

# **SSc- Standard of Care,2022**

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# Disclosures

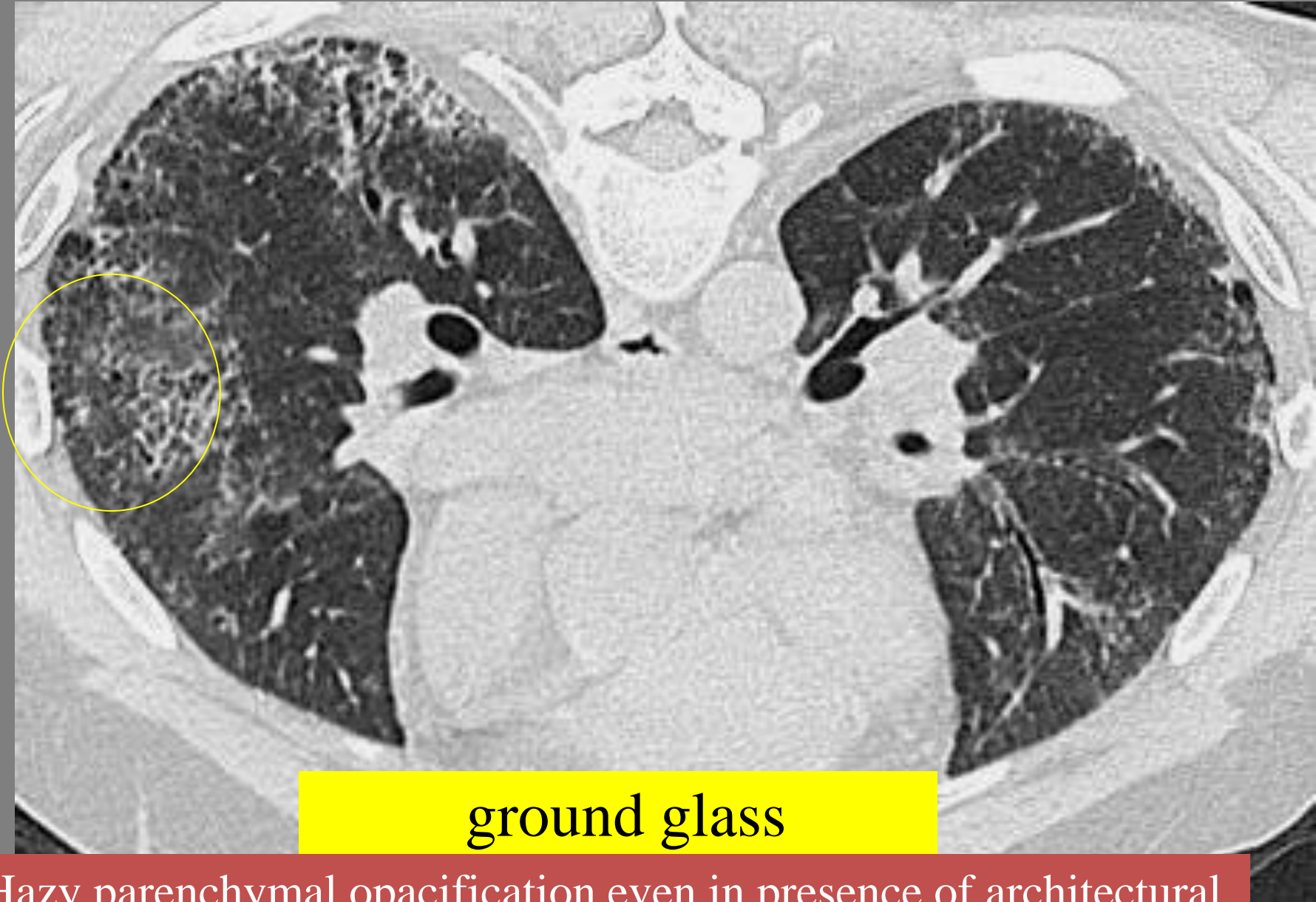
- **Abbvie**
- **Amgen**
- **Galderma**
- **Galapagos**
- **Horizon**
- **NIH**
- **Novartis**
- **Pfizer**
- **Prometheus**

# Treatment for Selected Aspects of SSc

- Interstitial Lung Disease
- Cardiac
- Severe Raynaud's +/- Gangrene

# CASE STUDY 1

- **A 45 y/o woman with scleroderma:**
  - rapidly progressive skin thickening over the past year,
  - new onset dry cough, SOB after 1 flight of stairs and fatigue.
  - PFTs show FVC 85% and DLCO 60%
  - HRCT shows fibrosis and some “ground glass”



ground glass

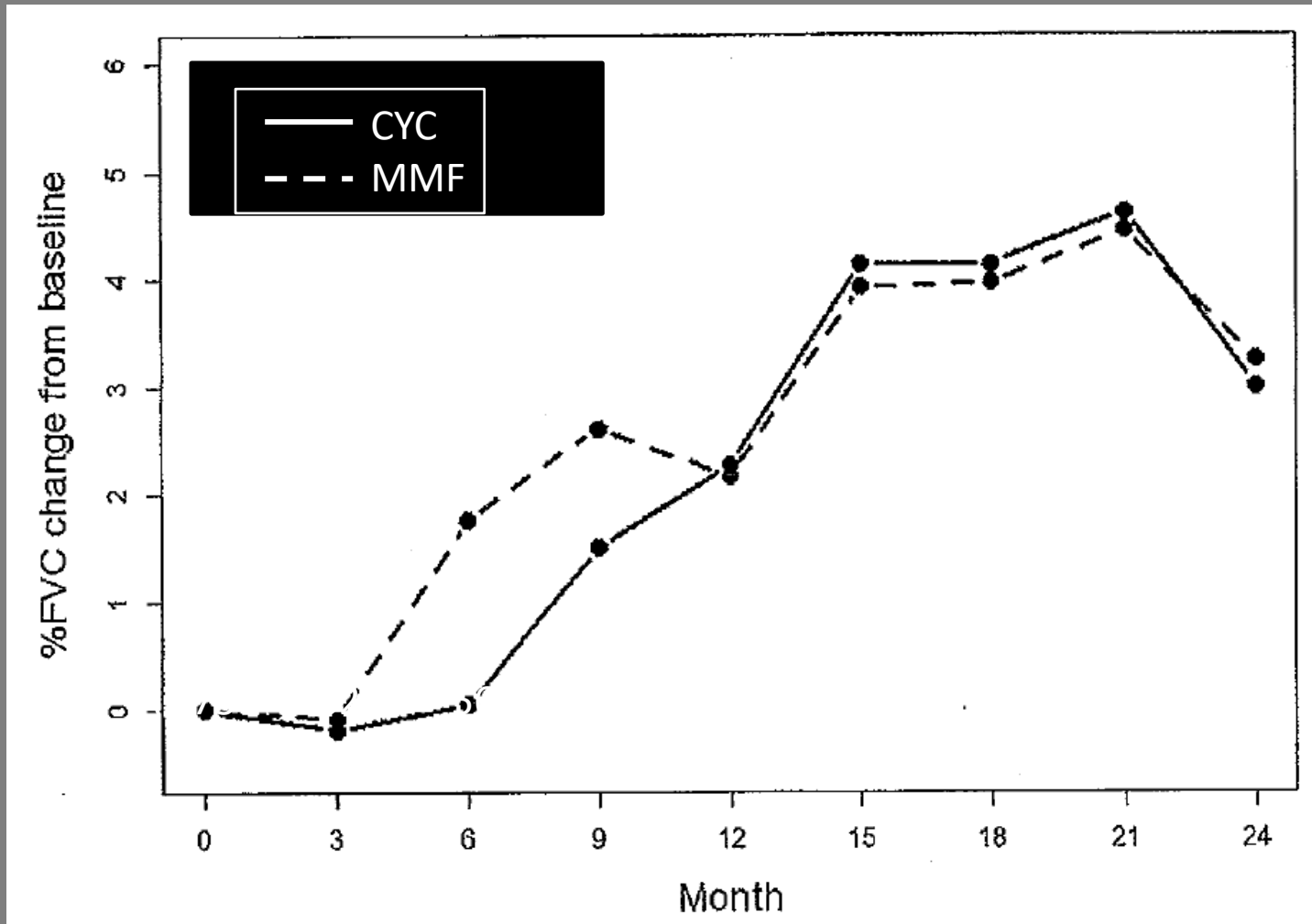
Hazy parenchymal opacification even in presence of architectural distortion or reticular interstitial thickening

# Patient 1

- The patient was placed on mycophenolate(MMF) 3 gm qd for 6 months but her skin worsened and her FVC decreased by 15 % predicted altho DLCO remained stable
- She had marked heartburn from the MMF, requiring both omeprazole and ranitidine

**A few words about Mycophenolate  
Mofetil, as a reminder**

# Absolute change in % pred FVC by treatment arm (all observed data, ITT)



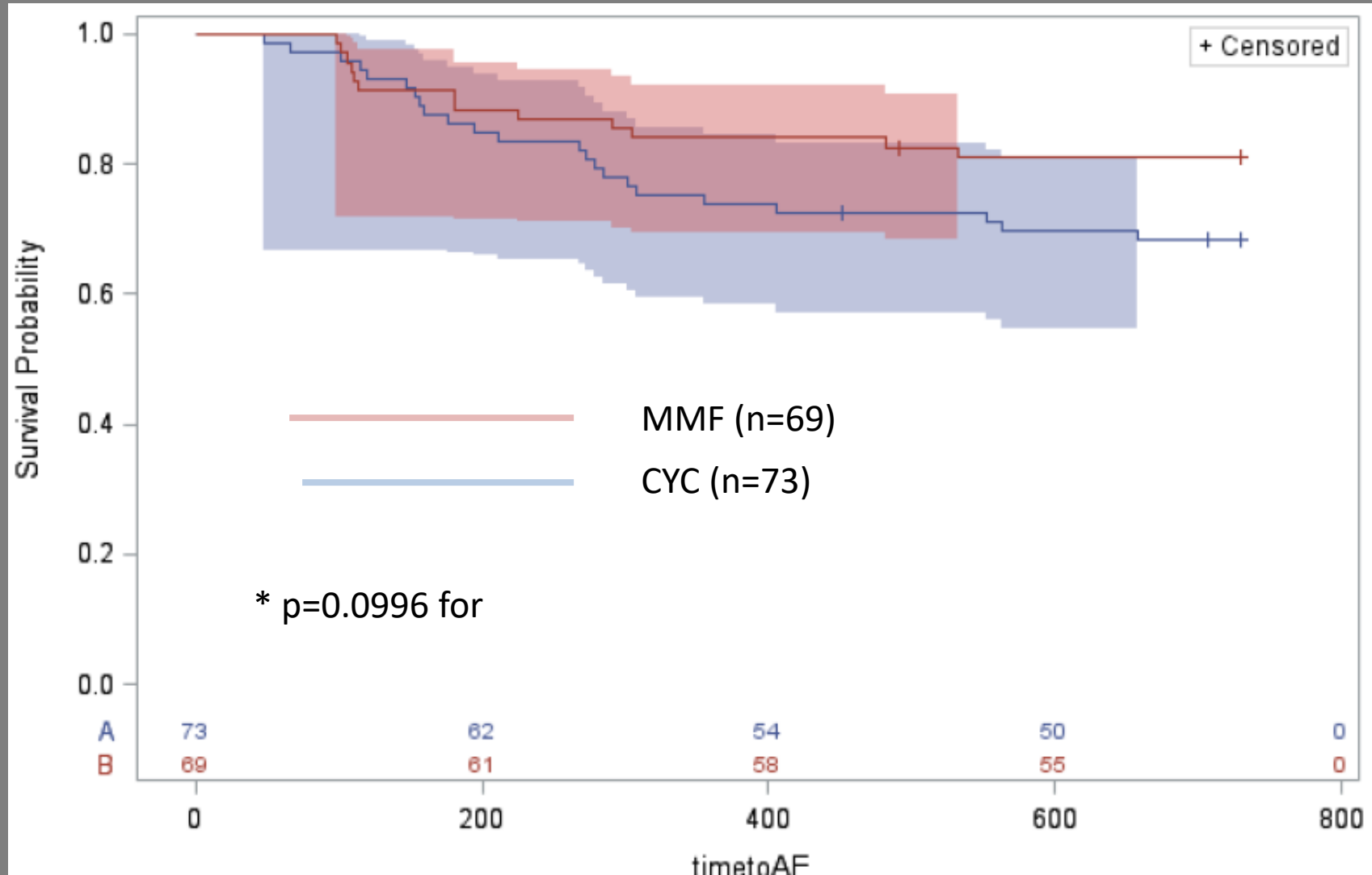


# Mean skin fibrosis score (mRSS) results by treatment assignment

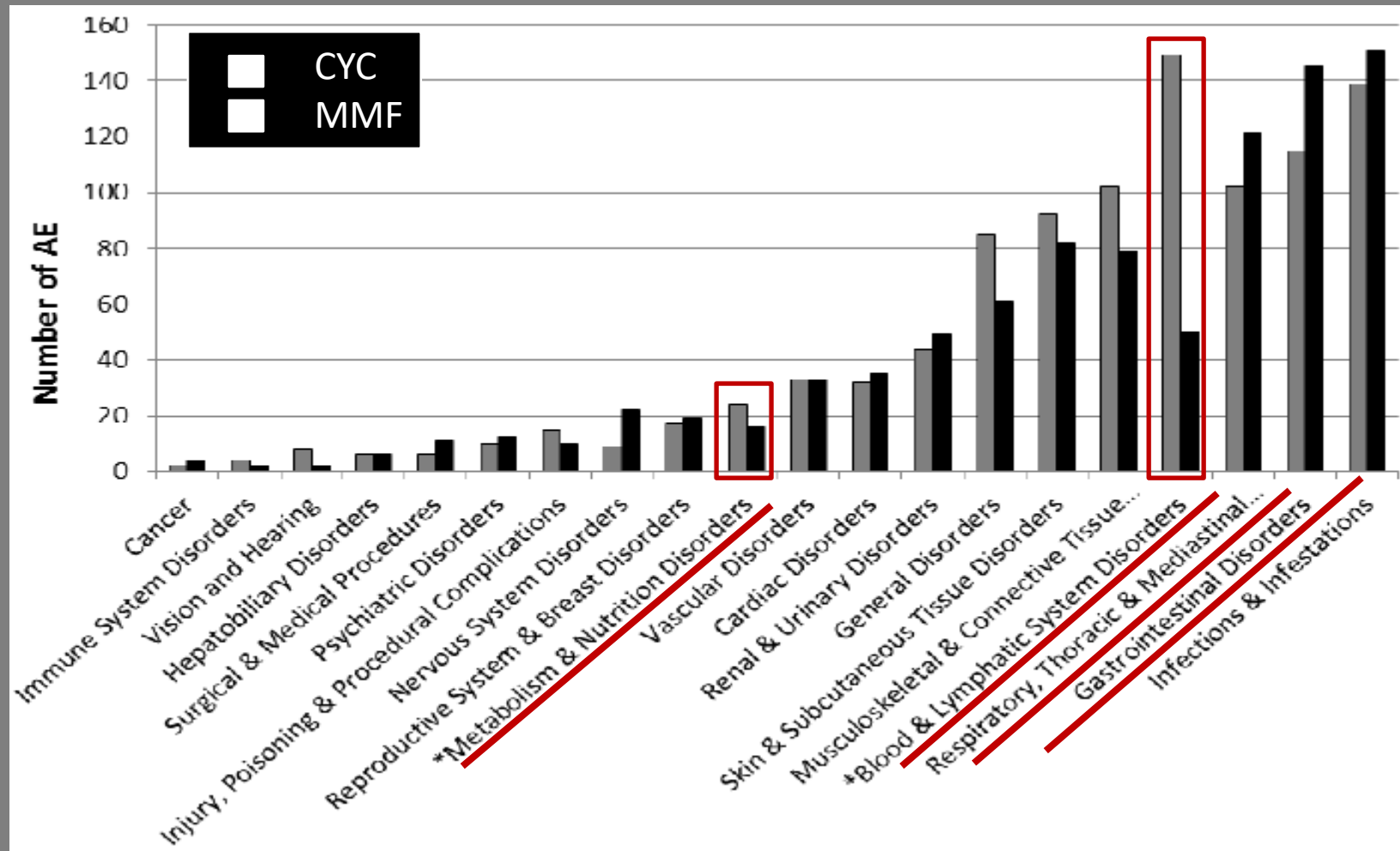
	CYC		MMF	
	N	Mean score $\pm$ SD	N	Mean score $\pm$ SD
Baseline	73	14.0 $\pm$ 10.6	69	14.3 $\pm$ 10.4
6 months	58	11.9 $\pm$ 10.3	60	14.4 $\pm$ 10.3
12 months	55	9.5 $\pm$ 7.9	58	12.4 $\pm$ 9.2
18 months	47	9.9 $\pm$ 7.8	50	12.0 $\pm$ 8.9
24 months	53	7.9 $\pm$ 7.4	53	11.4 $\pm$ 9.2

# Kaplan-Meier Survival Plots\*

No. of subjects at risk & 95% Hall-Wellner bands



# Adverse Events by Treatment Arm



\*P<0.05, Fisher's Exact Test based on # of participants with each type of AE

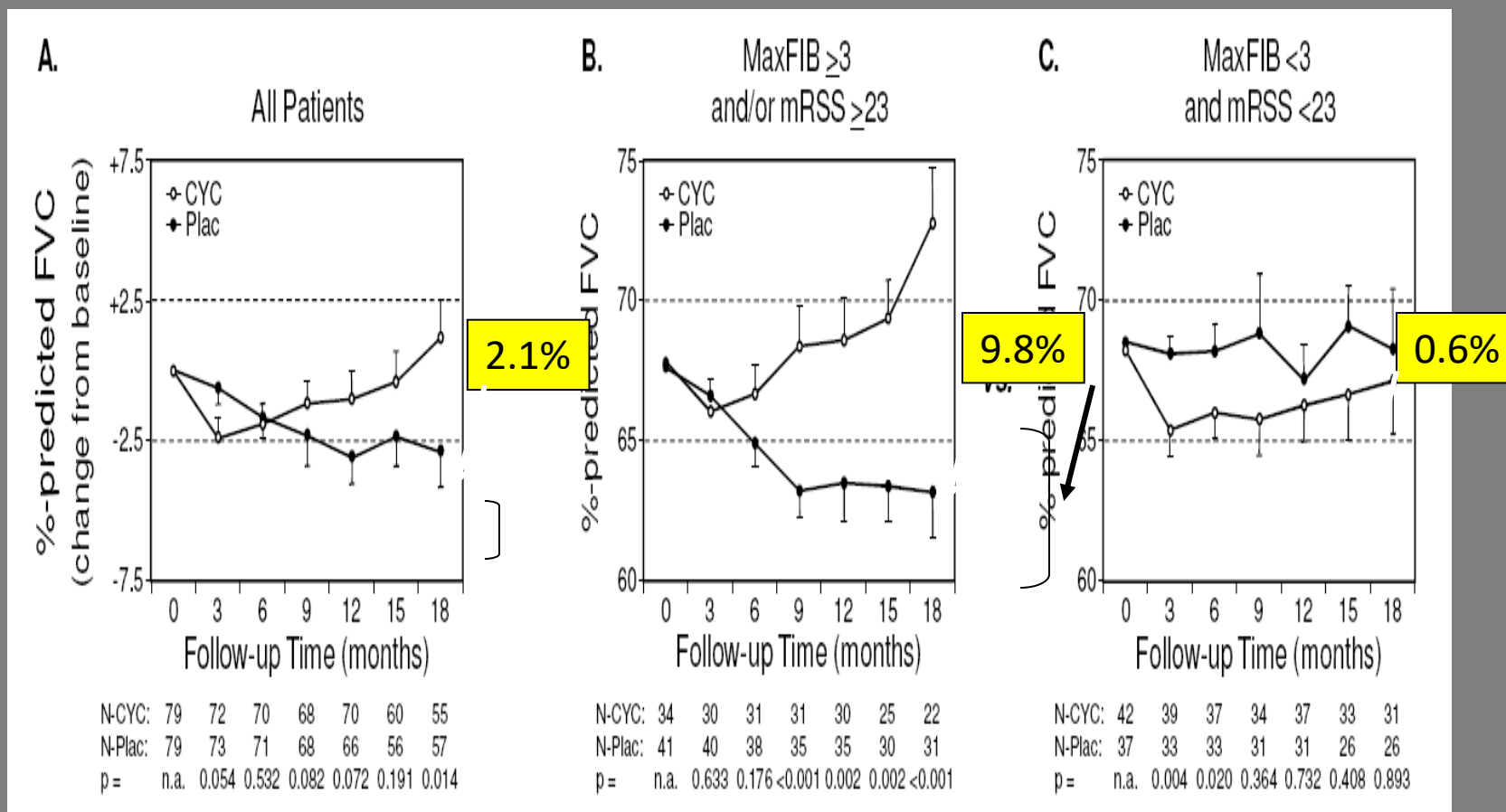
# What do you do next?

