



Raynauds phenomenon and systemic sclerosis

Turk Romatoloji Kongresi 2016

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Life expectancy and standardised risk of mortality in different rheumatic diseases

Mok-CC, Arthritis Rheum 2011;63:1182

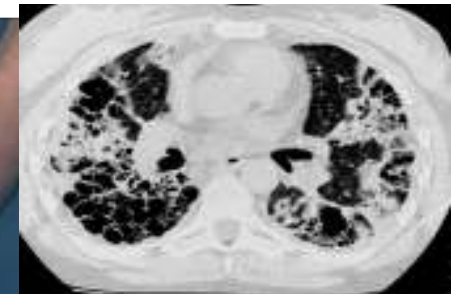
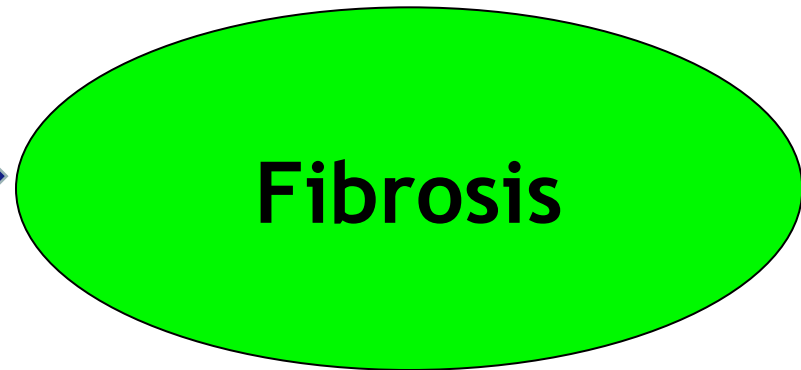
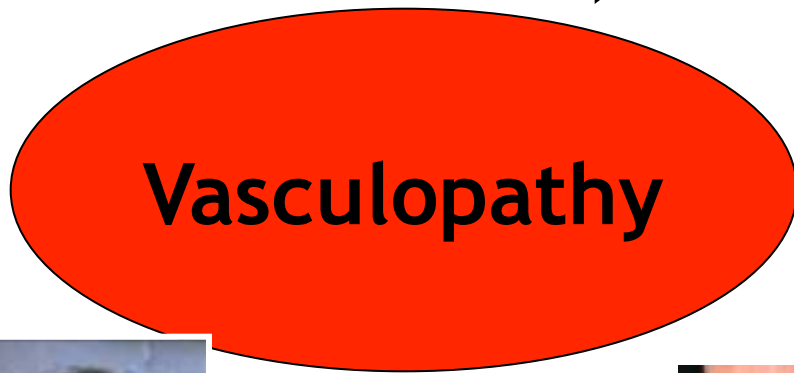
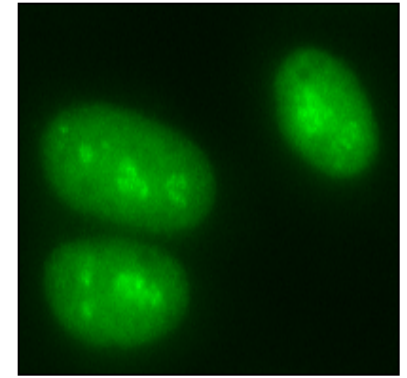
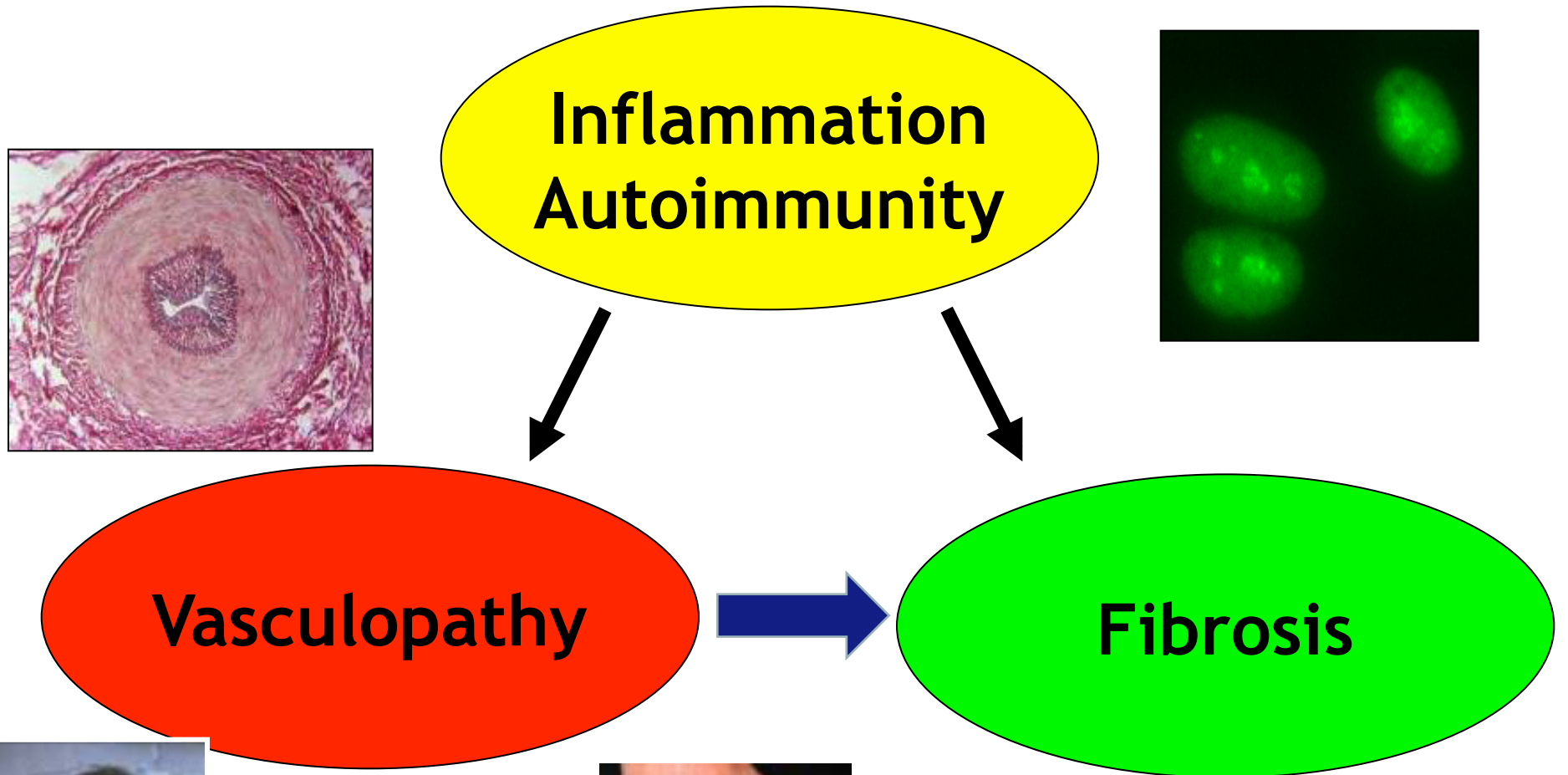
8367 Patients from 37 public hospitals from Hongkong admitted between , 1999-2008 were analysed

