being on PPI
- Domperidone 10 mg po TID vs. alginic acid 1 chewing tablet three times daily
- Alginic acid acts by precipitating as a gel and creating a relatively pH neutral mechanical barrier that floats on the surface of gastric contents.
- Patients were randomized to either domperidone (n = 38) or algycon (n = 37) therapy
- At 4 weeks the severity of symptoms, frequency scale for symptoms of GERD and QoL significantly improved in both groups

Foocharoen, et al. *Rheumatology* (Oxford). 2017 Feb;56(2):214-222.

Barrett's Esophagus

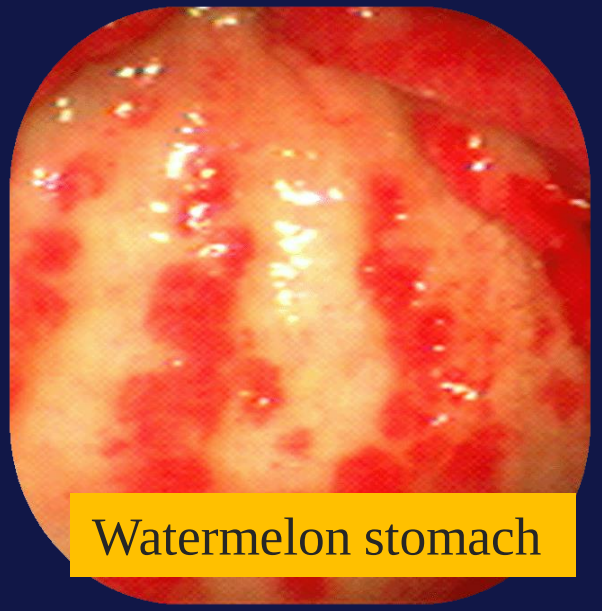
- Barrett's esophagus is a complication of long-standing GERD[1-3].
- Present in 13% consecutive people with SSc receiving chronic therapy with PPI[1].
- Prevalence of 6% in general population[4].
- Barrett's esophagus is associated with adenocarcinoma in SSc.
  —Incidence is 0.7%/year[3]



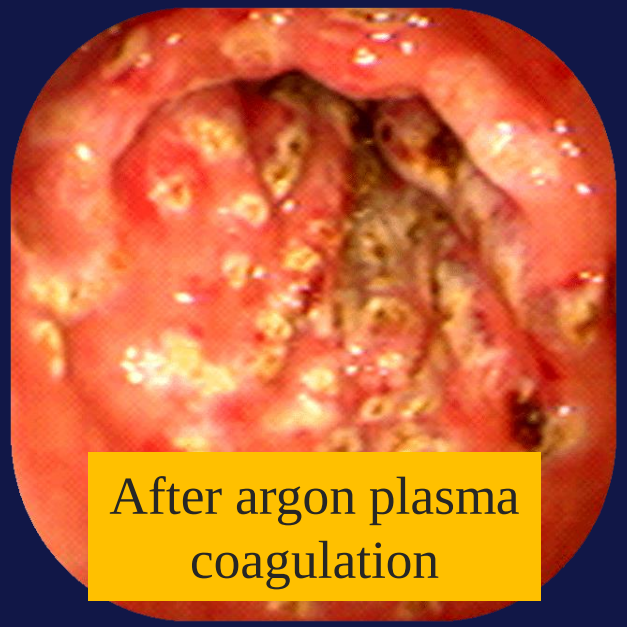
1. Wipff J, et al. *Arthritis Rheum* 2005 Sep;52(9):2882-8.
2. Derk CT, et al. *J Rheumatol* 2006 Jun;33(6):1113-6.
3. Wipff J, et al. *Rheumatology (Oxford).* 2011 Aug;50(8):1440-4.
4. Hayeck TH, et al. *Dis Esophagus* 2011 Aug;23(6):451-7.

Gastric Antral Vascular Ectasia (Watermelon Stomach)

- Cause of iron deficiency anemia
- Prevalence of GAVE in SSc from 9% to 23%[1,2]
- Presenting symptoms may be fatigue and tiredness
- Repeated blood transfusions may be necessary



Watermelon stomach



After argon plasma coagulation

1. Duchini A, et al. *Am J Gastroenterol.* 1998 Sep;93(9):1453-6.
2. Hung E, et al. *J Rheumatol.* 2013 Apr;40(4):455-60.