- Cyclophosphamide
- Tocilizumab
- Abatacept
- Rituximab
- Stem cell transplant

# Cyclophosphamide

# Predicting Response to CYC from the SLS1 study

MRoth,CH Tseng,PJClement,DEFurst et al, ATS,2011



# Skin Scores - 12-month\*

- Significant differences in mean adjusted skin scores in favor of CYC:

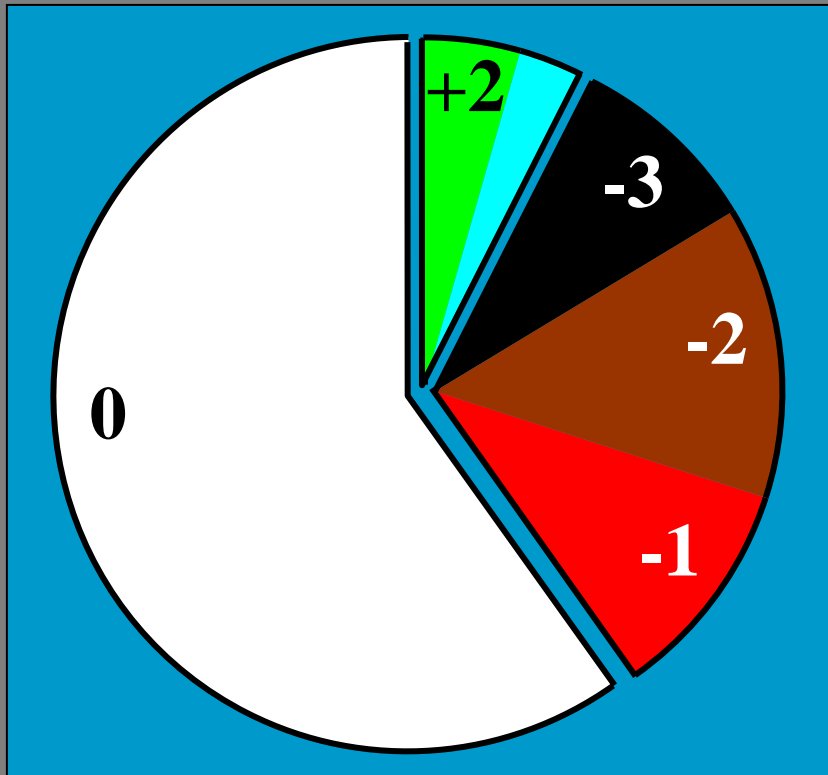
**-3.06** [95% C.I.: -5.84, -0.28]  
(p=0.03)

\*Covariance analysis; baseline score used as covariate;  
analysis confined to those with diffuse disease (N = 80)

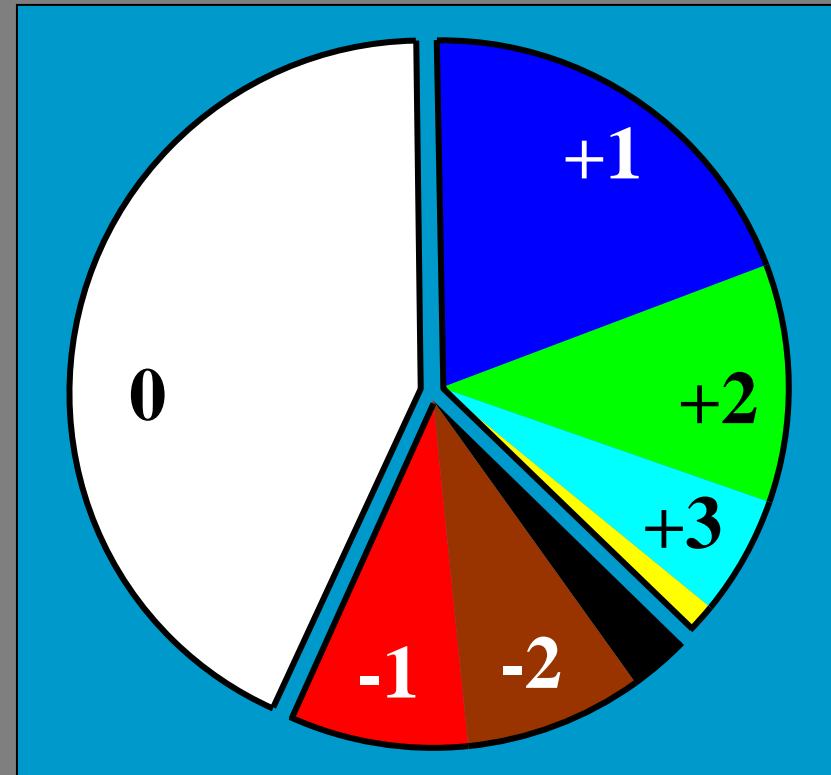
# Transitional Dyspnea Index

Magnitude of Effort @ 12 months

Placebo



CYC



( $p < 0.01$ )



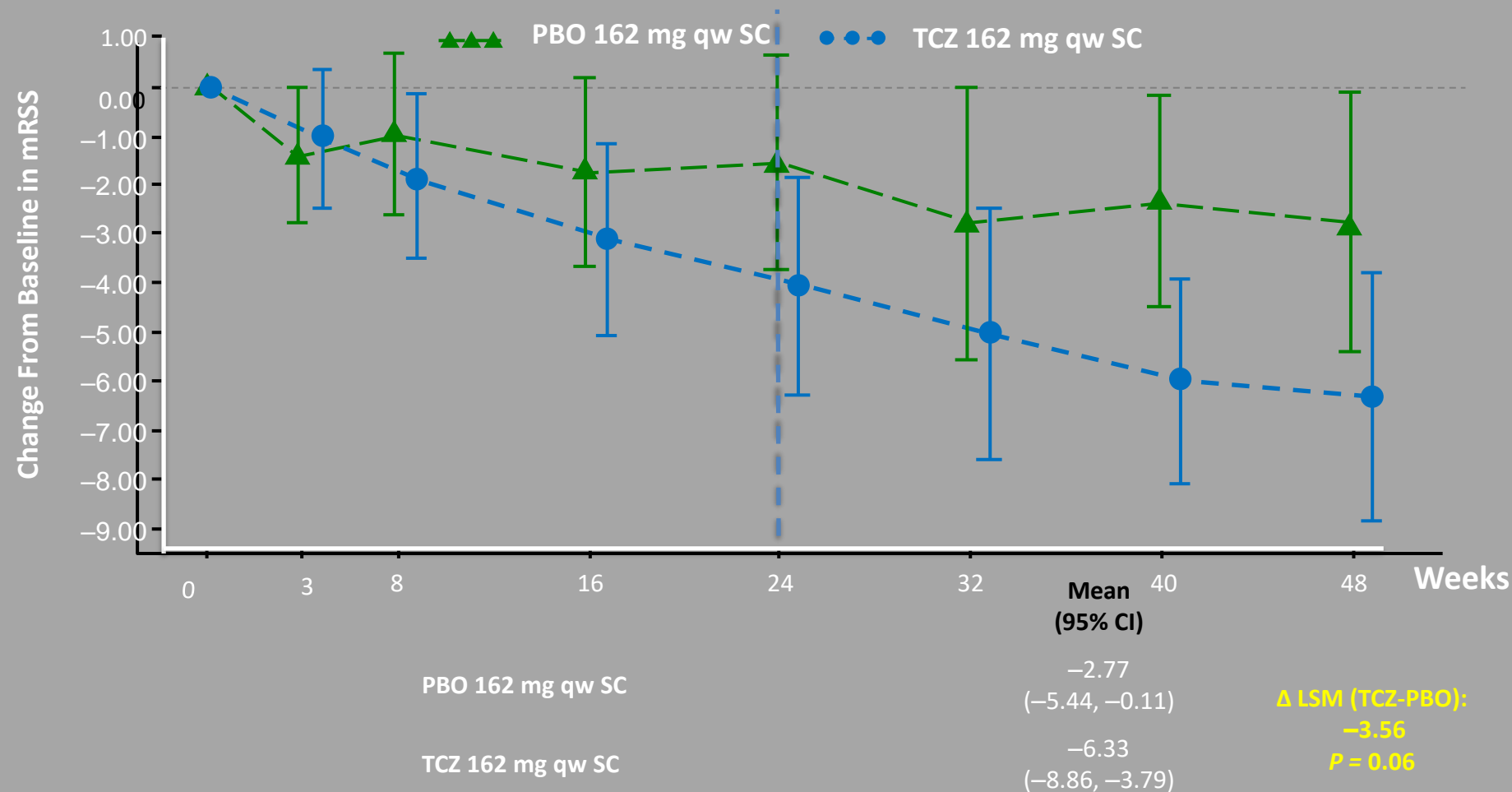
# Summary and Conclusions

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- A significant but modest effect on FVC (% predicted)
- A modest but real effect on the skin
- A real effect on dyspnea

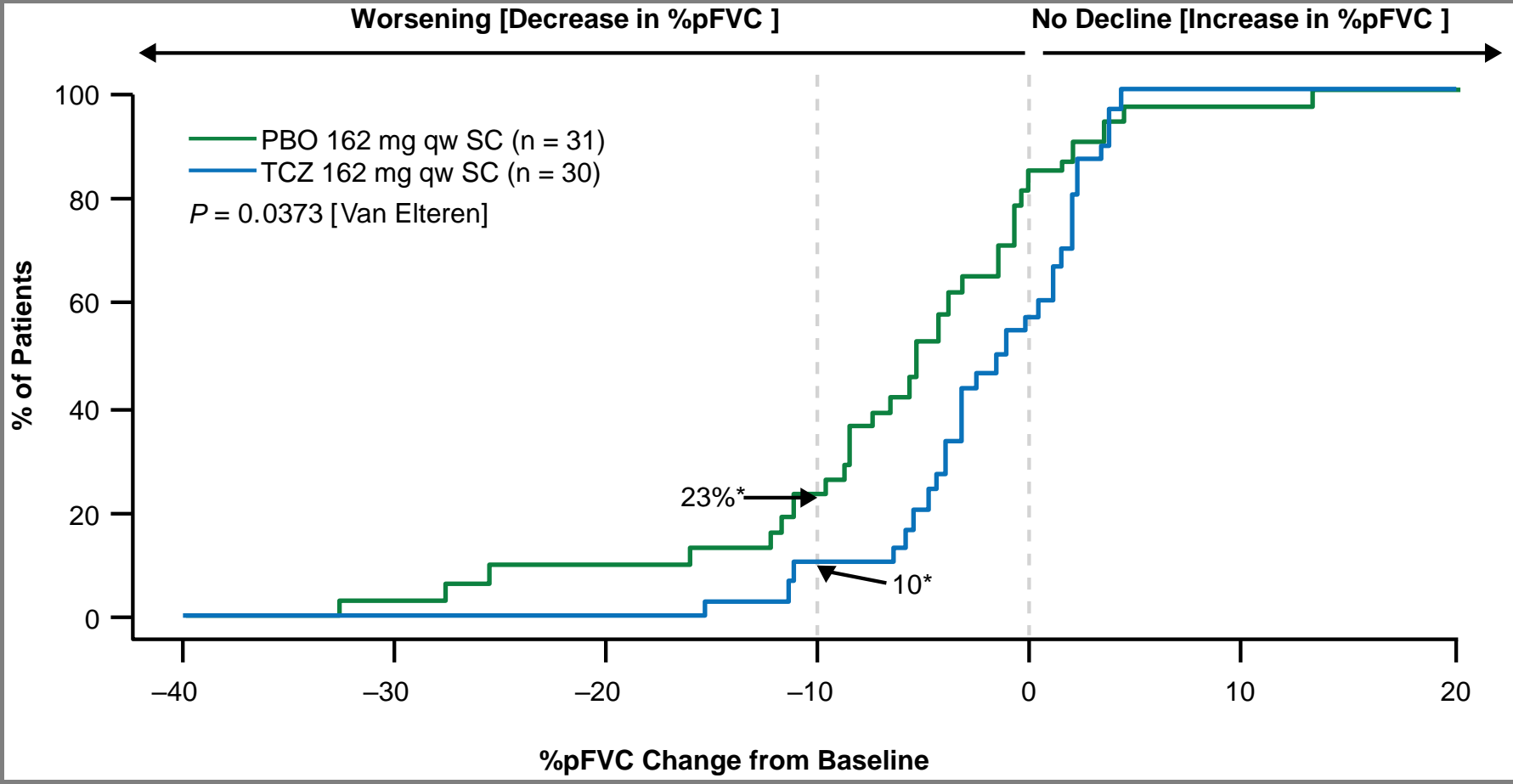
Tocilizumab

# Change From Baseline in mRSS at Week 24 (Primary Endpoint) and Week 48 (Secondary Endpoint)



Negative change indicates improvement. Means and 95% CI are from the repeated measures model.

# Cumulative distribution of patients by absolute change in %predicted FVC from baseline to week 48



\*Percentage of patients with  $\geq 10\%$  worsening in %pFVC.

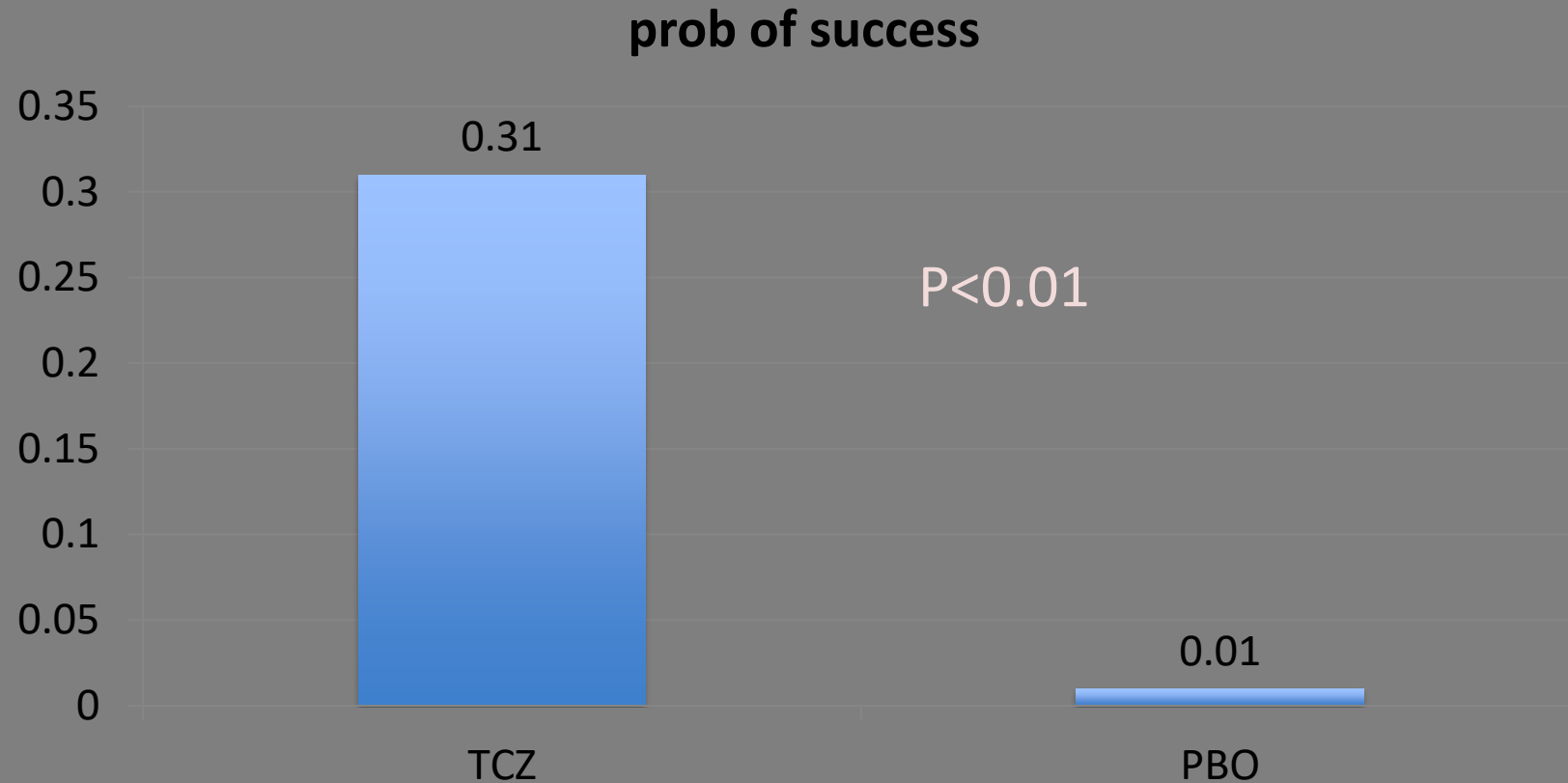
# Imputed data in faSScinat study (week 48)

Khanna D, Denton CP...Furst DE. Lancet. 2016.387:2630-2640

		TCZ group Mean (SD) N=43	PBO group Mean (SD) N=40	P-value*
48 Weeks	mRSS, 0-51*	-5.26 (7.18)	-3.0 (5.76)	0.12
	FVC% predicted	-2.21 (2.33)	-6.50 (3.48)	<0.00001
	HAQ-DI, 0-3*	0.15 (0.69)	0.23 (0.50)	0.53
	Patient global assessment, 0-10*	-0.85 (2.22)	-0.36 (2.26)	0.33
	Physician global assessment, 0-10*	-3.18 (2.62)	-1.88 (2.74)	0.03