1. Age- and sex-matched standardised Mortality-Ratio (SMR)

	SLE (5243)	RA (8367)	AS (2154)	PsA (778)	SSc (449)	SV (1636)
aSMR female	5,6	1,7	1,4	2	4.3	2,7
aSMR male	3,9	1,6	1,9	1,4	2,6	2,6
SMR	5,2	1,7	1,9	1,6	3,9	2,6
Life expect. Females in years (Y)	-19,7	-6,9	-1,2	-6,5	-34,1	-19.3
Life expect. Males in y	-27	-5,2	-7	n.d.	-16	-28,3

SV systemic vasculitis

Features of systemic sclerosis (SSc)

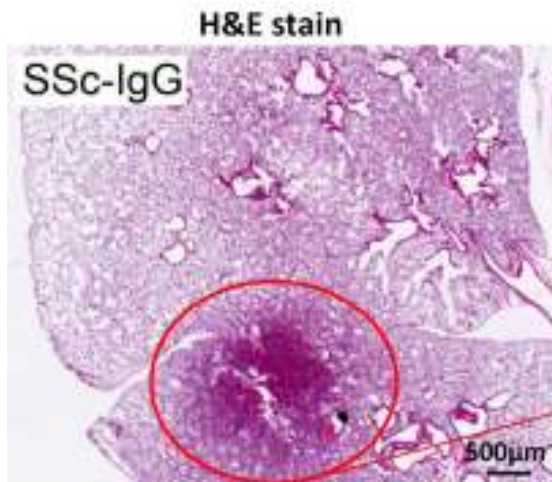
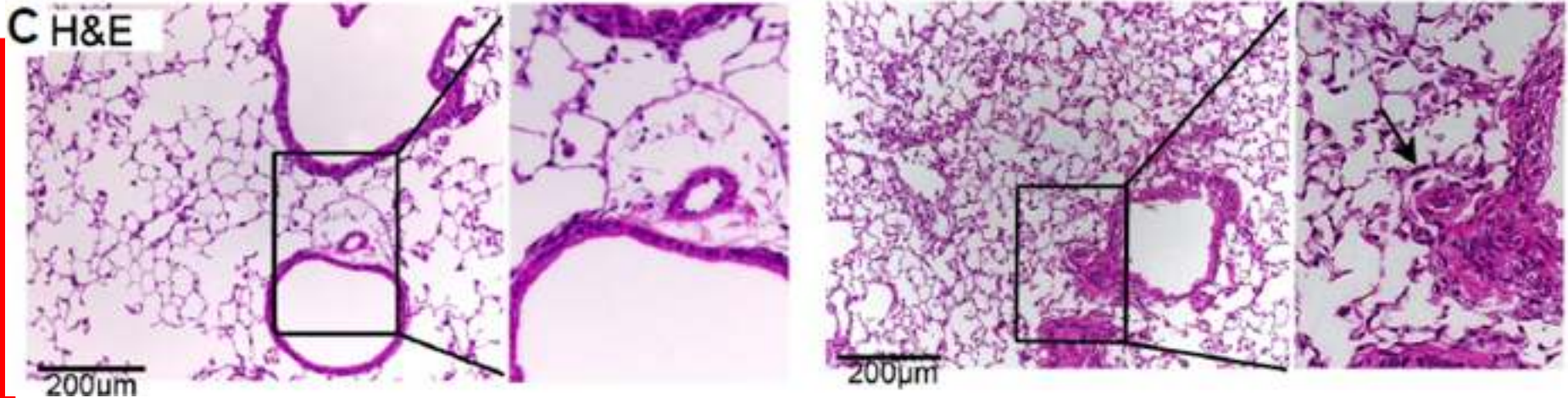