Colon

- Constipation
  - Caused by weakening of the gut muscle and slow contractions
  - Use of stimulant laxatives (docusate, lactulose,senna) -acts on nerve endings in the gut wall that make the muscles in the intestine contract with more force
  - Liberal use of fluids
  - Avoid high-fiber diet and bulk-forming laxatives in slow transit constipation; may make constipation worse
  - Take medication every other day to maintain a healthy bowel regimen

New Medications approved for management of idiopathic constipation

Linaclotide

Guanylate cyclase-C (GC-C) agonist and binds with high affinity to the GC-C receptor, which is located almost exclusively in the intestines.

Dosage for IBS-C
290 µg once daily

Take on empty stomach ≥30 minutes prior to first meal of the day.
Contraindicated in pediatric patients up to 6 years of age.

Lubiprostone

Locally acting ClC-2 chloride channel activator.; promotes fluid secretion into the intestinal lumen.

Dosing for IBS-C
8 µg BID

Contraindicated in patients with mechanical GI obstruction
Negative pregnancy test and contraception recommended in women of childbearing age.

Prucalopride

Stimulates peristalsis.

Dosage for IBS-C
1-2 mg daily

Contraindicated in patients with mechanical GI obstruction.

PROGRASS trial

- Prucalopride is a 5-HT4 receptor agonist
  - —Increasing peristalsis
  - —Approved for chronic idiopathic constipation
- Open-label cross-over study
  - —40 SSc patients with self-reported mild-to-moderately-severe constipation
  - —Randomized 1:1; prucalopride 2 mg/day vs no Rx for one month
- UCLA GIT 2.0 and the number of spontaneous bowel movements was recorded
- Prucalopride was associated with:
  - Significantly more spontaneous bowel evacuations ($p < 0.001$)
  - Improvement of UCLA GIT constipation, reflux and bloating ($p < 0.05$) scores

Vigone B, et al. *Arthritis Res Ther.* 2017 Jun;19(1):145.

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MITSUBISHI

A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE EFFICACY, SAFETY, AND TOLERABILITY OF MT-7117 IN SUBJECTS WITH DIFFUSE CUTAENOUS SYSTEMIC SCLEROSIS

INCLUSION CRITERIA:

- Diffuse cutaneous form of SSc according to Leroy and Medsger's criteria.
- Disease duration ≤ 3 years from the first non-Raynaud's phenomenon manifestation.
- Has an mRSS of 15 to 45 units at screening and have clinical skin involvement proximal and distal to the elbows, knees, or both or any truncal involvement, with or without face involvement.

EXCLUSION CRITERIA:

- Treatment of SSc disease with more than 1 of the immunosuppressant therapy listed below, has changed medication within 12 weeks prior to screening, or not on a stable dose of the same medication for at least 12 weeks prior to screening:
  - Hydroxychloroquine (up to 400 mg/day),
  - Mycophenolate (up to 3 g/day),
  - Mycophenolic acid (up to 2.14 g/day),
  - Met
  - Lefl
  - Aza

BRAVOS

EVALUATION OF BRENTUXIMAB VEDOTIN FOR DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS: A PHASE 1/2 MULTICENTER, RANDOMIZED, DOUBLE BLINDED, SAFETY STUDY

INCLUSION CRITERIA:

- Diagnosis of dcSSc, as defined by LeRoy and Medsger.
- mRSS units ≥ 15 and ≤ 45.
- Documentation of at least 12 weeks of immunosuppressive therapy for SSc at the time of enrollment, and at least 4 weeks of at a stable dose, of one of the following:
  - Methotrexate ≤ 25 mg/week, or
  - Mycophenolate mofetil ≤ 3 grams/day or mycophenolate sodium ≤ 2.16 grams/day, or
  - Azathioprine ≤ 3mg/kg/day.

EXCLUSION CRITERIA:

- Rheumatic disease other than dcSSc; it is acceptable to include patients with osteoarthritis, fibromyalgia, sicca symptoms, and scleroderma-associated myopathy.
- Pulmonary disease with FVC ≤ 60% of predicted, or DLCO (corrected for

ACV01

BOOSTER EFFECTS WITH AUTOIMMUNE TREATMENTS IN PATIENTS WITH POOR RESPONSE TO INITIAL COVID-19 VACCINE:

INCLUSION CRTIERIA:

- Individuals 18 years of age or older that meet classification criteria for Systemic Lupus Erythematosus, Systemic Sclerosis, Rheumatoid Arthritis, Multiple Sclerosis, or Pemphigus.
- Documented full COVID-19 vaccination (CDC card or documentation in medical records) that was completed at least 4 weeks prior and no more than 36 weeks prior to the Screening visit.

EXCLUSION CRTIERIA:

- History of severe allergic reaction to the initial COVID-19 vaccine regimen, or any component of any of the COVID-19 vaccines, or to polyethylene glycol (PEG).

For referral: ssc-coordinator@med.umich.edu