\*Negative is improvement

## CRISS scores at 48 weeks (using MCID of CRISS:>0.60)

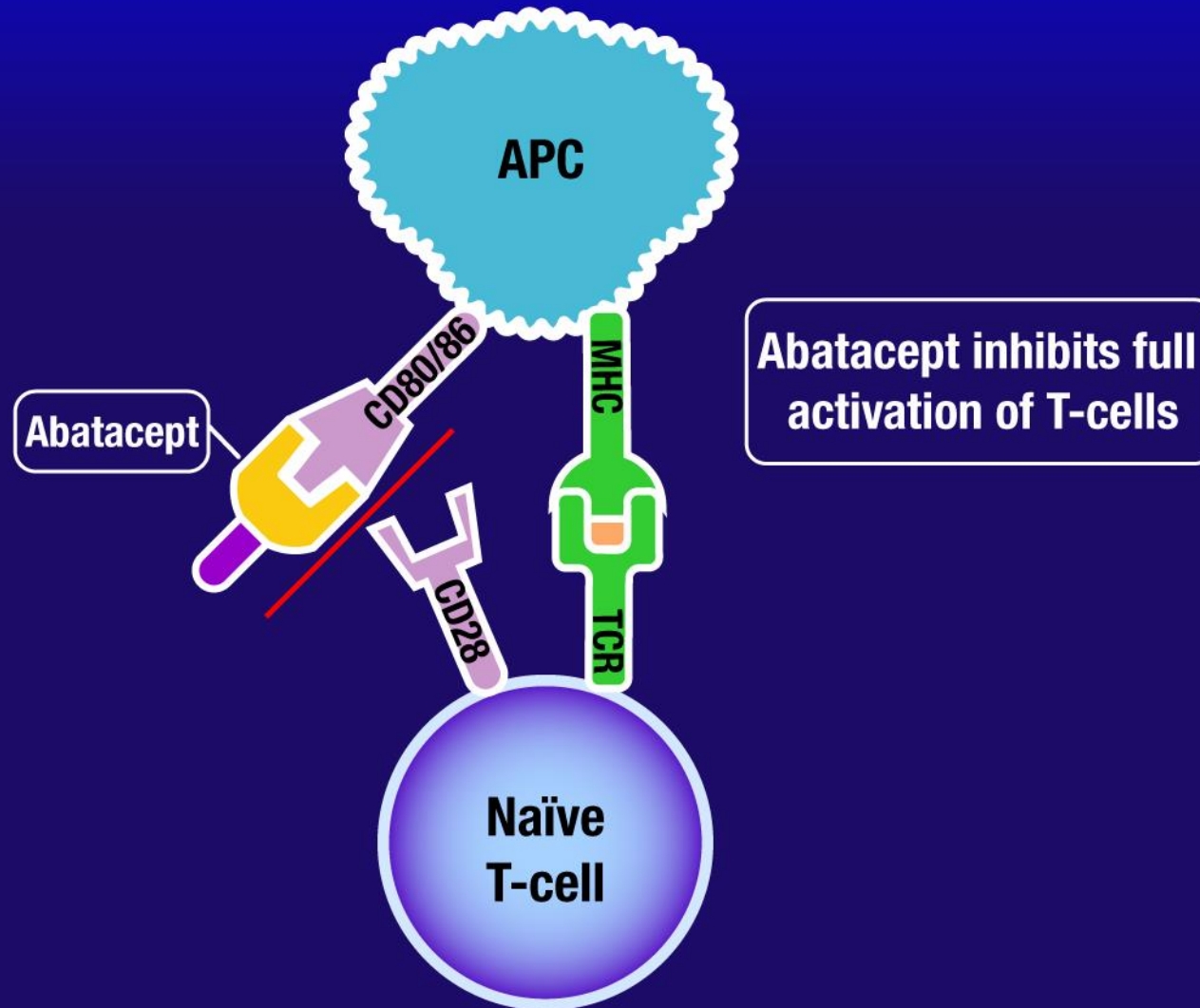


# Overall Adverse Event Summary at Week 48

	PBO 162 mg qw SC n = 44	TCZ 162 mg qw SC n = 43
n (%)	BL to week 48	BL to week 48
Total patients with ≥1 AE	40 (90.9)	42 (97.7)
Total patients with ≥1 infectious AEs	22 (50.0)	24 (55.8)
Total patients with ≥1 SAE	15 (34.1)	14 (32.6)
Total patients with ≥1 infection SAE	<b>2 (4.5)</b>	<b>7 (16.3)</b>
Total patients with ≥1 noninfection SAE	<b>14 (31.8)</b>	<b>10 (23.3)</b>
Total patients who withdrew due to an AE	5 (11.4)	6 (14.0)
Deaths	1 (2.3)	3 (7.0)

- No anaphylaxis and no gastrointestinal perforation observed
- Deaths: PBO: heart failure (unrelated to study drug); TCZ: pulmonary infection (related), malignant arrhythmia (unrelated), multiorgan failure (unrelated)
- Serious infections: PBO: bone, skin and pulmonary infections; TCZ: bone, skin, pulmonary, and GI infections

# Abatacept selectively modulates co-stimulation via CD80/86:CD28 pathway



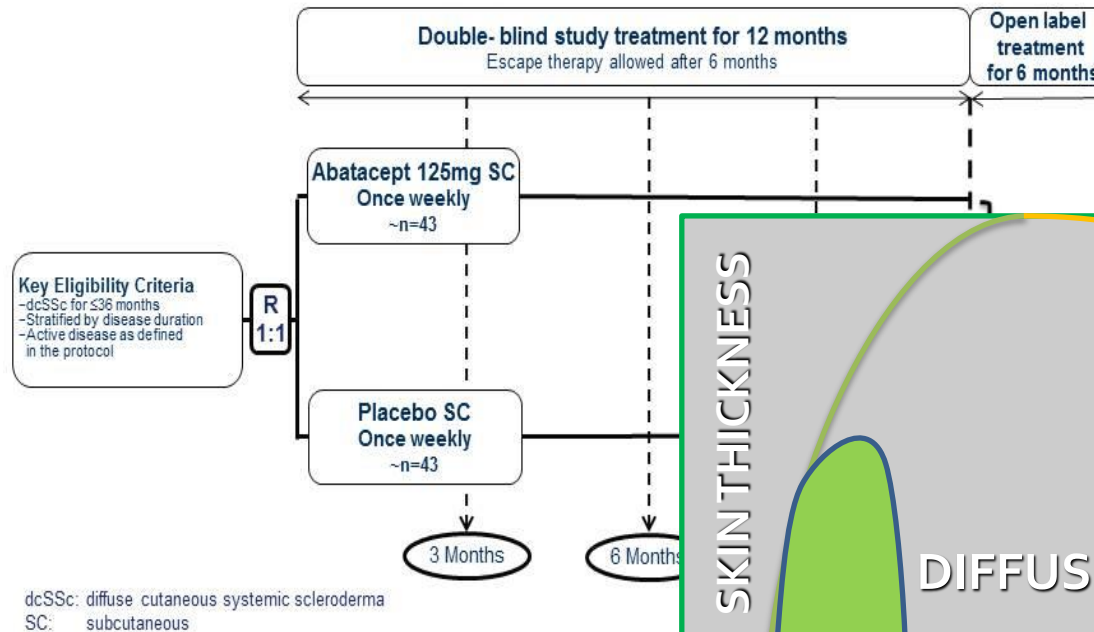


# Study design

ClinicalTrials.gov Identifier:  
NCT02161406

- Multicenter, Placebo controlled, double blind trial
- Predefined active disease
- NO background immuno-suppressives

Enrichment  
criteria:  
Early  
disease



PI: Dinesh Khanna; Steering Committee  
(UCLA), Lorinda Chung (Stanford Univ), Yannick Allanore  
(Paris), Marco Mattucci (Italy), and Chris Denton (UK)

# ASSET- Abatacept vs Placebo in SSc- Secondary endpoints

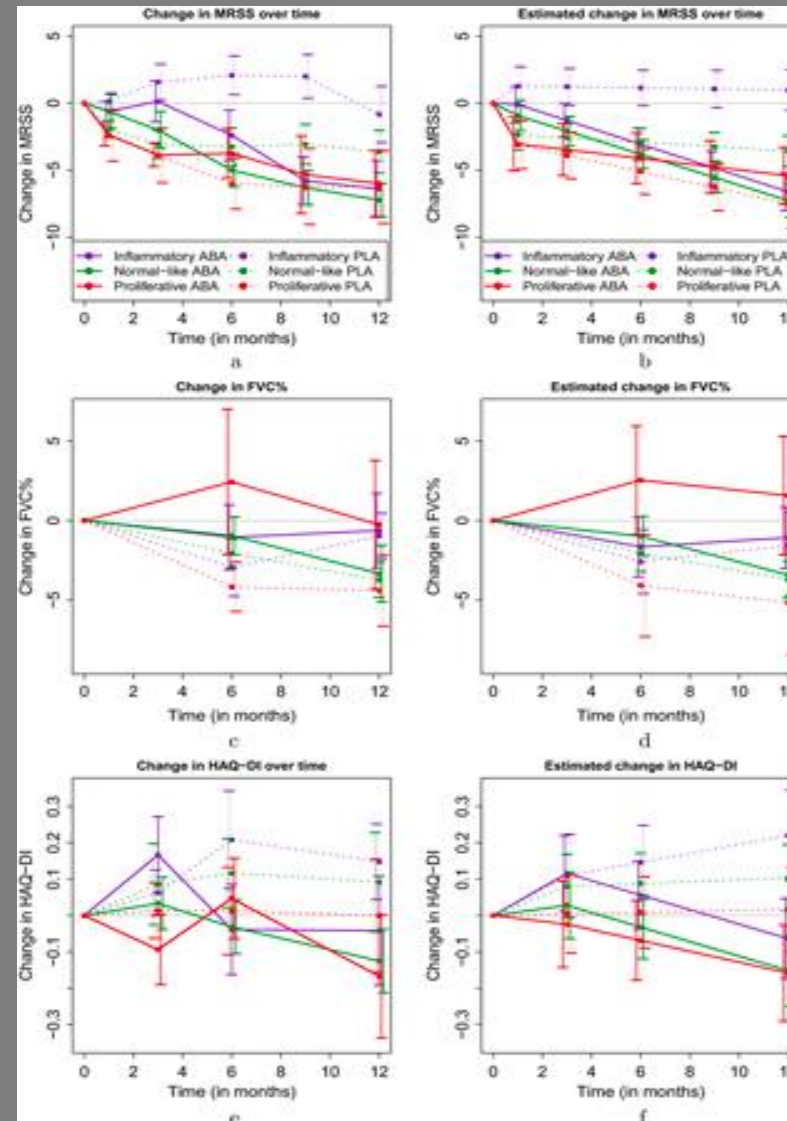
	Diff from Placebo
<b>Pt Global</b>	<b>NS</b>
<b>MD Global</b>	<b>&lt;0.05</b>
<b>FVC % ped</b>	<b>NS</b>
<b>HAQ-DI</b>	<b>&lt;0.05</b>
<b>CRIS</b>	<b>0.03 at 6 months; 0.006 at 12 months</b>

# Clinical Efficacy based on genetic signatures

- n= 33(39%) with inflammatory signature
- n= 33(39%) with normal-like signature
- n=18(21%) with fibro-proliferative signature
- Did NOT separate for mRSS or FVC without separation into genetic signatures

p<0.001 vs plac.

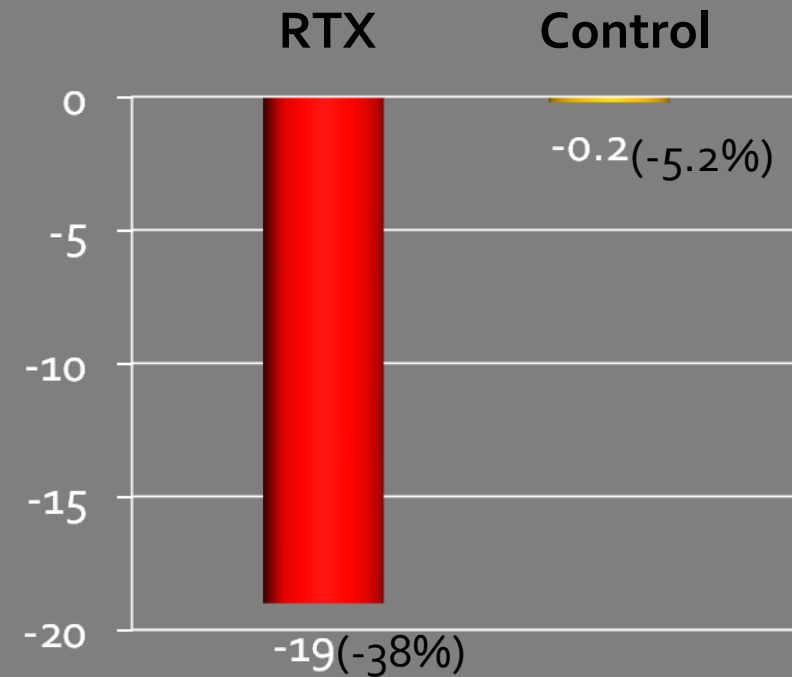
p=0.03 vs plac.



RITUXIMAB

# One Yr,Open,Controlled Trial of Rituximab for SSc- Results-Skin

Daoussis D et al. Rheum,2009(epub,5/15/09)

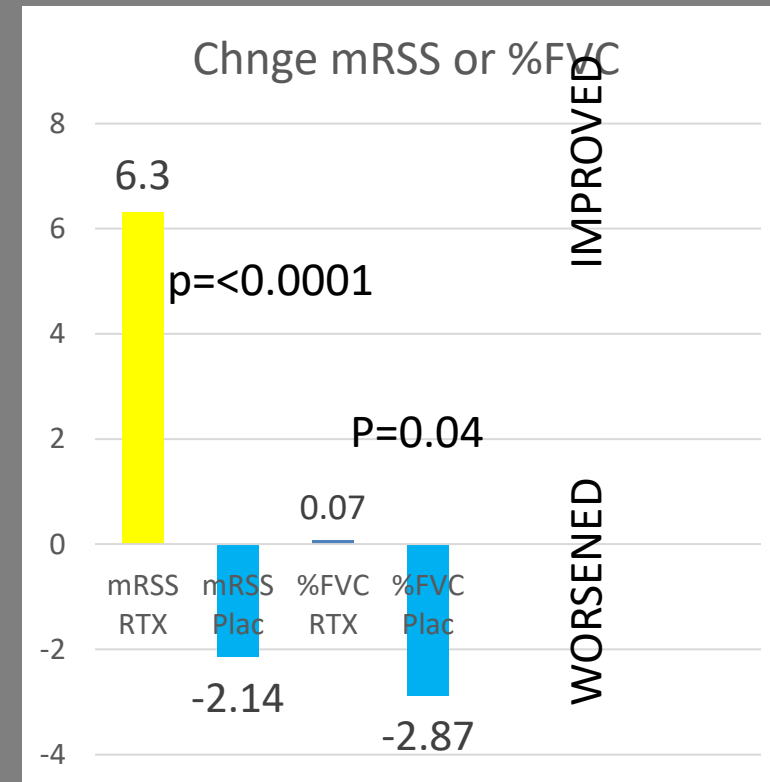


Change in Collagen  
Deposition in 24 wks  
(Computerized view of trichrome staining)

## 24 week DB – RCT of rituximab for systemic sclerosis

Ebata S, Yoshizak A et al A&R 2021. 73(Suppl 10): abs 496

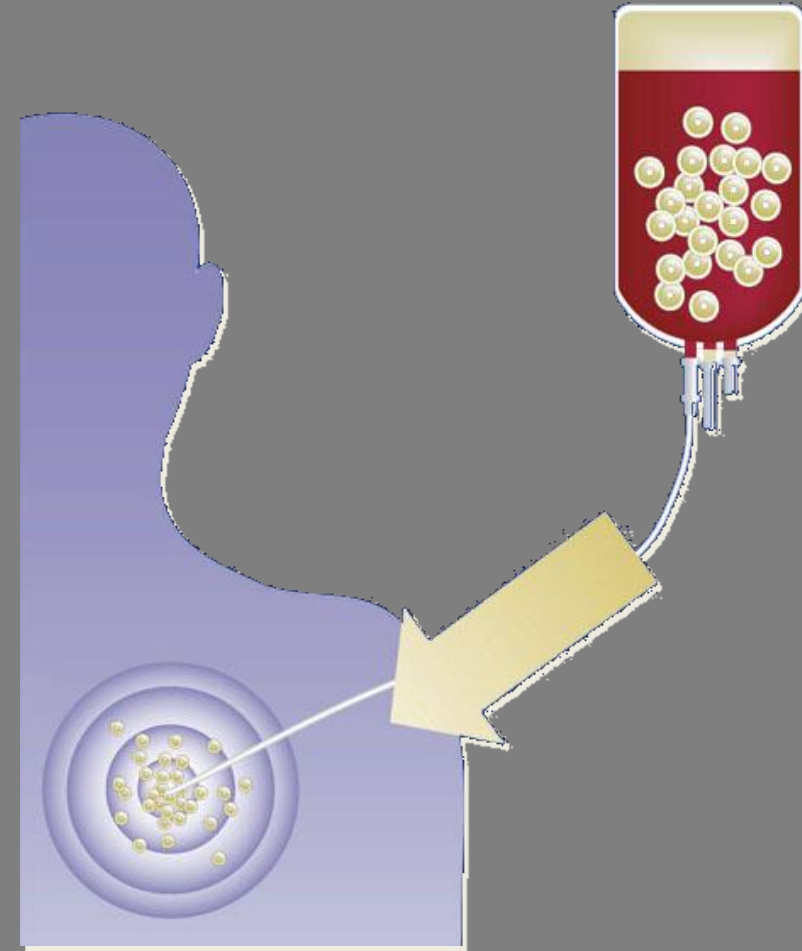
- N = 27/group
- rituximab 375 mg/M2 versus placebo weekly times 4 weeks.
- Outcomes:
- MR SS.
- Change percent predicted FVC



**Conclusion: first actual CONTROLLED trial showing that rituximab works in SSC**

# Stem Cell Transplantation

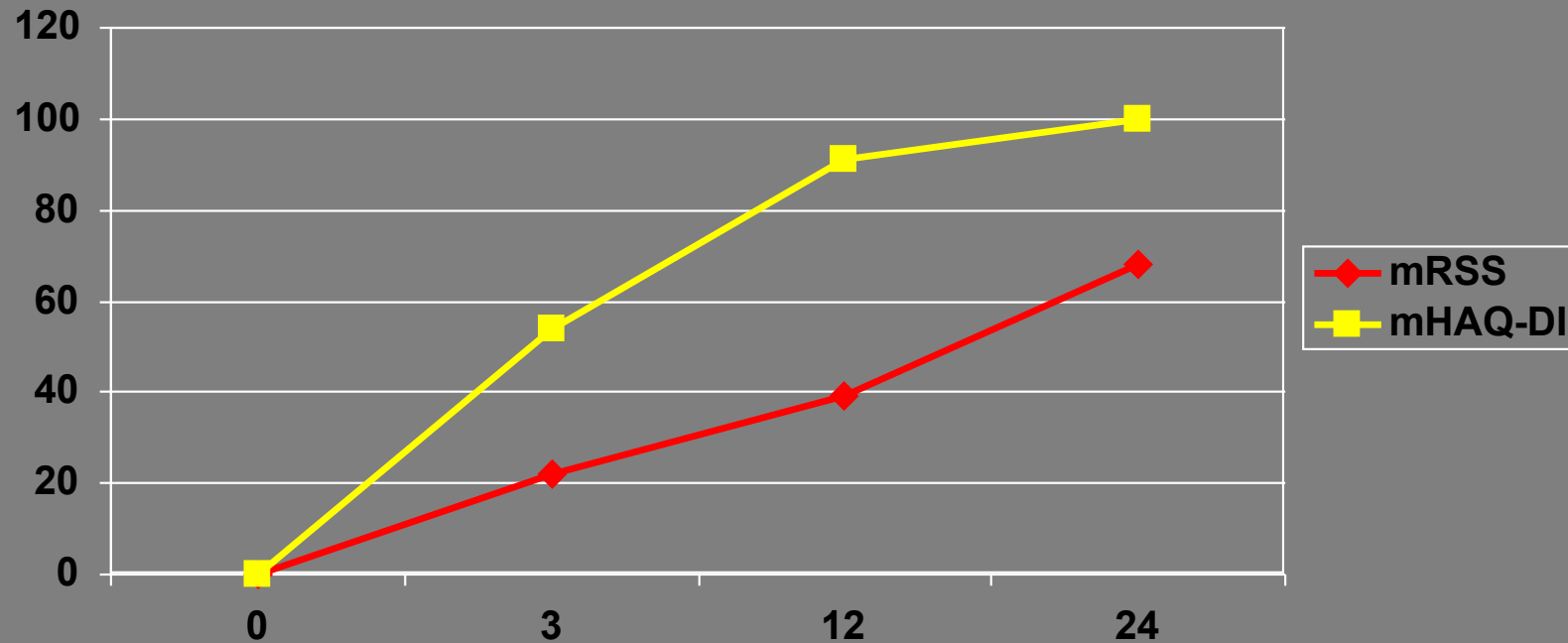
- Autologous (self) purified stem cells infused after high dose immune suppression
- Goal: Reset the immune system<sup>1,2</sup>



<sup>1</sup> Murano et al. *JEM* 2005; 201:805-816.