Antibodies from SSc patients induce signs of vasculopathy and fibrosis in mice

NC-IgG

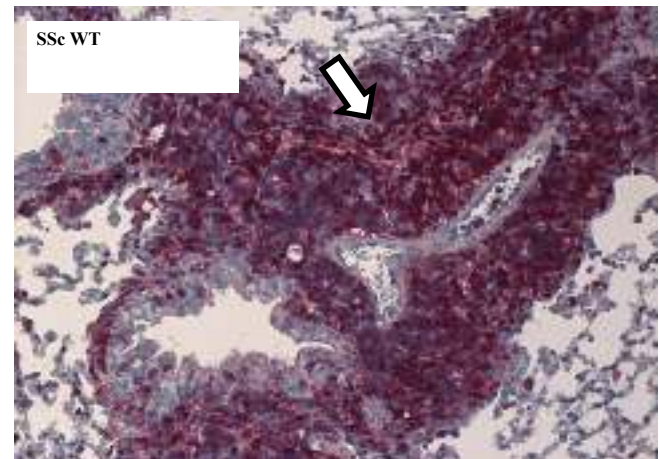
repetitive doses

SSc-IgG

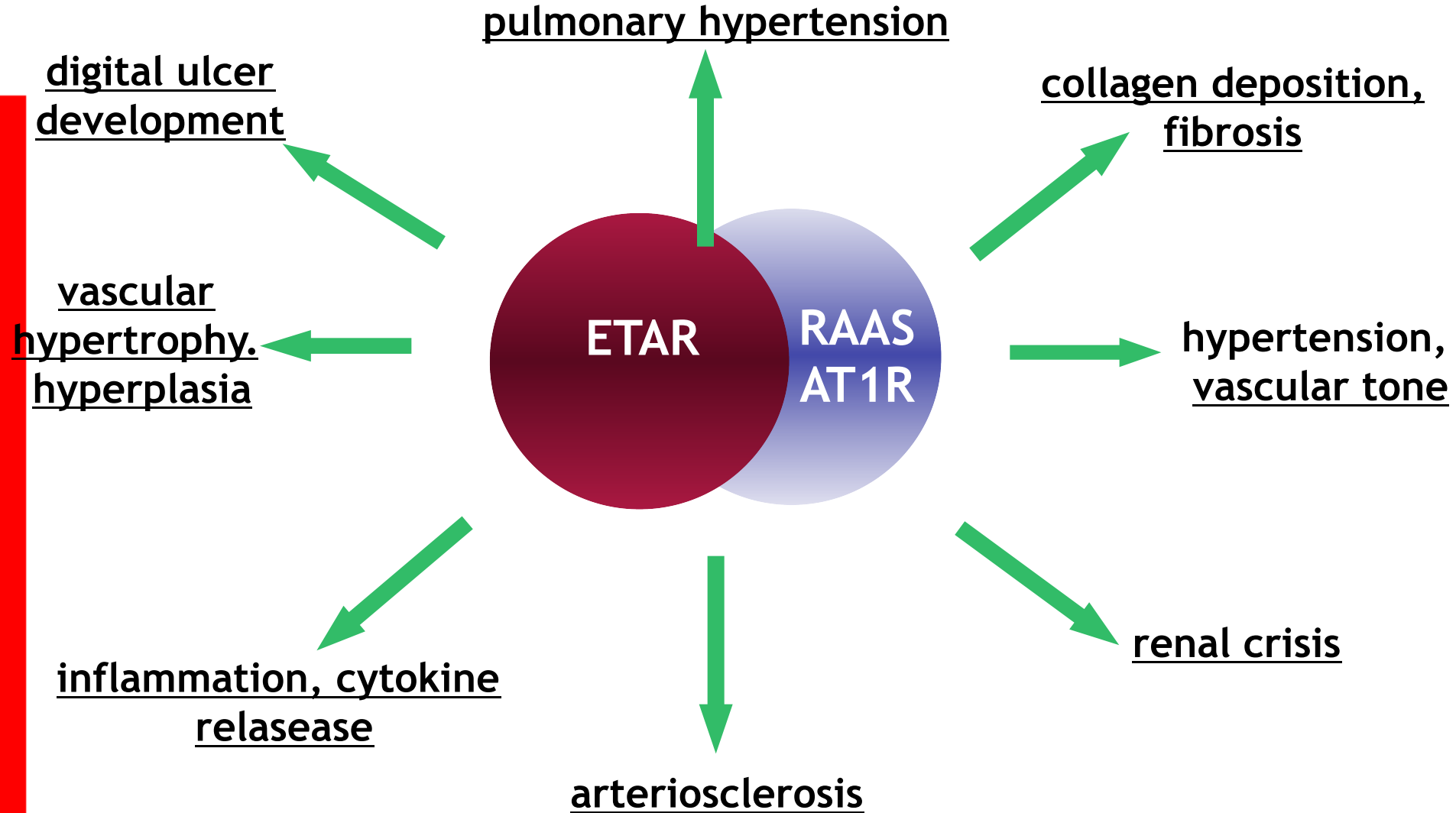


C57BL/6J

C57BL/6J
X 119



Systemic sclerosis: important role of angiotensin II type-1 (AT1R) and endothelin-1-receptor (ETAR) activations