<sup>2</sup> Hakim et al. *JCI* 2005; 115:930-939.

# Improvement in mRSS and mHAQ after SCT for SSc(n=19)

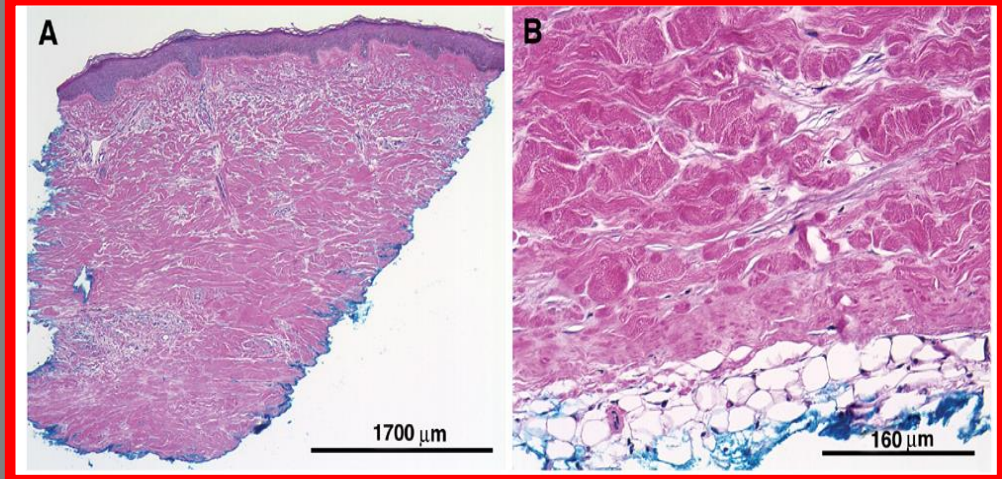




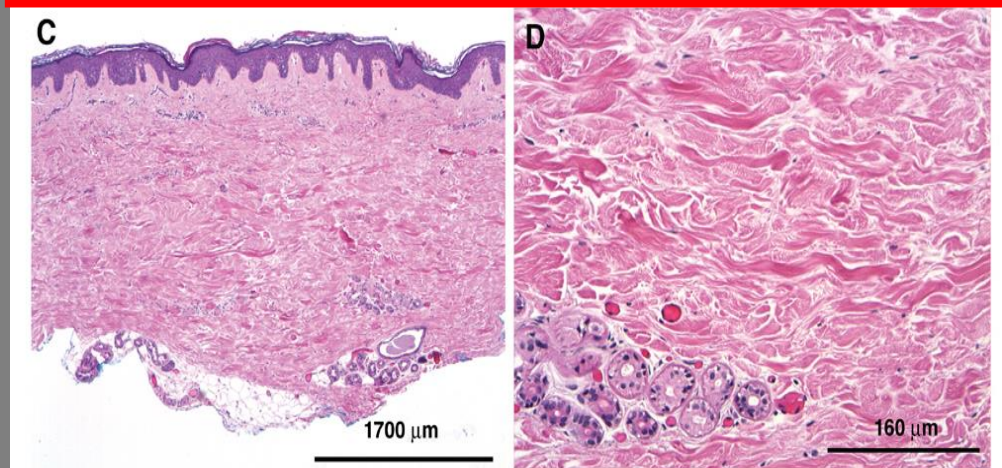
# Resolution of Dermal Fibrosis: Pt 11 Skin Biopsy

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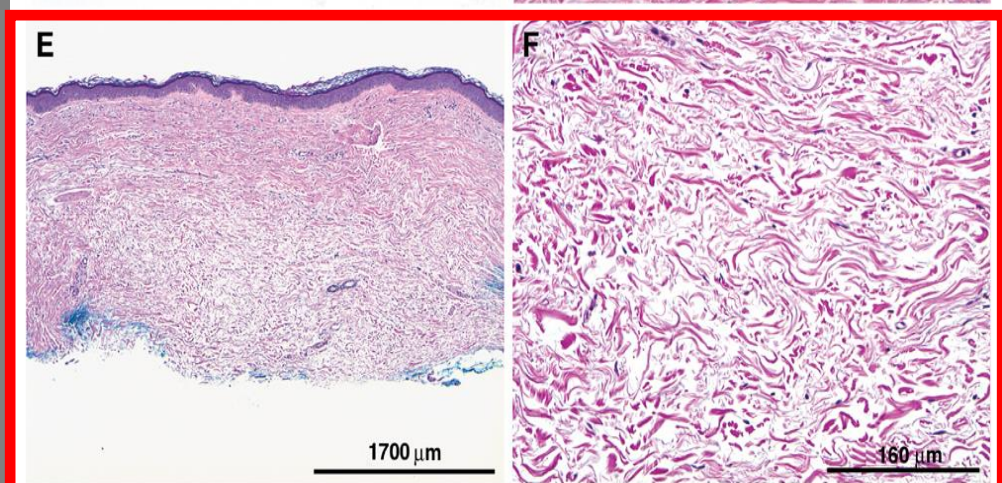
**A+B** : Pre-HCT: *grade 5;*  
*low + high power*



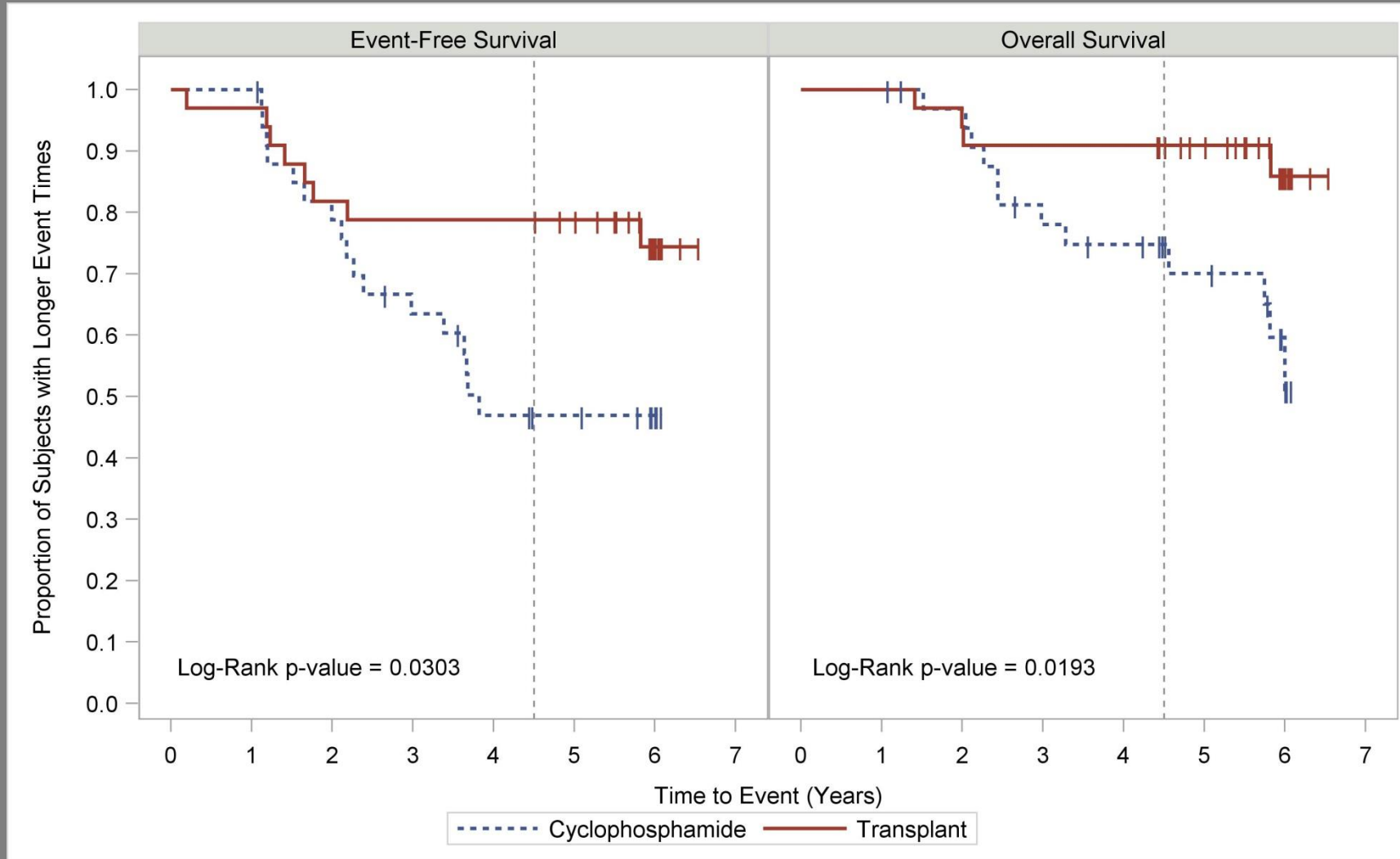
**C+D** : 1 year post-HCT:  
*grade 2-3; low + high*  
*power*



**E+F** : 5 years post-HCT:  
*grade 0; low + high*  
*power*



# Kaplan-Meier Survival Estimates: (Treated Population)



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

# What do you do next?

- Cyclophosphamide
- **Tocilizumab**
- Abatacept
- Rituximab
- Stem cell transplant

# Patient-Jennifer

- 35 yr. old female with a 2 year history of exertional dyspnea
- Presently raising 3 children and performing daily activities
- Short of breath when climbing 1 flight of stairs or an incline
- Physical Exam: distant heart sounds; 2+ lower calf edema

## Social History

- No history of smoking, alcohol abuse, recreational drug use, or anorexigens

## Labs:

FVC: 62%pred; DLCO: 55% predicted TLC:84% predicted

EKG: low voltage, occasional PVC

## Chest CT

- No signs of interstitial lung disease or pulmonary emboli
- Enlarged Heart

Serum creatinine: 0.70 mg/dl(ULN: 1.3)

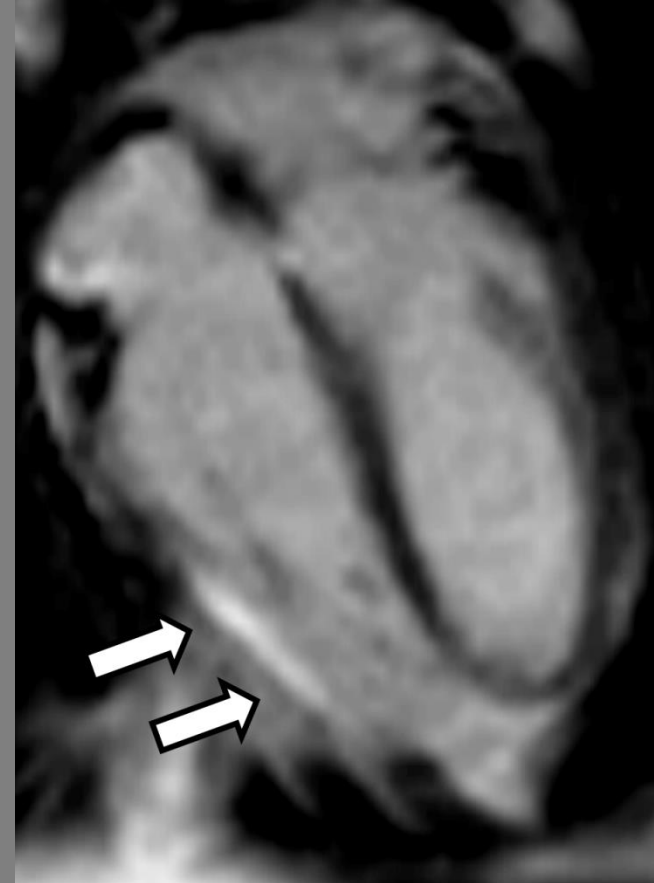
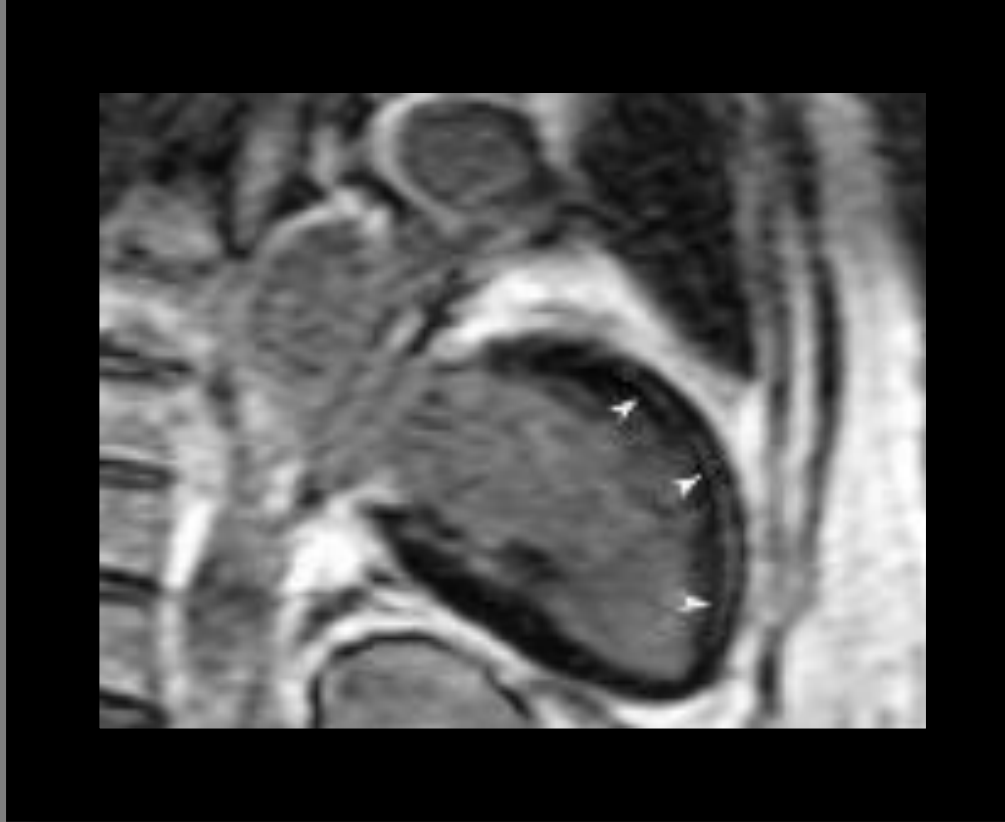
## Case #2

What is your diagnosis?

- Pulmonary Hypertension
- Interstitial Lung Disease
- Cardiomyopathy
- Renal Failure
- Myositis
- Fatigue from trying to care for the children and working and caring for husband

# Inflammation

## INPUT FROM CARDIAC MRI



*Tzelepis et al, Arthritis Rheum 2007;56:3827-3836*

Thanks to Marco Matucci-Cerenic  
and Silvia Bellando-Randon

# What is your diagnosis?

- Pulmonary Hypertension
- Interstitial Lung Disease
- **Cardiomyopathy**
- Renal Failure
- Myositis
- Fatigue from trying to care for the children and working and caring for husband

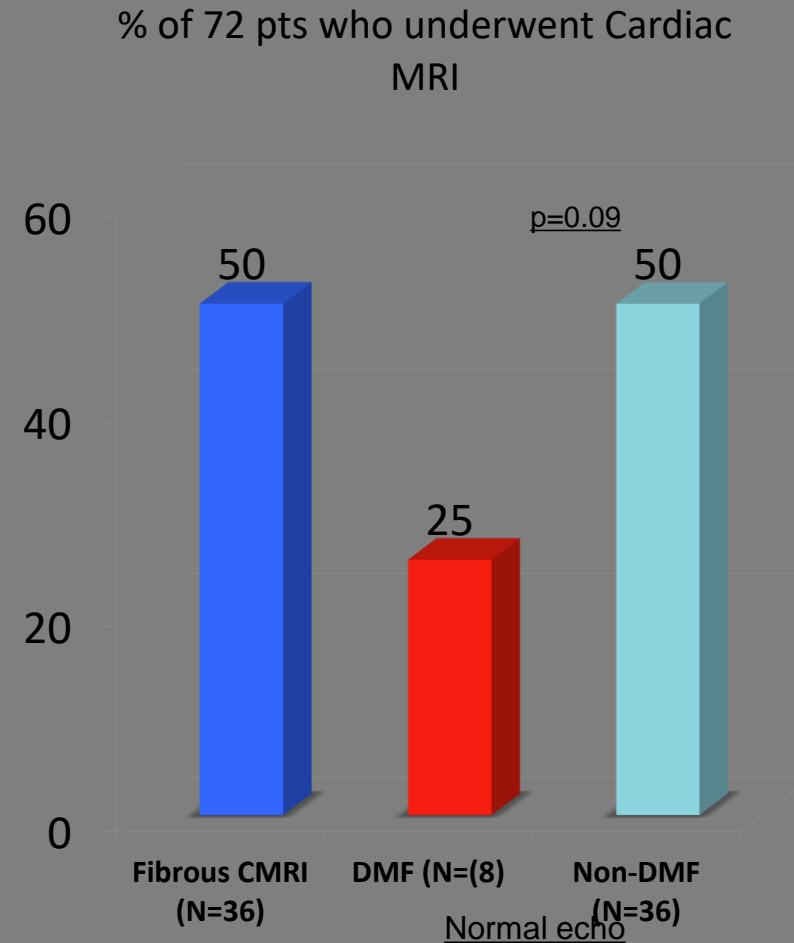


# Cardiac MRI detects diffuse fibrosis in SSc

Poindron V, Chatelus E, et al. ARD. EULAR, 2017. OPO128. (page 106)

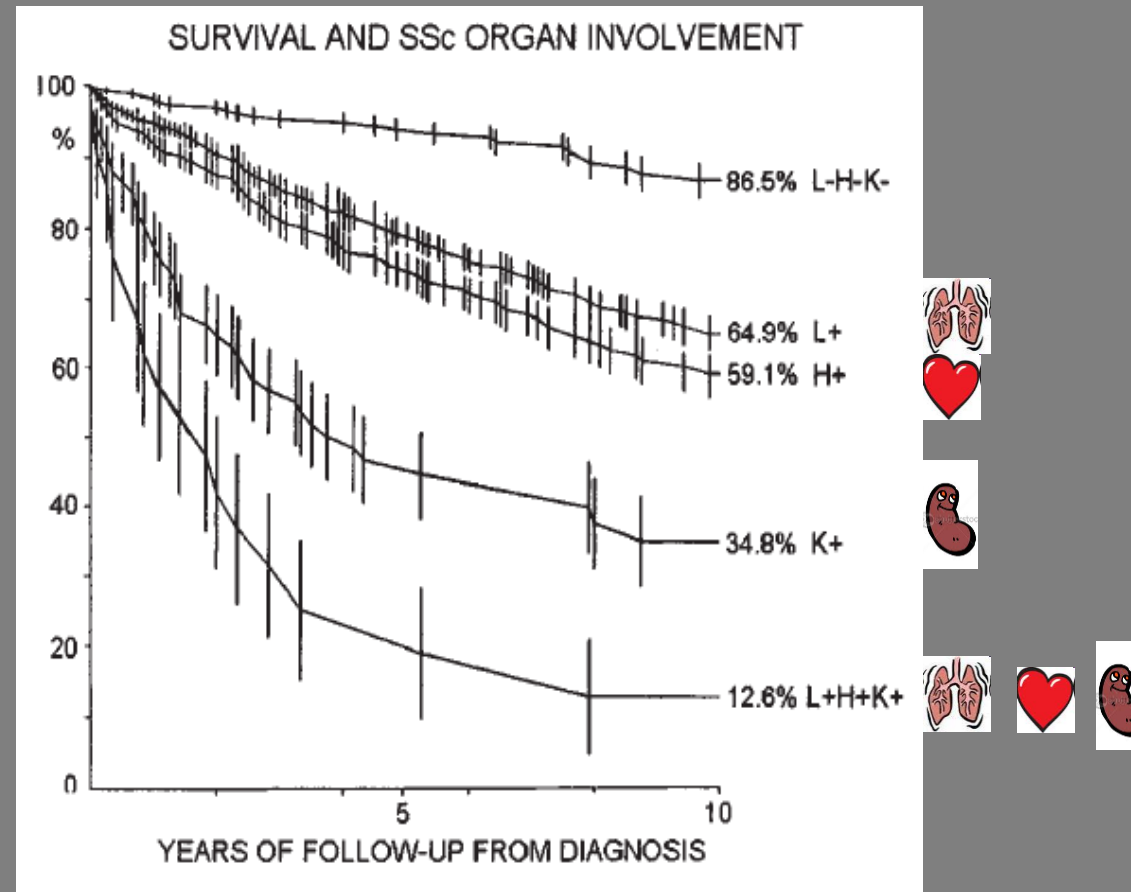
- N=72 SSc pts
  - Diffuse: 52%
  - Anti-Scl70: 40.3%
  - RNAP3: 8.3%
- Cardiac MRI -1.5T and gadolinium enhancement and echo
- Normal echo: 50% of the 36 diffuse myocardial fibrous by MRI

**Conclusion: Diffuse myocardial fibrosis in 50% of pts and in 50% with normal echo (ie; fibrosis can occur with normal echo)**



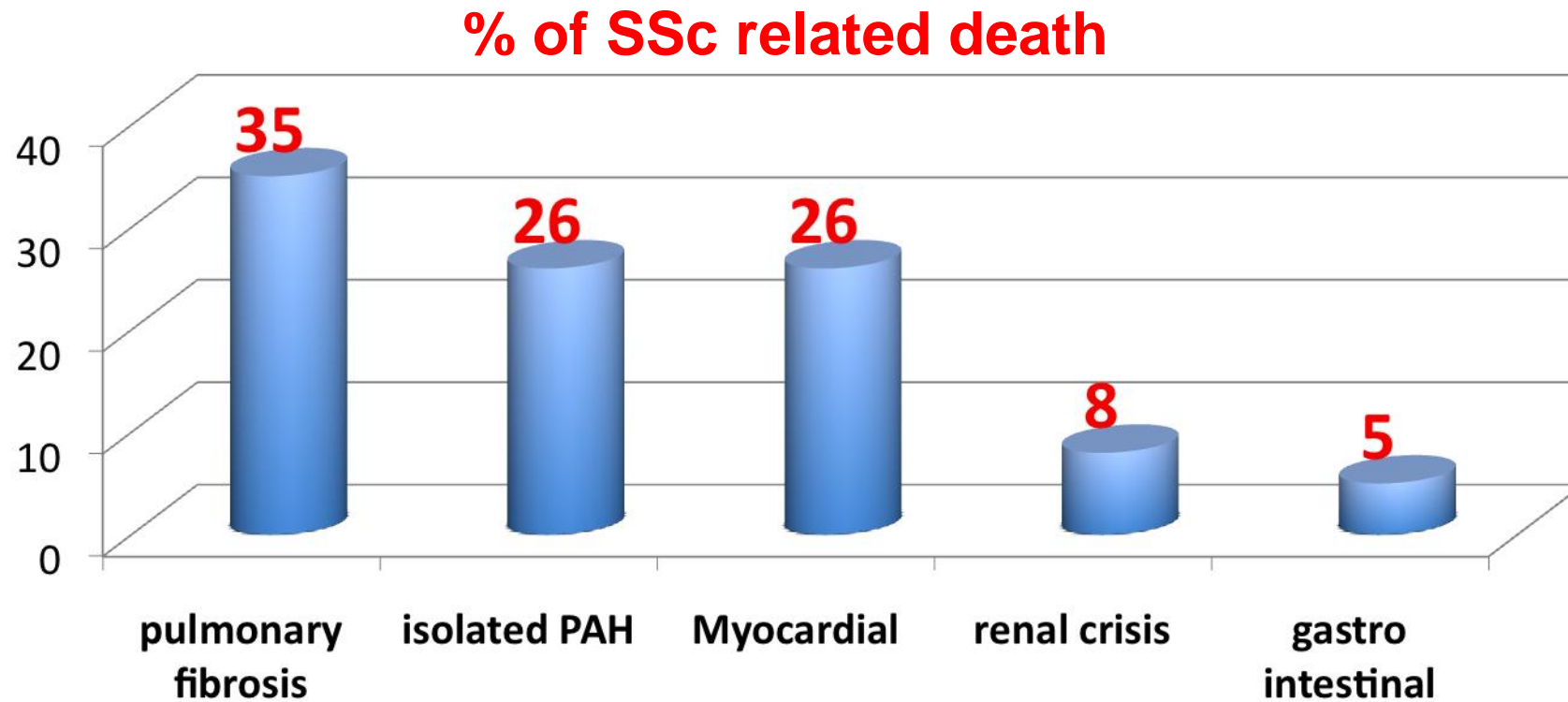


# Cardiac involvement in **systemic sclerosis** (SSc) has high prognostic relevance.



Clements PJ...Furst DE et al. *Arthritis Rheum* 1991.  
Ferri C et al. *Medicine* 2002.

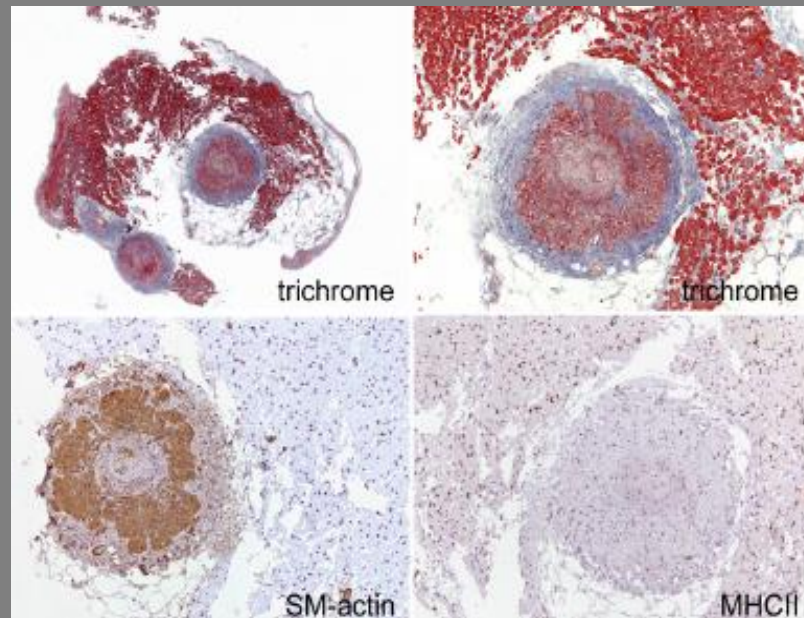
# EUSTAR database: 234 deaths including 128 SSc-related



# Clinical and Histopathological Features of Patients with Systemic Sclerosis Undergoing Endomyocardial Biopsy

Mueller KA et al . PlosOne May 12

**If clinical signs of cardiac with mildly impaired LVEF, prognosis was poor with 28% MI within 22.5 months FU and associated with the degree of cardiac inflammation and fibrosis.**



two arterioles with fibrosis and inflammation in the vessels  
Immunohistological staining with SM-actin : hyperplasia of smooth muscle in the vessel

Thanks to Marco Matucci-Cerenic and Silvia Bellando-Randon

# What do you do next?

- Observe
- **Diuretic**
- **Cardiotonic**
- Steroids
- Pacemaker
- Beta-blocker
- Anti-Arrhythmic

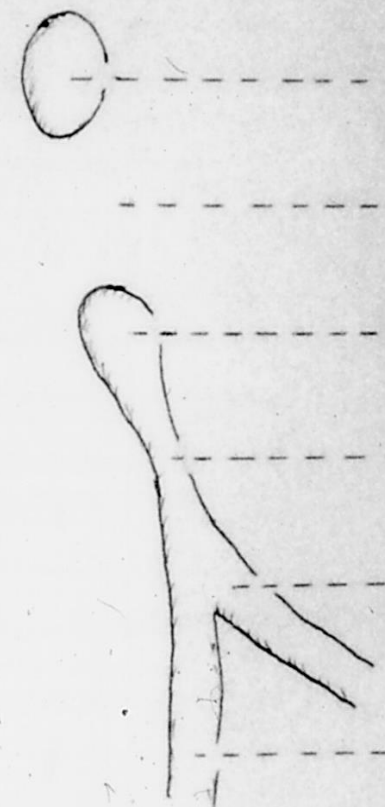
## Patient #2- Jennifer

- She was given Furosemide 40 mg qod plus digoxin 0.125 mg qd and she felt better. Her mild edema disappeared and she could now climb 2 flights of stairs. Her energy improved.
- 3 months later, she comes in complaining of recurrent dizziness, lasting seconds occurring 2-5 times daily and fainting when she got up this morning. On exam, she has multiple PVCs.
- Holter monitor confirms multiple PVCs with one triplet and one 5 beat run of VT.

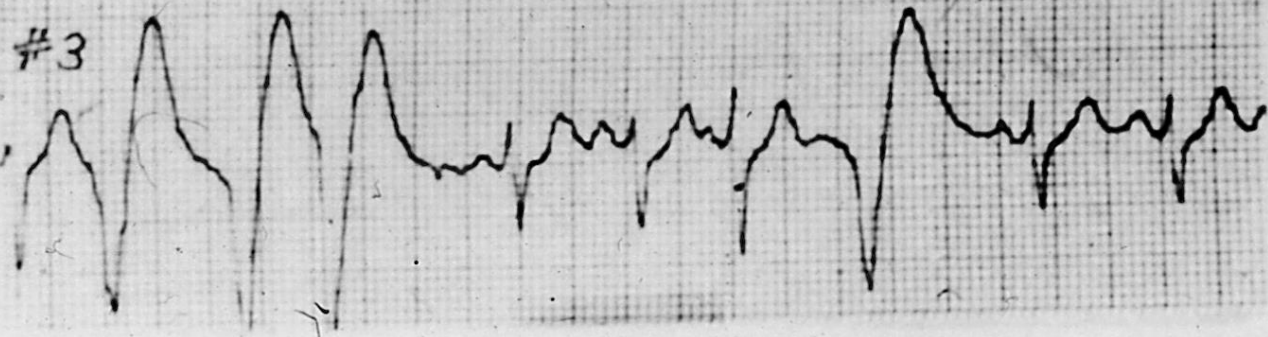
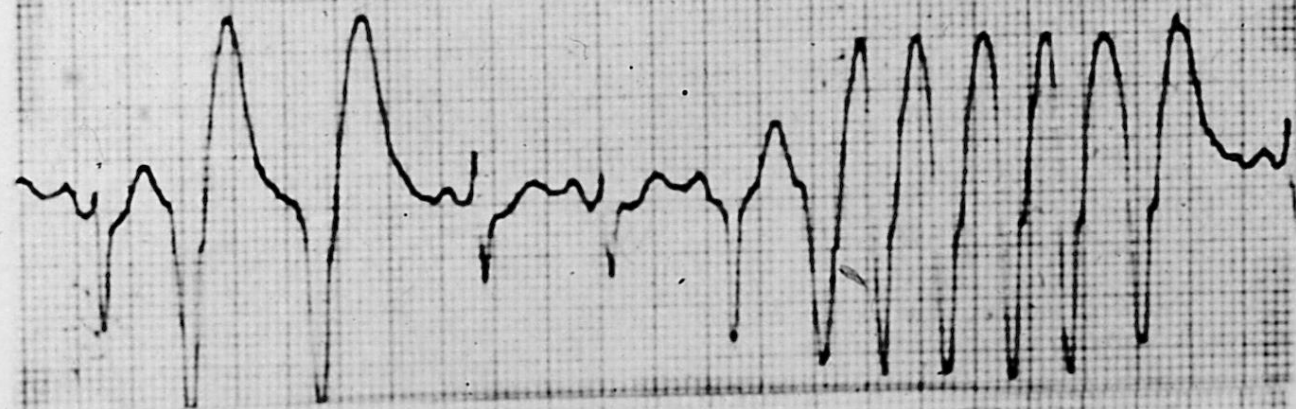
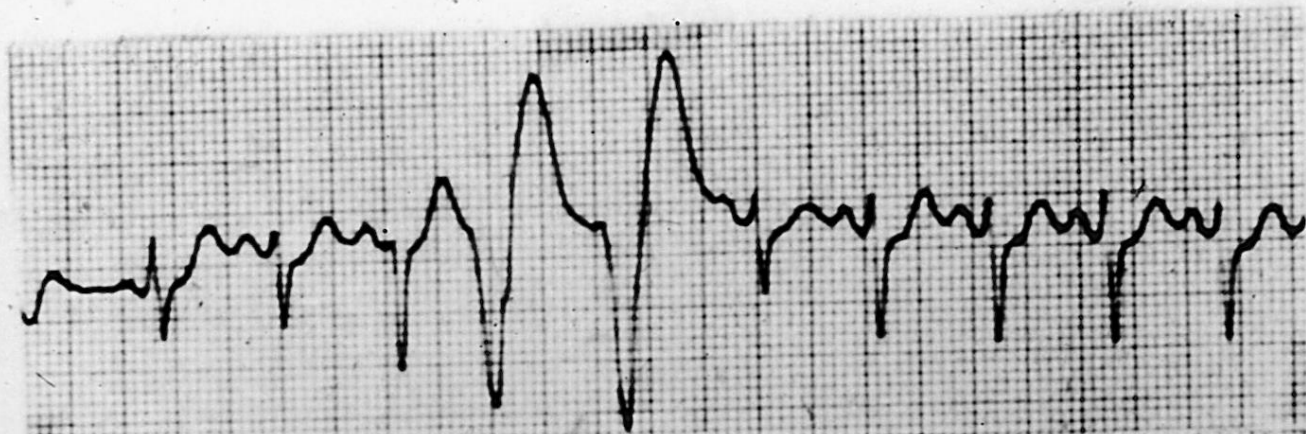
# What do you do next?

- Observe
- Steroids
- Pacemaker
- Beta-blocker
- Anti-Arrhythmic

INCIDENCE OF ELECTROPHYSIOLOGIC ABNORMALITIES  
ON HIS BUNDLE ELECTROGRAM (EPY) IN 10 PSS PATIENTS\*

	<u>ANATOMIC AREA STUDIED</u>	<u>PROPORTION OF EPY ABNORMAL</u>
	SINUS NODE	7/20
	RT. ATRIUM	8/20
	AV - NODE	10/20
	HIS	1/20
	RIGHT BUNDLE	2/9
	LEFT BUNDLE	N.D.

\* EPY STUDIES ABNORMAL IN 14 OF 20 PATIENTS STUDIED





# What do you do next?

- Observe
- Diuretic
- Cardiotonic
- Steroids
- **Pacemaker**
- Beta-blocker
- Anti-Arrhythmic

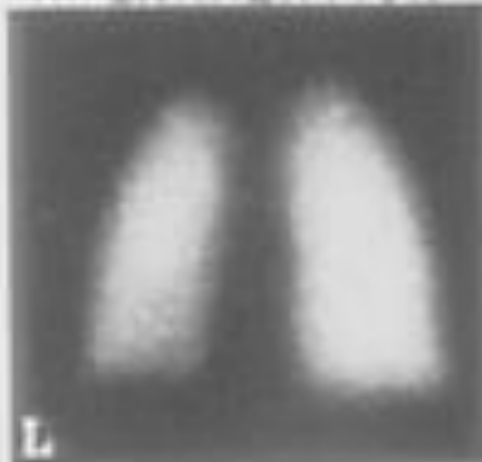
# SUMMARY

- Observe
- **Diuretic**
- **Cardiotonic**
- Steroids
- **Pacemaker**
- Beta-blocker
- Anti-Arrhythmic