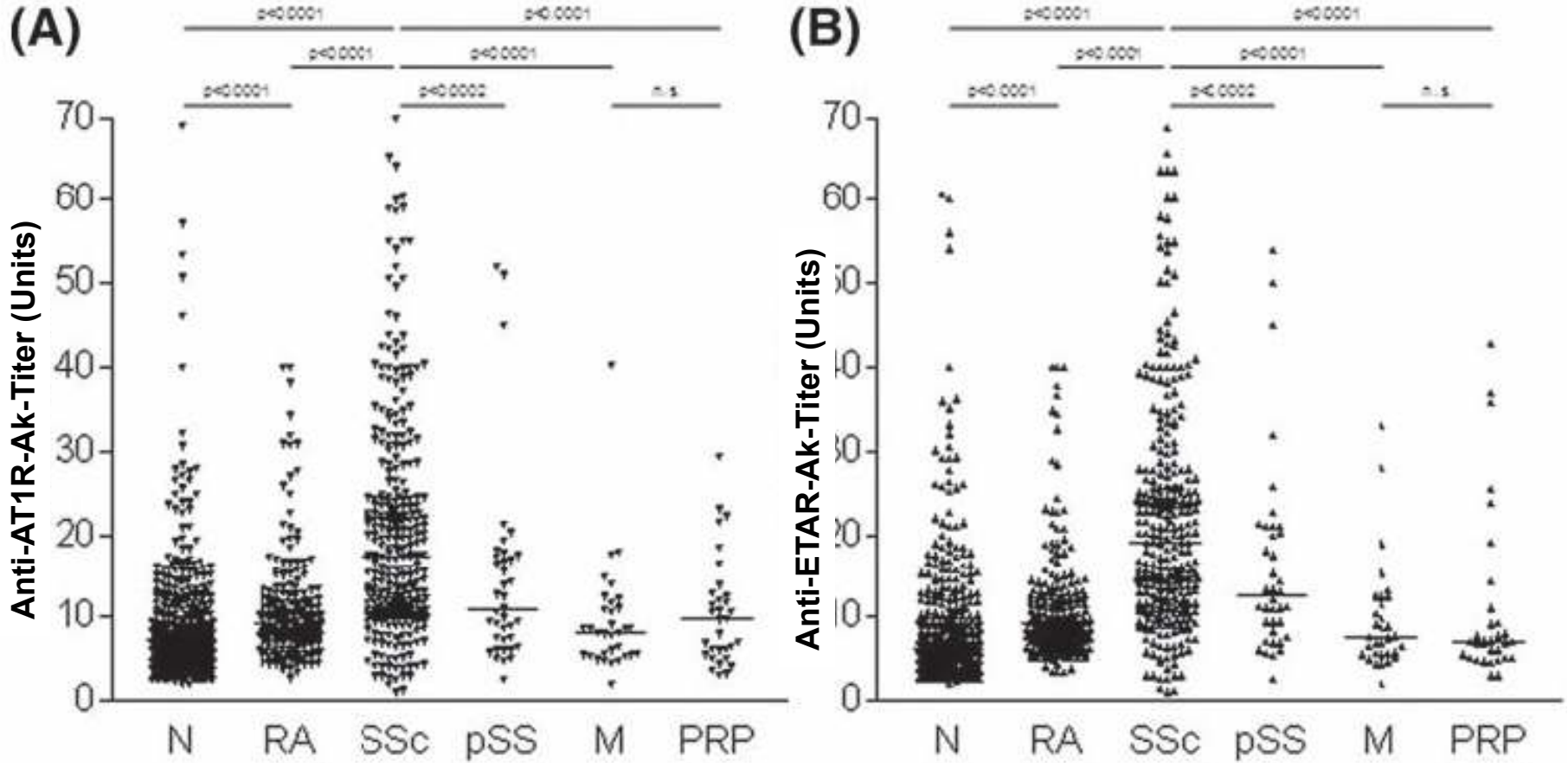


Effects are dependent on cytokine milieu, cell type, receptor expression

Anti-AT1R and anti-ETAR autoantibodies in systemic sclerosis