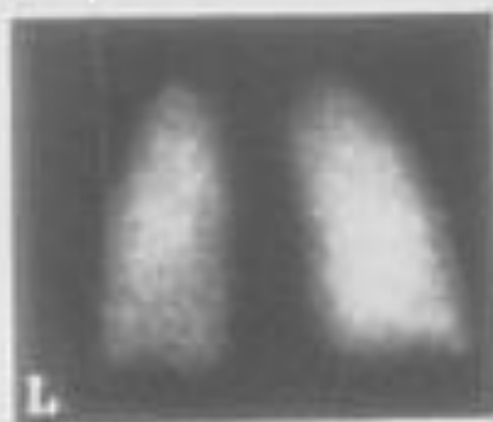
# Raynaud's Phenomenon



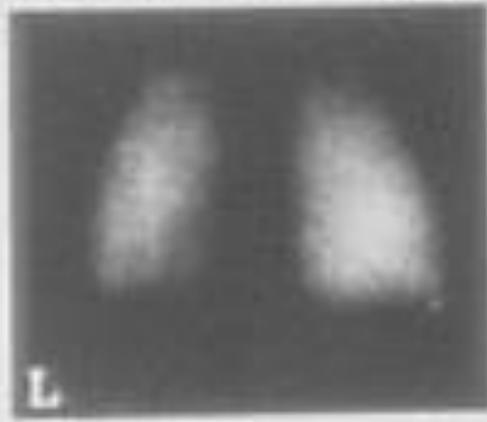
Kr INHALATION



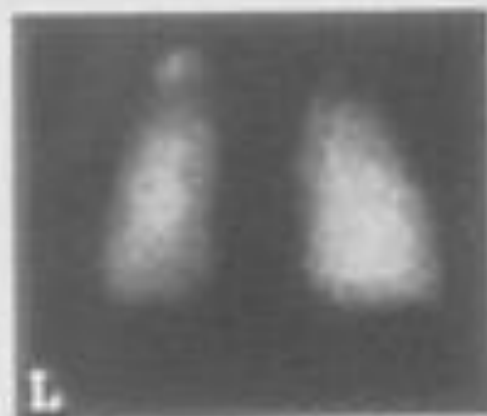
$^{81m}\text{Kr}$  PERFUSION



BASELINE

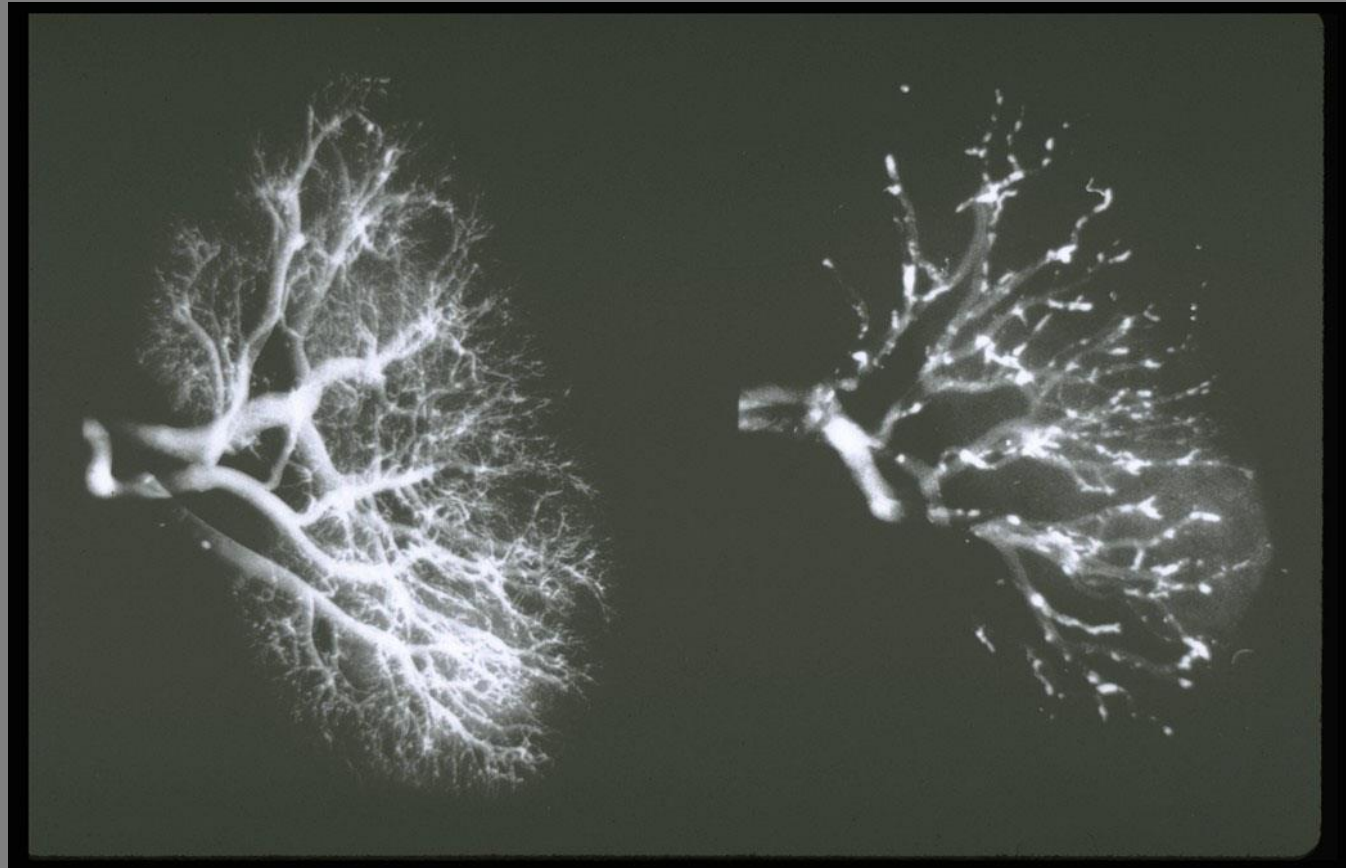


HANDS IN ICE  
WATER FOR 3 MIN



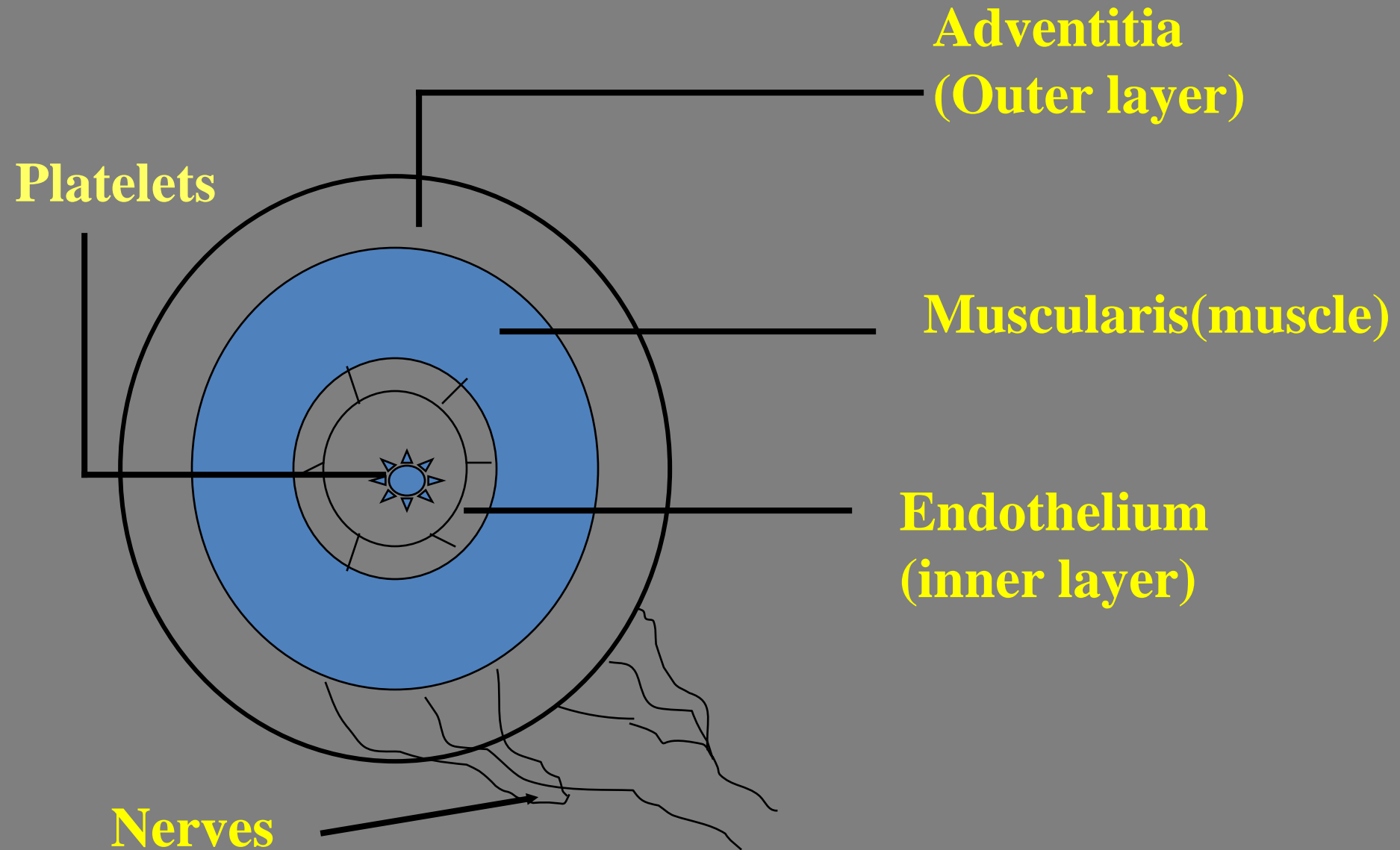
5 MIN AFTER  
HANDS OUT OF  
ICE WATER

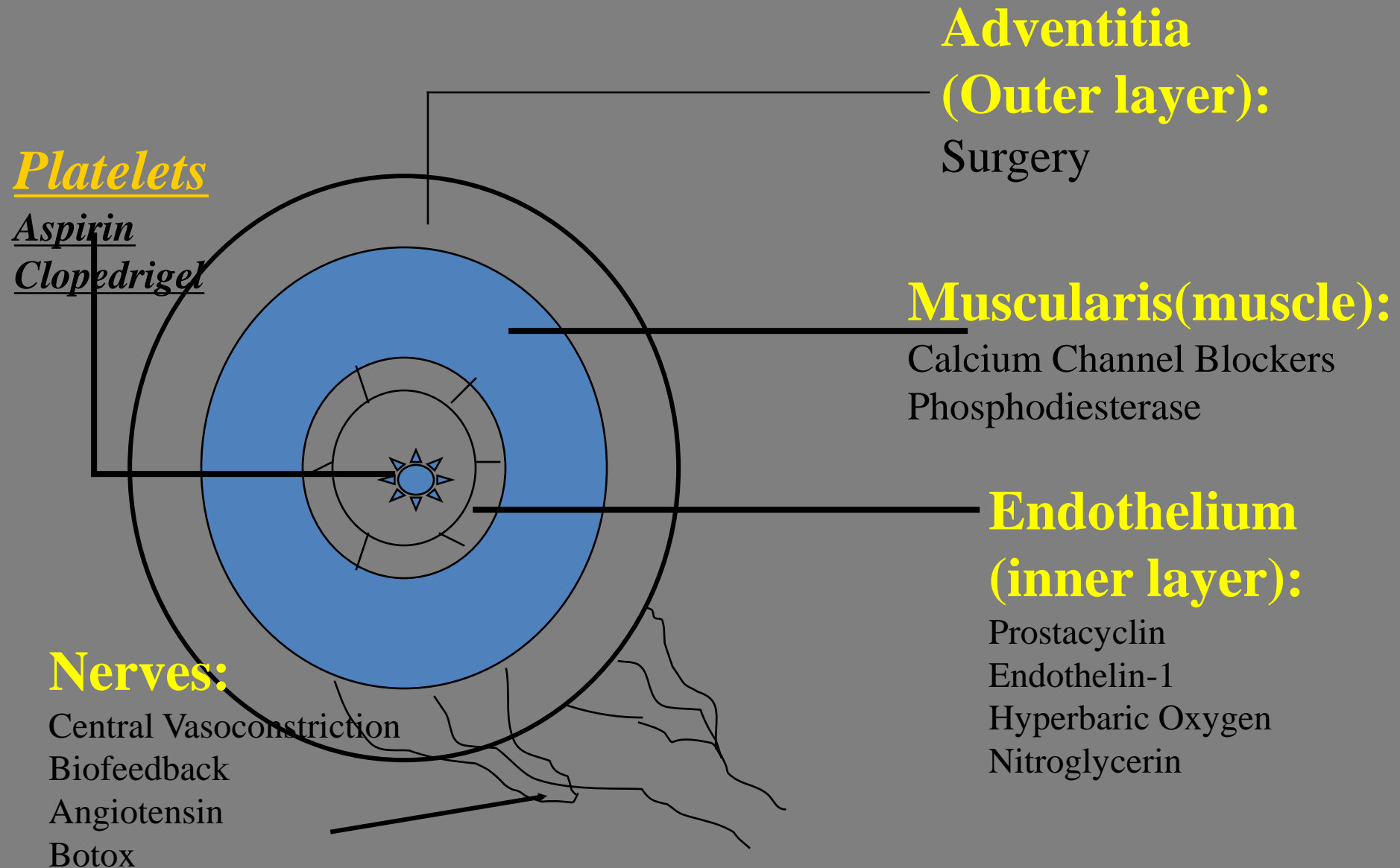
# Renal Angiogram



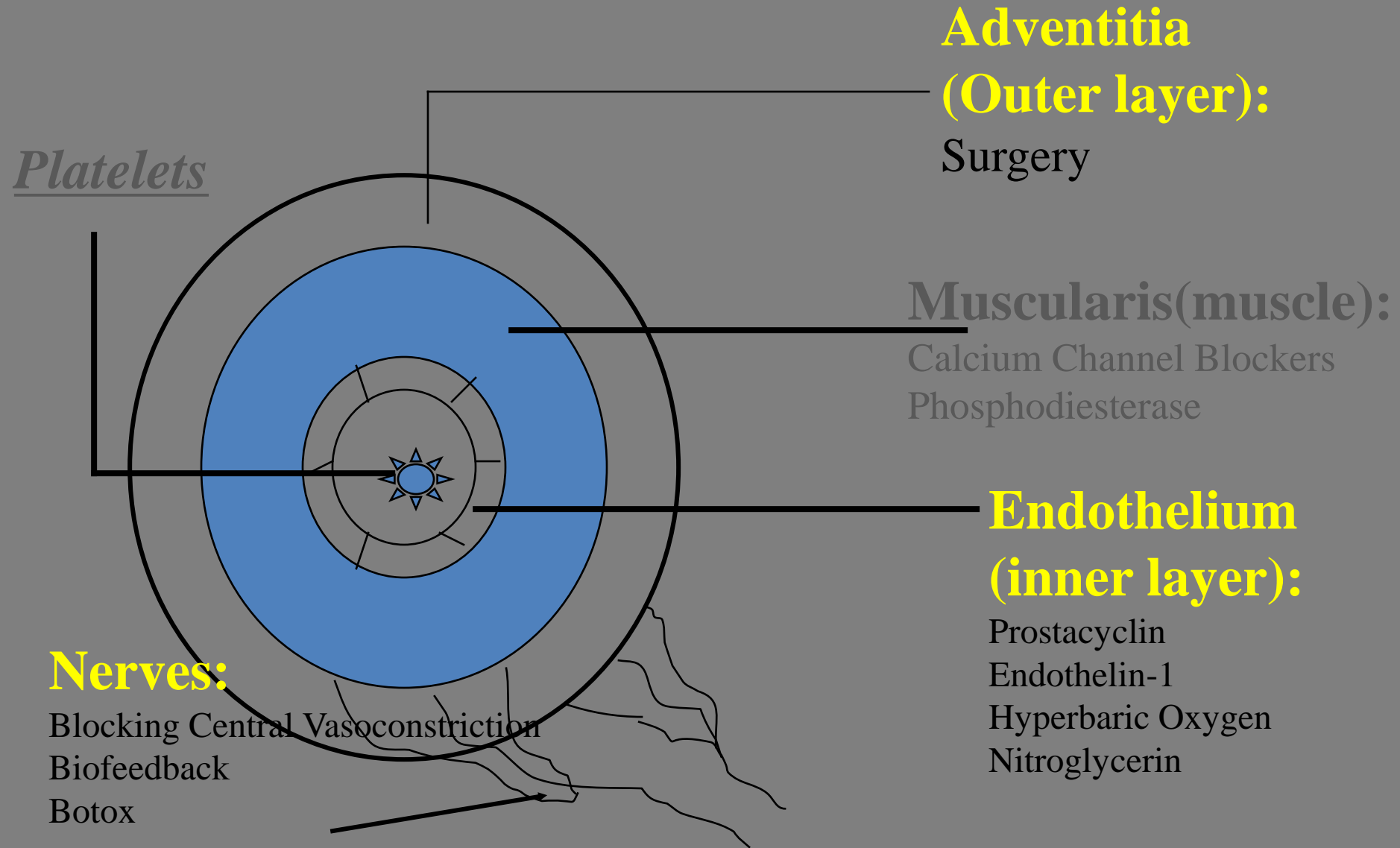
# Mrs. Johnson

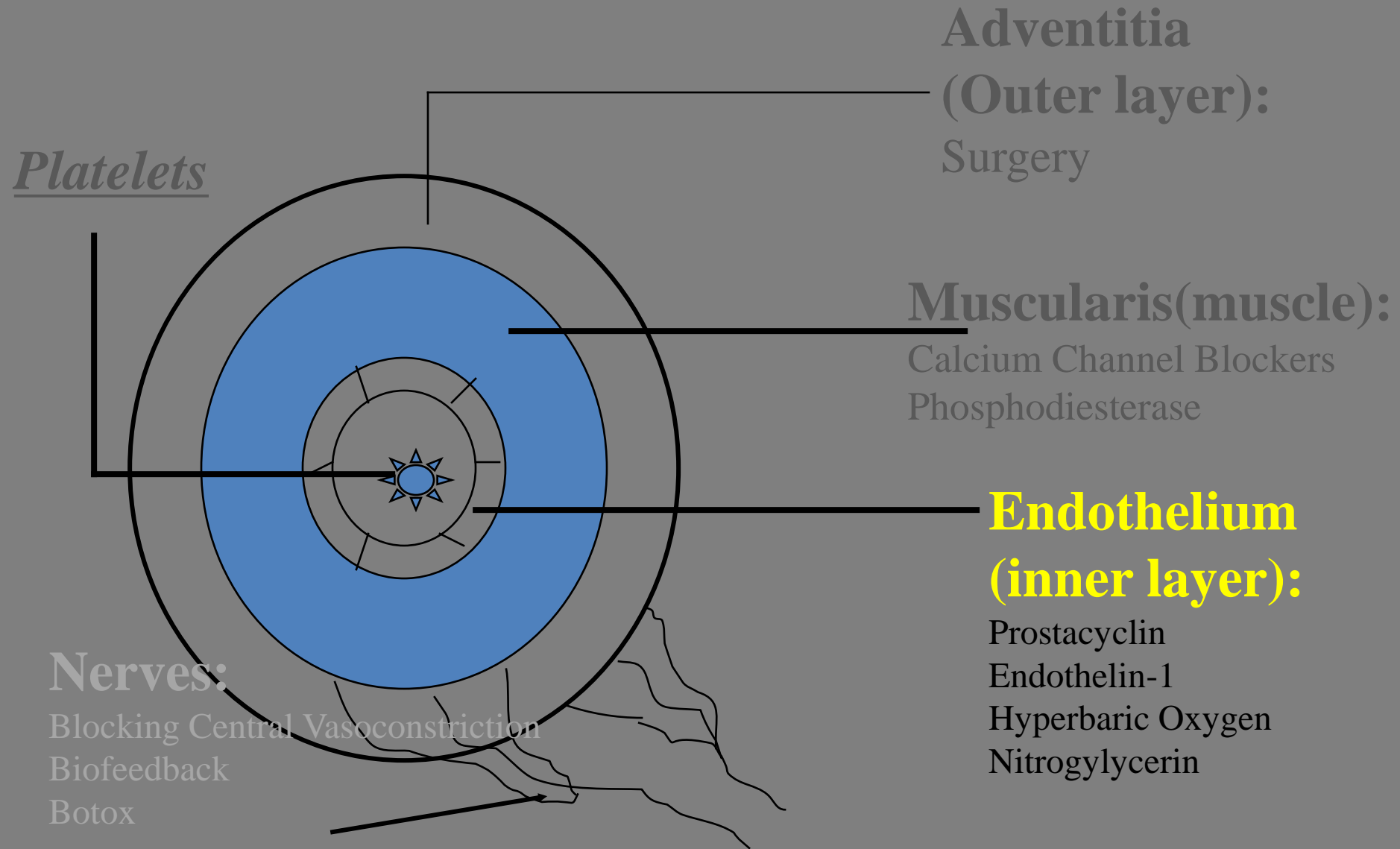
- 43 yr old with SSc for 4 yrs characterized by Raynaud's 5-10 x daily, ILD(FVC:65%; DLCO: 58%),mild ground glass on HRCT, mild dysphagia to meat and tenderness of wrists, PIP, knees. She is on Mycophenolate mofetil 2 gm daily and Aspirin 325 mg daily.
- She used nifedipine 90 mg qd but it didn't improve her Raynaud's
- She then used Losartan 25 mg qd with edema so it had to be stopped
- Sildenafil caused orthostasis despite using only 20 mg qd







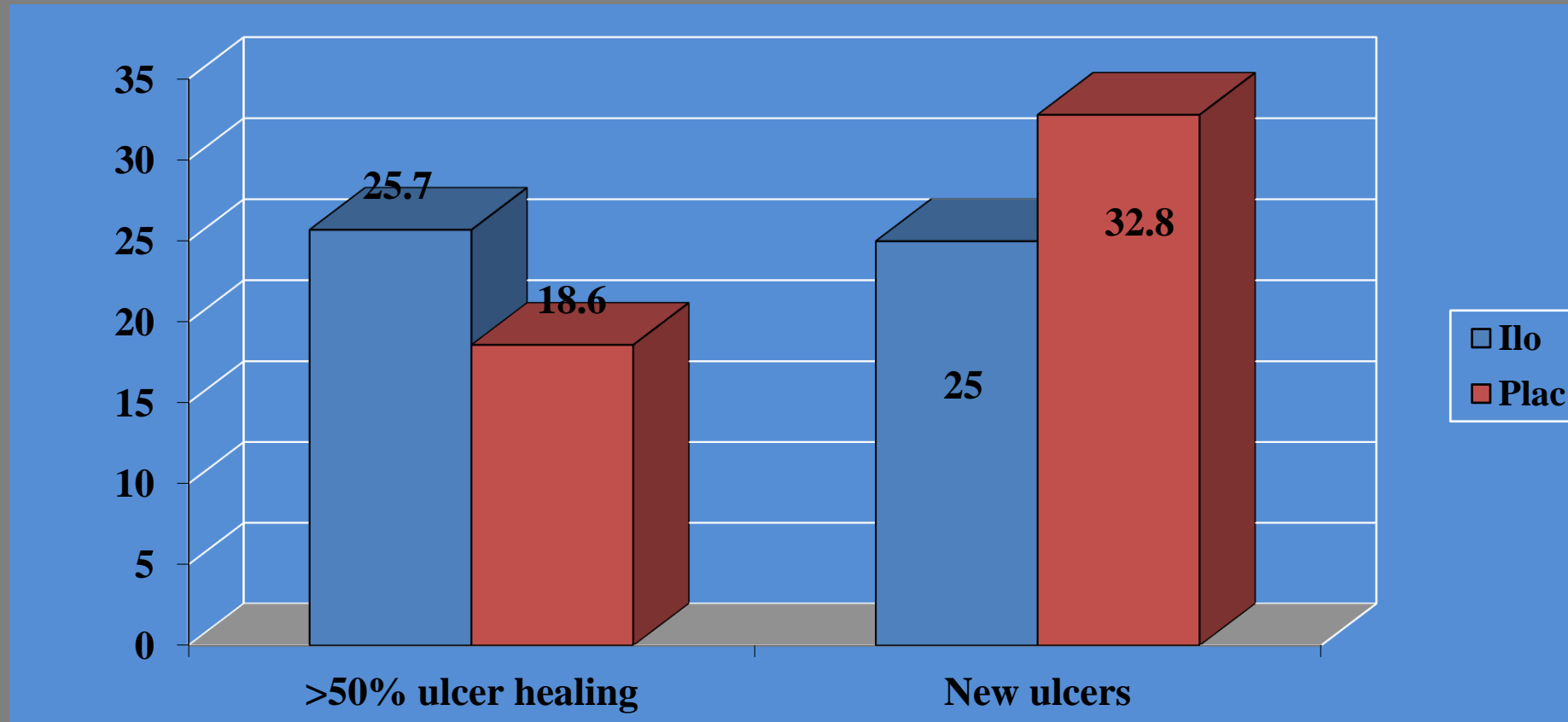




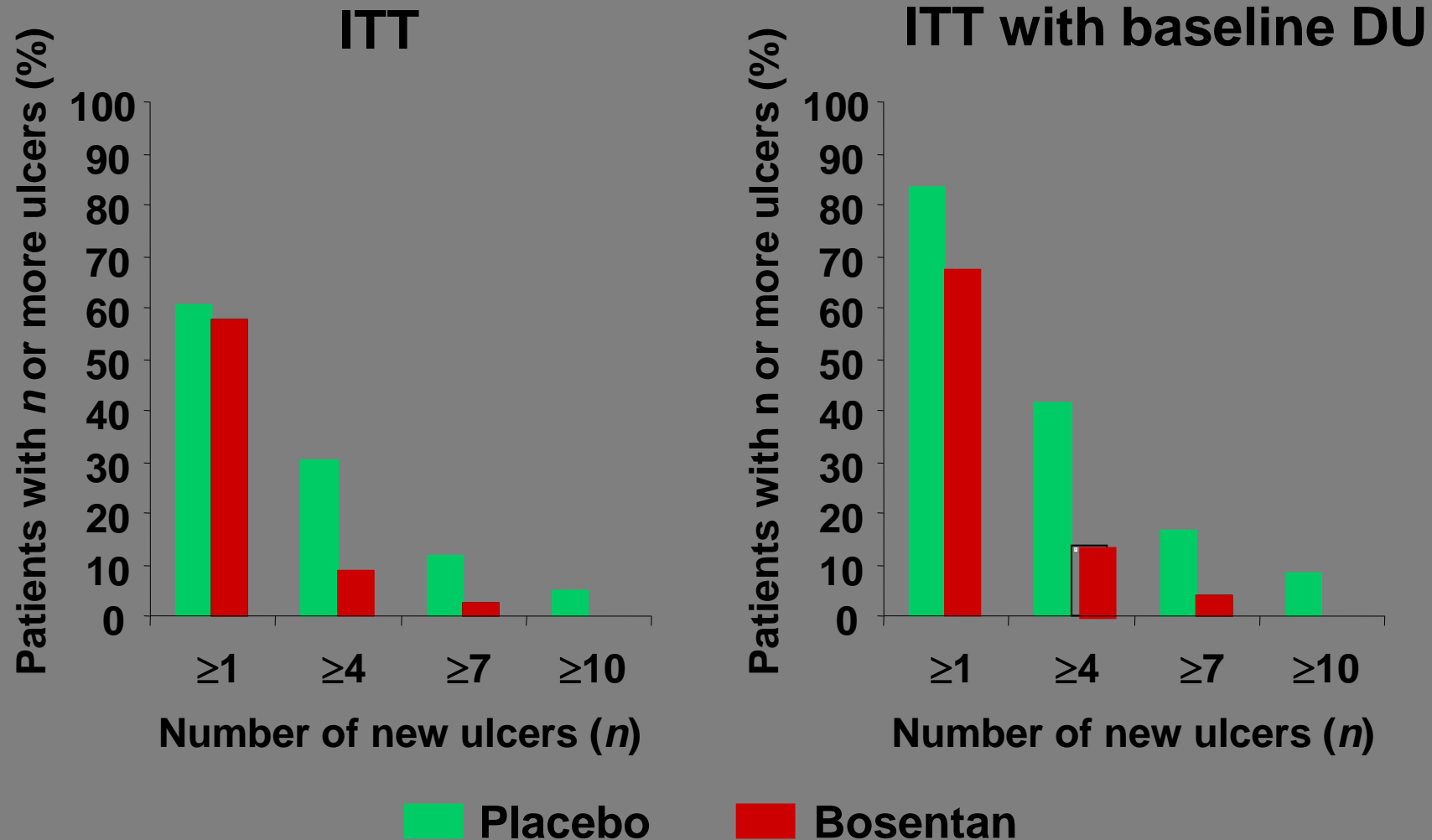
# IV Iloprost for SSc Raynaud's 7-9 wk Results ( $p < 0.05$ for $>50\%$

,NS for new)

Wigley FM et al, AnnInt Med 1994,120:199



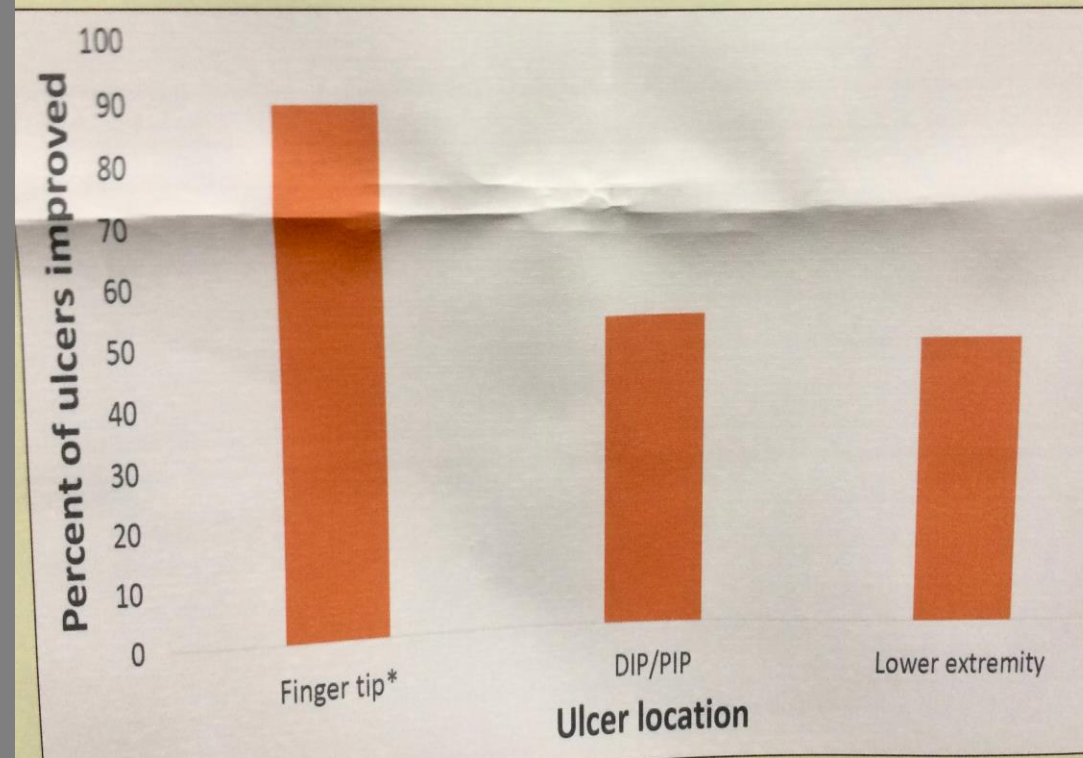
# Bosentan reduces number of patients with new digital ulcers



# Hyperbaric Oxygen Treatment(HBOT) for Severe DU

Armstrong S, Evans A et al JSRD. 2018. 3:185 (P247)

- 36 HBOT treated ulcers among 2261 pts in a Toronto cohort(1.6%)
- 30-50 treatments per pt, 2.5 atmos., 5 days/wk
- 13 not fully treated
  - (“not healable”-no increased O<sub>2</sub> in the lesion,2; technical,4; Anxiety,1)
  - AE: ear pain,2; Nausea,2



64% improved

# 14 day, Double-blind, cross-over study of Nitroglycerin(0.2 mg/hr) in Raynaud's

- N=21 primary Raynaud's Disease and 21 SSc patients
- 7 days of Patches(NTG vs Placebo) applied to the chest wall
- Then 7 days of cross-over

	Comparison of NTG vs Placebo	
# Raynaud's attacks/wk	<u>Raynaud's</u> 0.002	<u>SSc</u> 0.01
Numbness	0.002	0.009
Pain	0.004	0.034
Severity	0.002	0.036

- **NTG Improved: # attacks /wk, Numbness,**
  - **Pain, Severity**

# DB RCT of topical NTG in Raynaud's

Seibold JR, Khanna D, et al. JSRD 2018. 3:227-228

- N= 65 with 32 SSc Crest?
- DB X-over, single dose
- 16 minute trial

Conclusion: no effect in a single dose study.

**Table 1: Change from Baseline in Peak Main Raynaud's Symptom (MRS) Score at Visits 5 & 6 (Primary Endpoint)**

	Top. NTG	Vehicle	Tx Difference
N =	65	65	
Tx Response	-20.19 mm	-18.63 mm	-1.56 mm
P-value	0.55		
Avg. Base-line Score	78mm		

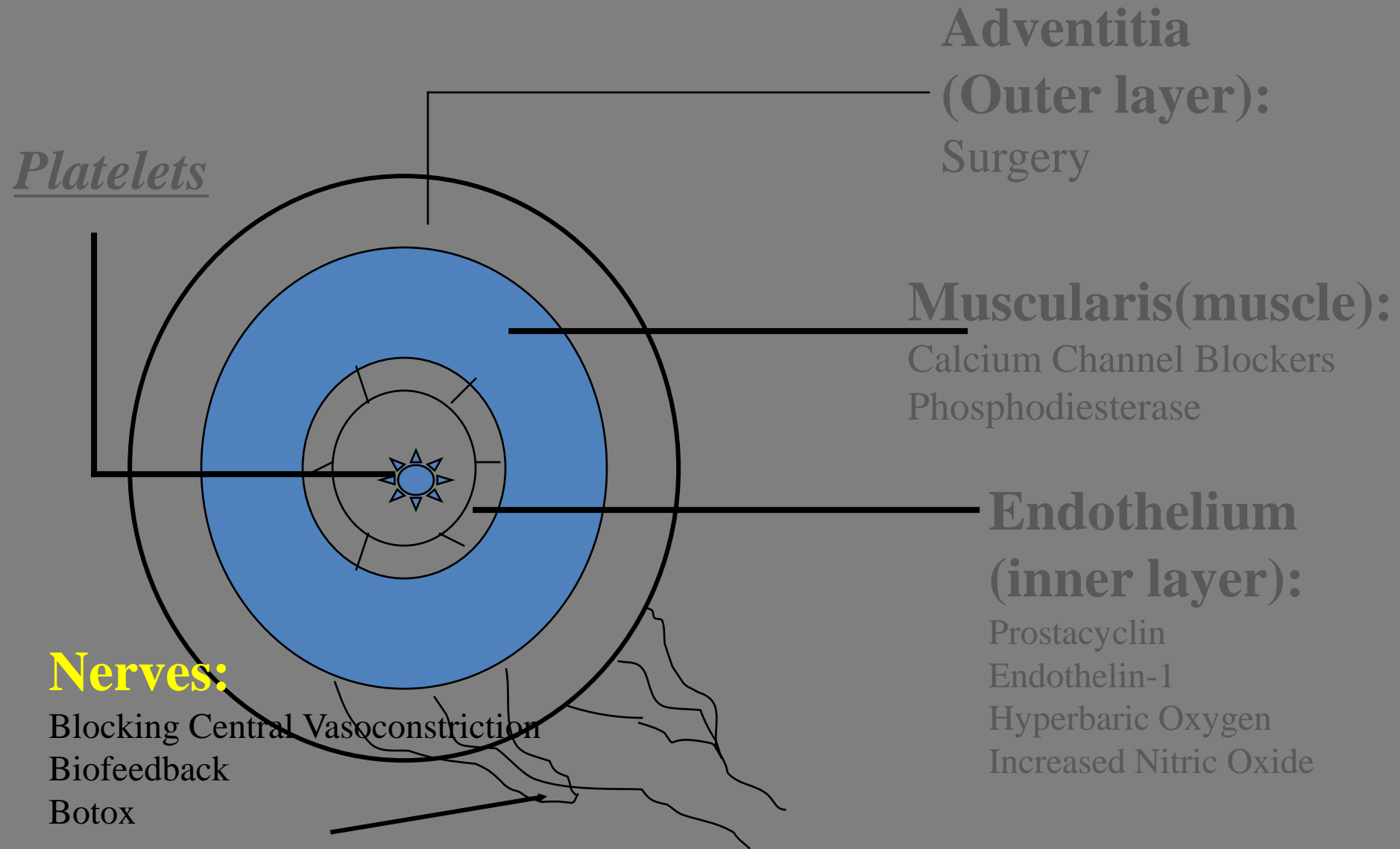
## Mrs Johnson(2)

- Bosentan helps her Raynaud's by 60% but is expensive.
- She wants to stop her medications.



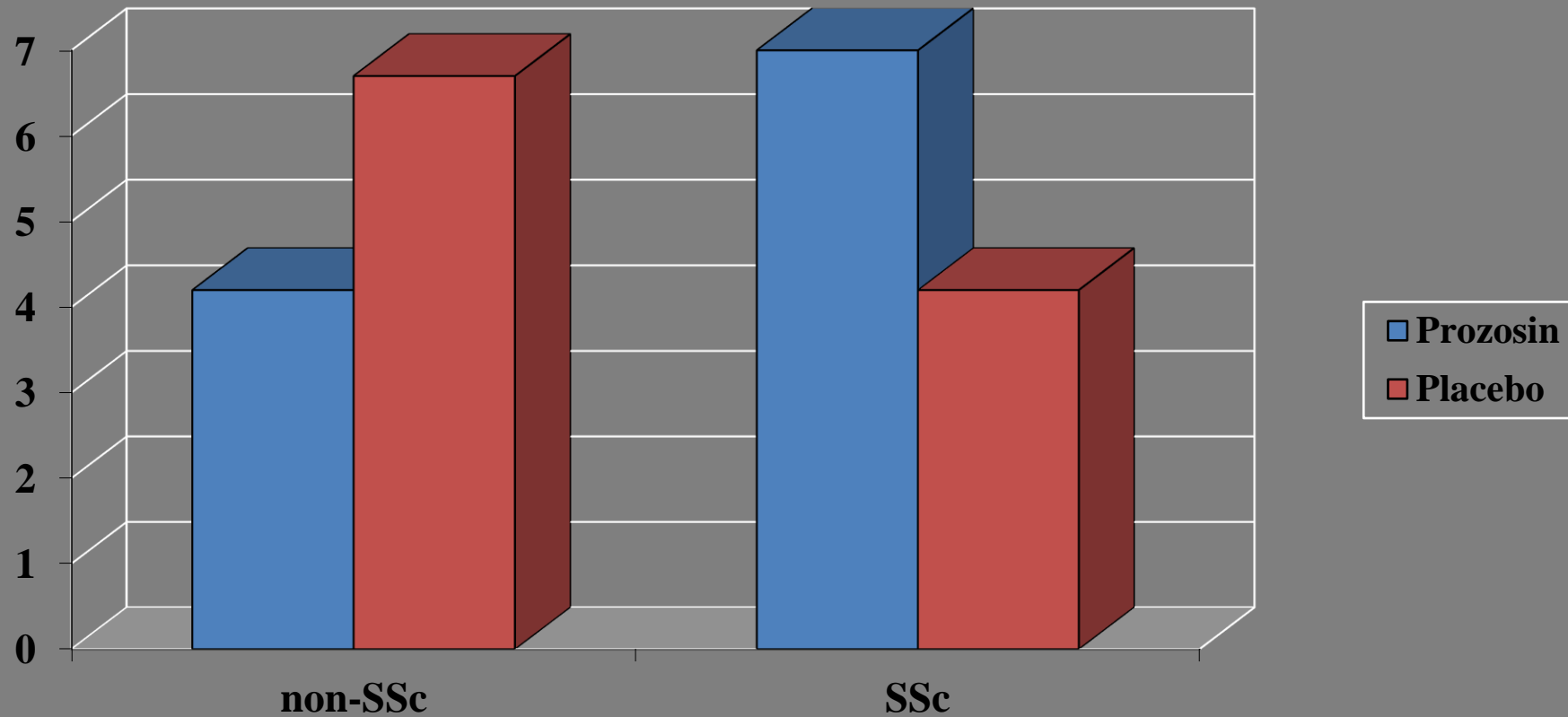
# Mrs. Johnson (3)

- During summer, she stopped her Raynaud's medications but ulcers of the 2 and 3 finger tips developed and this interfered with sleep because they were so painful(8/10 pain VAS). On exam, the 2<sup>nd</sup> finger tip ulcer is infected. It is treated with local therapy and antibiotics and oxycodone
- What do you suggest?
  - IV Iloprost
  - Biofeedback
  - Sympathectomy of the palmar arch
  - Botoxin injections
  - Amputation of the finger distal phalanx



# Prazosin(4 mg/d) for Raynaud's-Episodes / 2 wks( $P<0.05$ )

Russell IJ J Rheum 1985;12:94



Prazosin (Minipress)-alpha 1 blockade

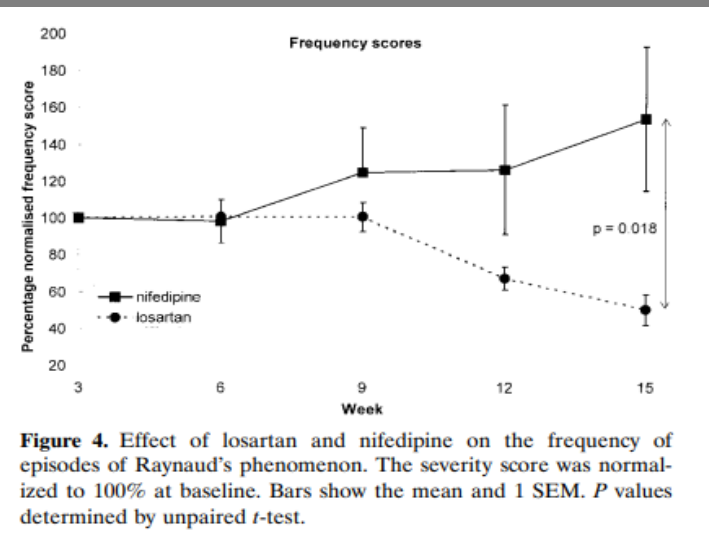
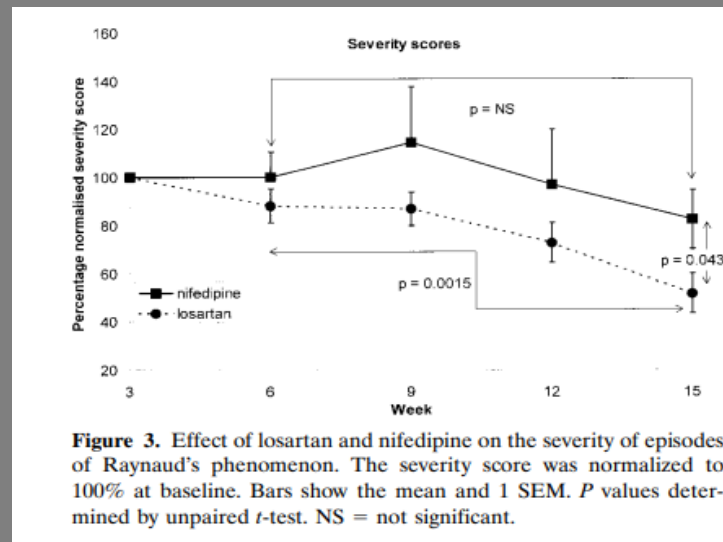
# Losartan 50 mg vs Nifedipine 40mg of Raynaud's

Dziadzio M, Denton C P et al A&R 1999. 42; 2646-2655

N= 25 primary Raynaud's and 25 SSc-related Raynaud's  
15 week, **open**, randomized, controlled trial

**Both groups improved—Primary > SSc (data not shown)**

Reduced VCAM-1 and procollagen type 1 N-terminal propeptide if symptoms improved



**Conclusion: Losartan worked better than nifedipine—  
MAJOR flaw: too low dose nifedipine**

# Biofeedback Training for SSc-Related Raynaud's Results (8/gp)

Freedman RR et al J Behavioral Med 1984;7:343



# Biofeedback for SSc-Raynaud's

Sporbeek B et al. Rheum Intern. 2012.32:1469-73

- 3x/wk open, randomized controlled 4 wk study
- N= 10 Oscillation (swinging), 8 Temp. biofeedback; 10 waiting control)

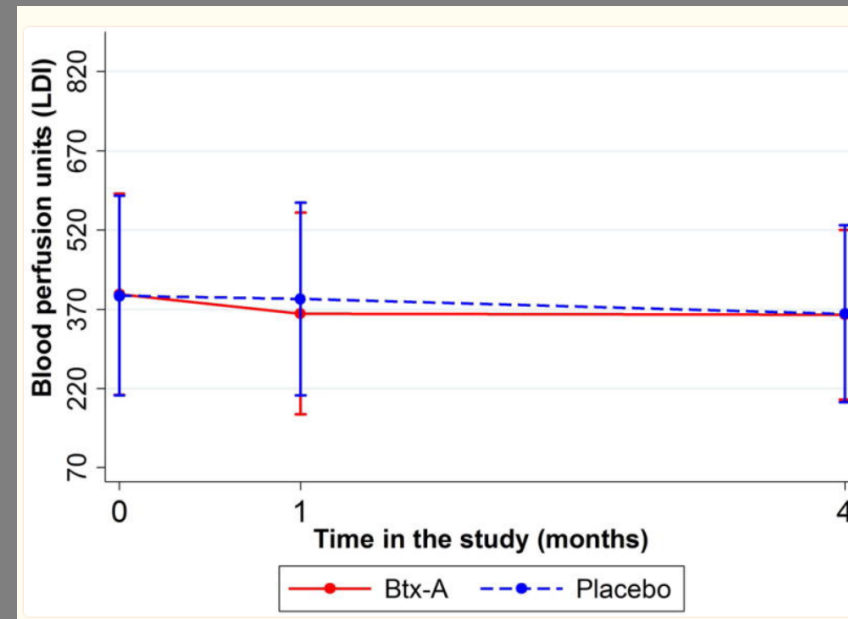
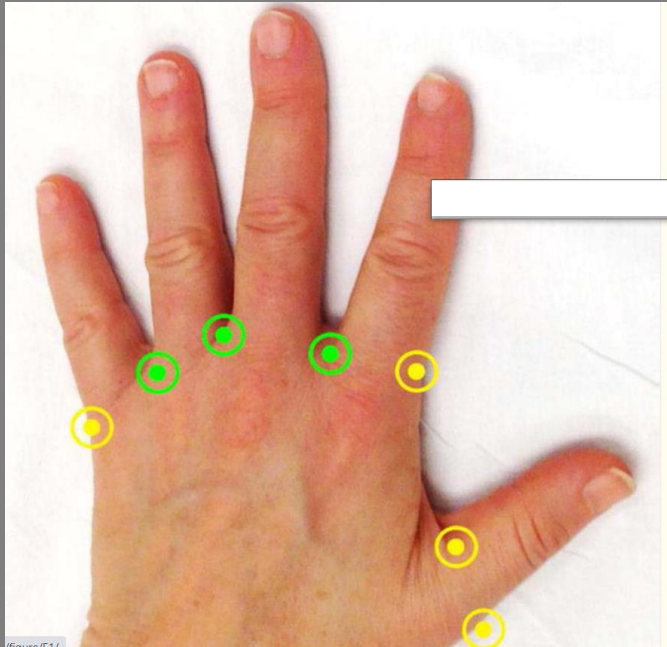


**Conclusion: very few pts, open but randomized, controlled---biofeedback worked**

# Pilot DB-RCT of Botox for Raynaud's Phenomenon in SSc

40 SSc pts  
4 months

1 hand injected with Botox 20 units; other hand injected with saline  
Caveat: ? Systemic effect from doses in 1 hand??

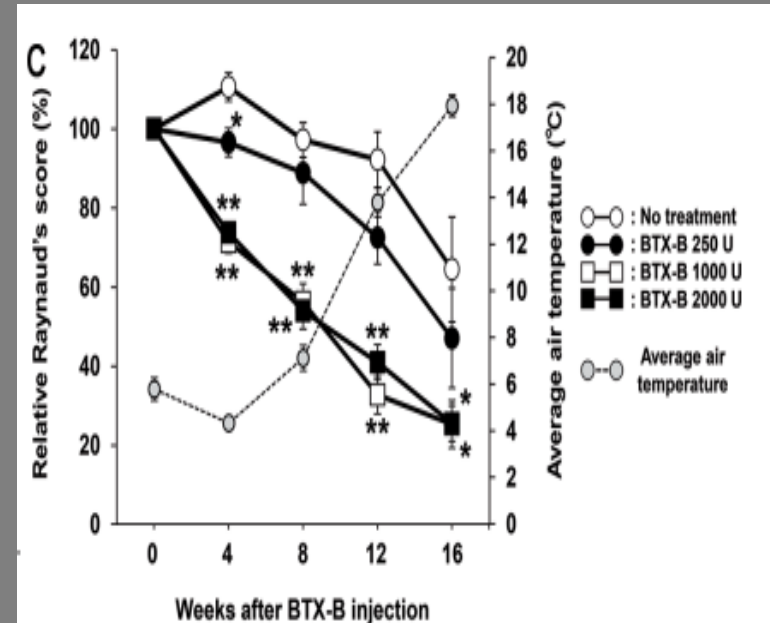


Conclusion: Botox had no effect

# Partly double-blind, RCT dosing study of Botox B in SSc – Raynaud’s Phenomenon

Motegi S-I, Liehara A et al Acta Dermat Vener 2017. 97: 843-850

- N= 8-10/gp
- No Rx or 250,1000,2000 units Botox B
- Dosing blinded but “no rx” gp open



**Conclusion: Despite flawed design, presence of blinded dose effect strongly favors efficacy of Botox B**



# Mrs. Johnson (4)

- 2 months later, the ulcers are worse despite Iloprost and biofeedback and there is gangrene of the 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> finger tips



# Mrs. Johnson (3)

- What do you suggest?
  - Sympathectomy of the palmar arch
  - Amputation of the finger distal phalanx

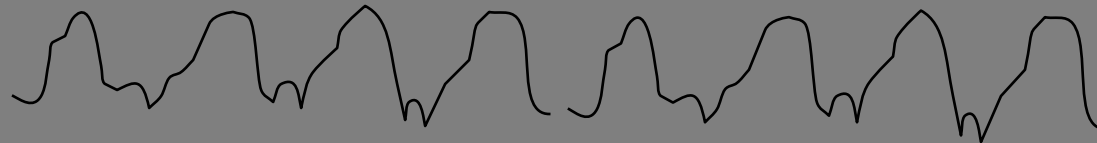
# Pulse Pressure in Digital Artery after Adventitial Stripping(N=5)

B Balogh et al J Hand Surg 2002; 27A:1073

**BEFORE**



**AFTER**

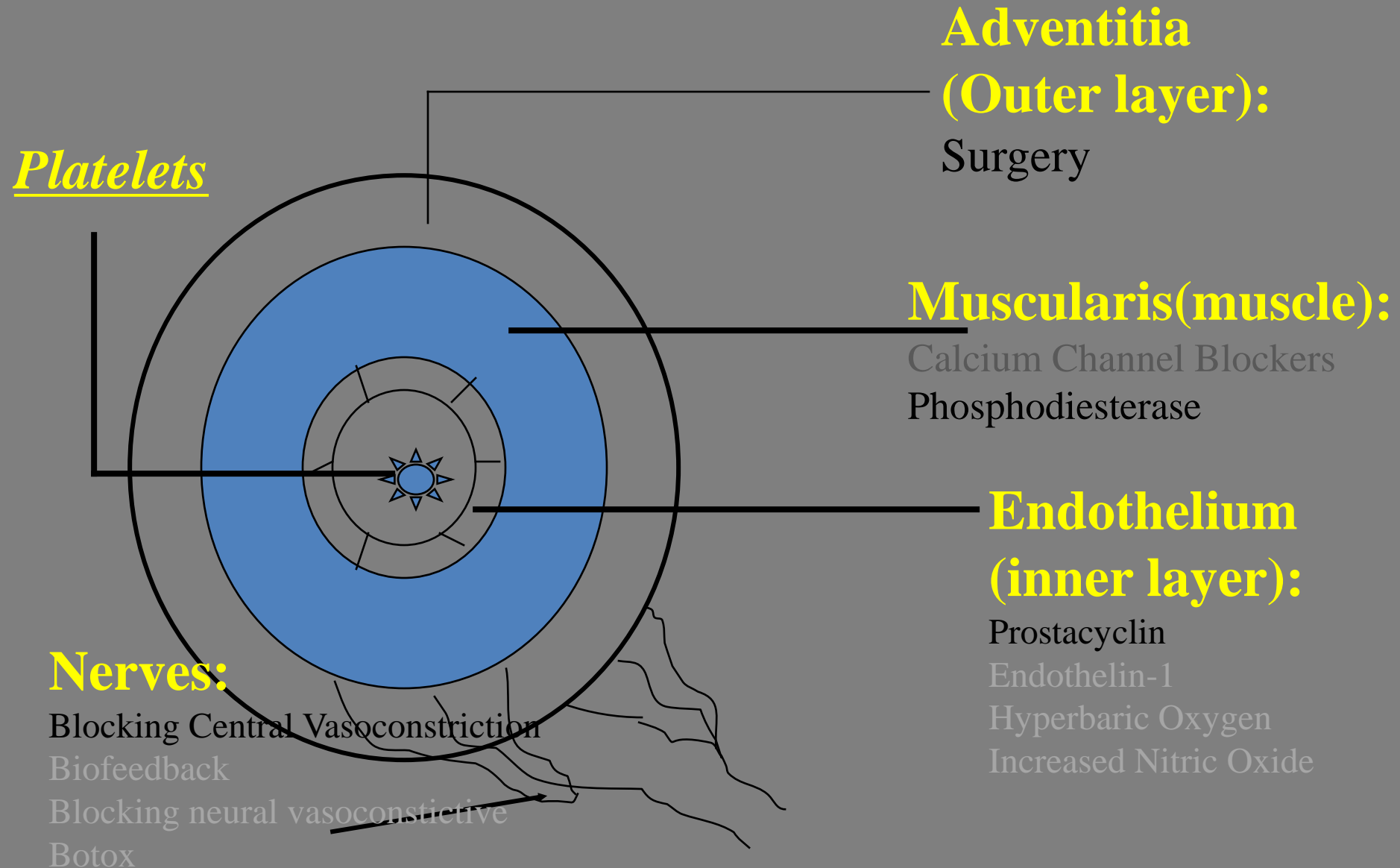


# Peri-arterial Sympathectomy for Refractory Digital Ischemia in SSc

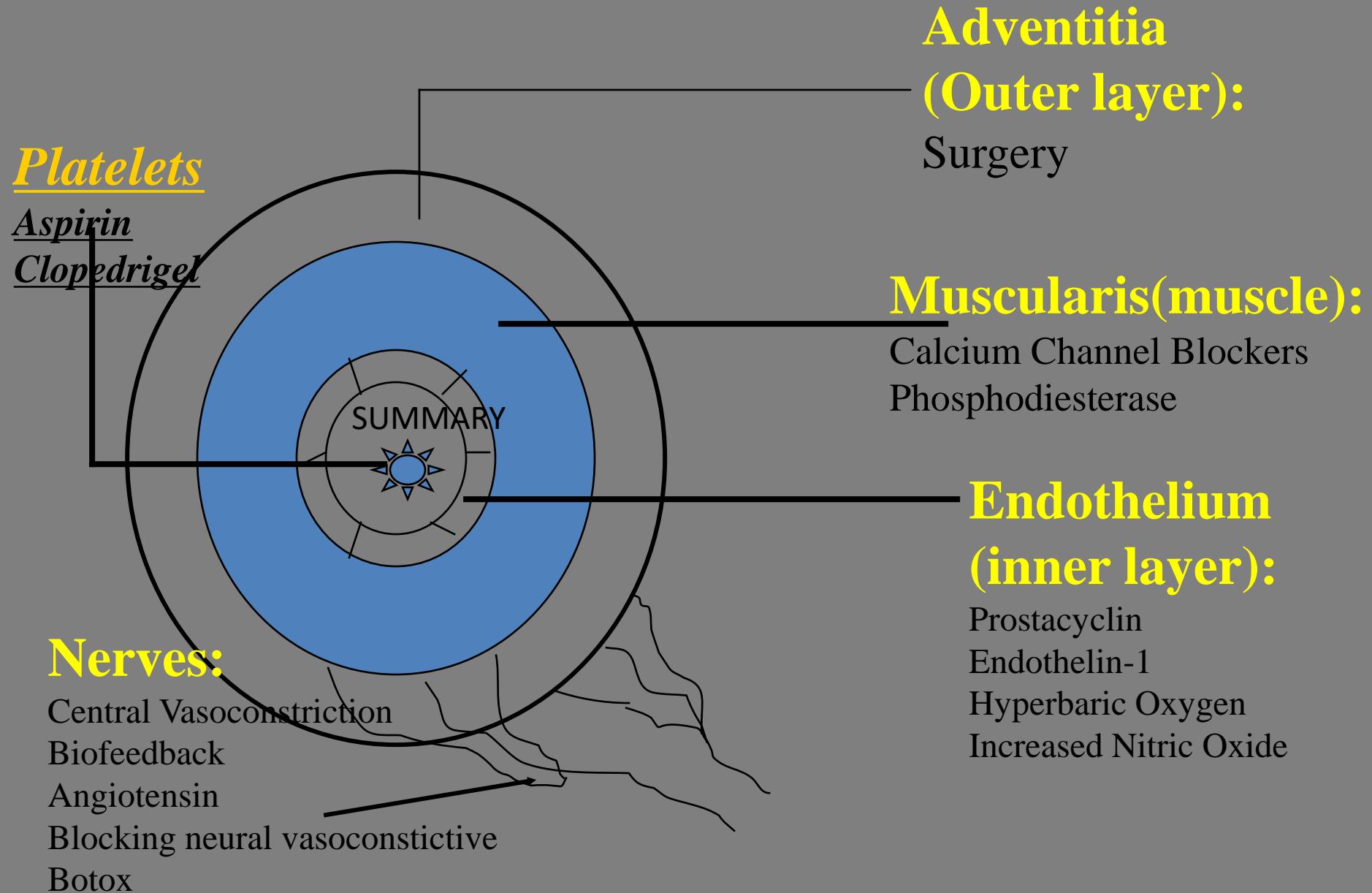
NJ Sweiss et al abs 1437 ACR 2003

- Very Short Follow-up- only 4.6 months
- 129 fingers among 38 pts
- 81% healed within 2.3 months
- (range: 0.3-83 months)
- 5/129(4%) did not heal

# Mrs Johnson



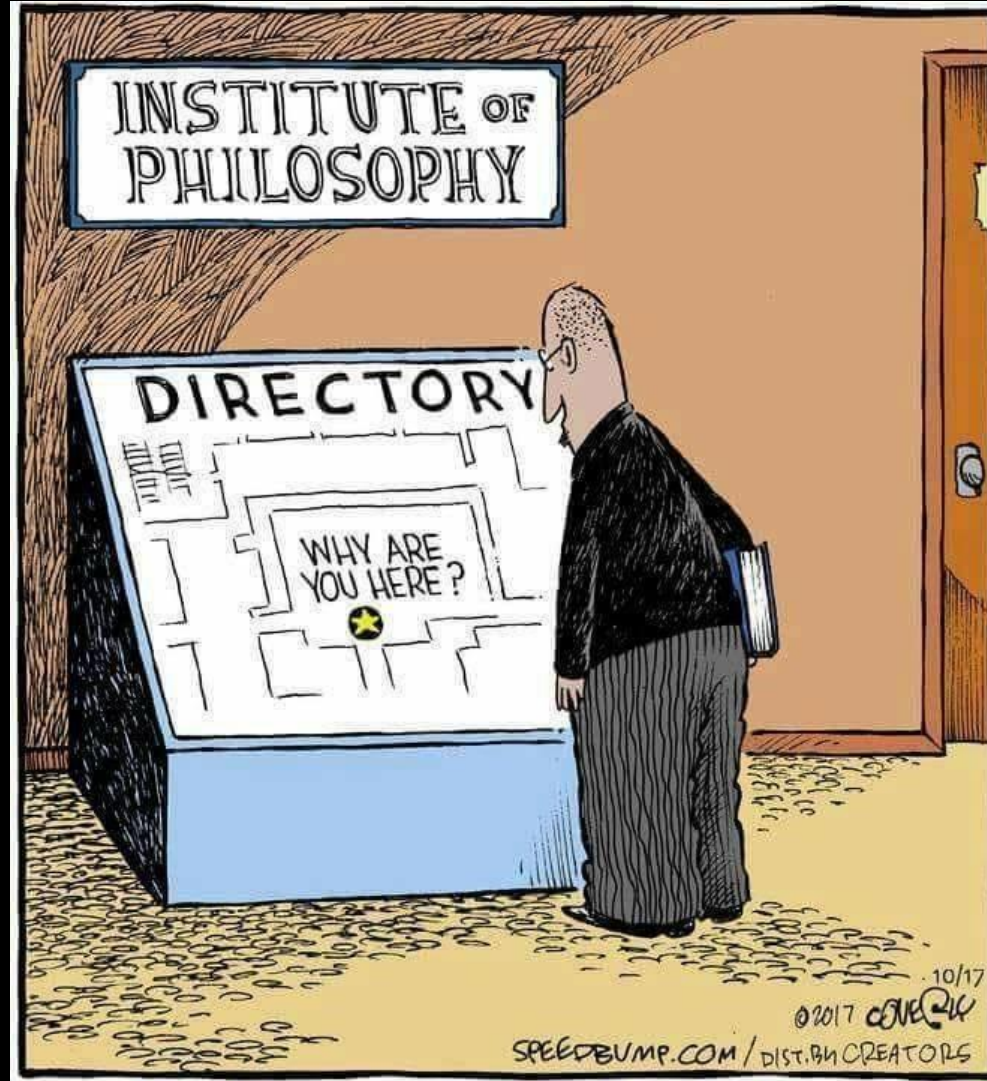
# SUMMARY



# Treatment for Selected Aspects of SSc

- Interstitial Lung Disease
- Cardiac
- Severe Raynaud's +/- Gangrene





Thank you for your attention