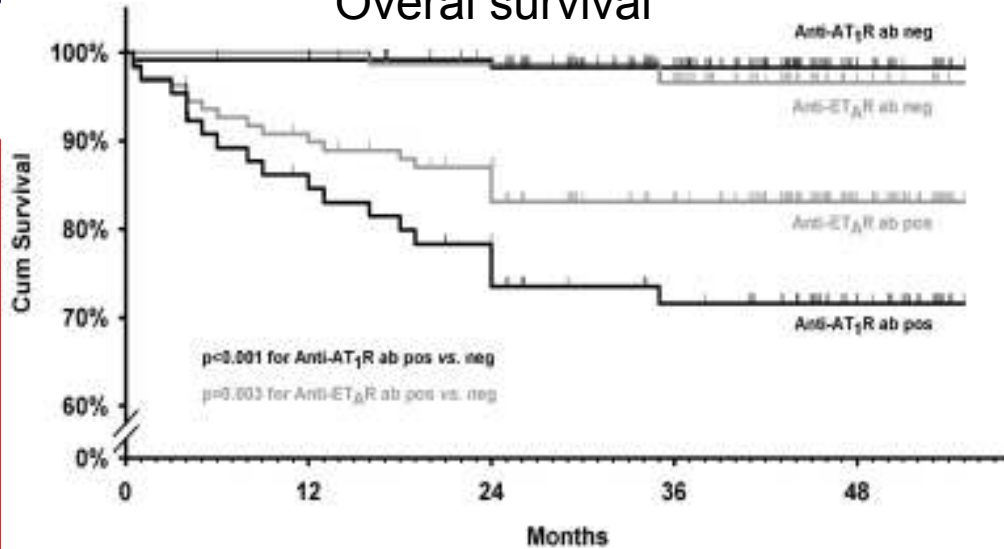
Anti-AT1R ab

Anti-ETAR ab

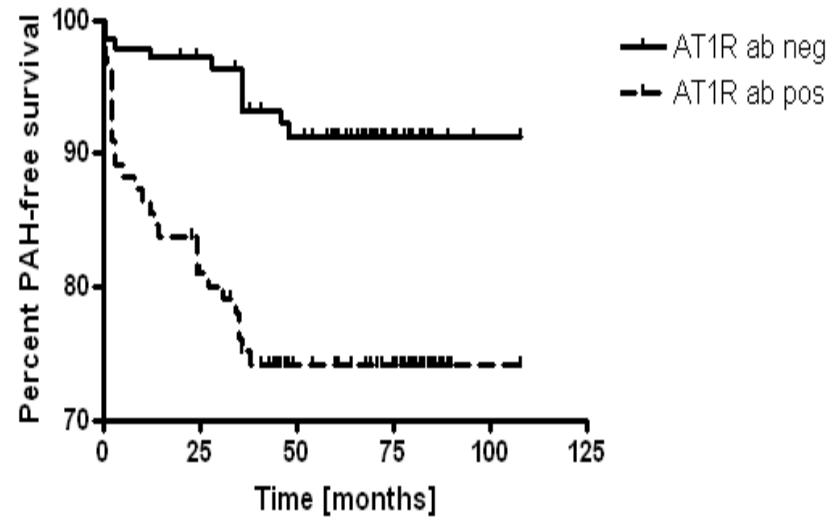


Anti-AT1R/ETAR ab as predictors for survival, PAH, and digital ulcers

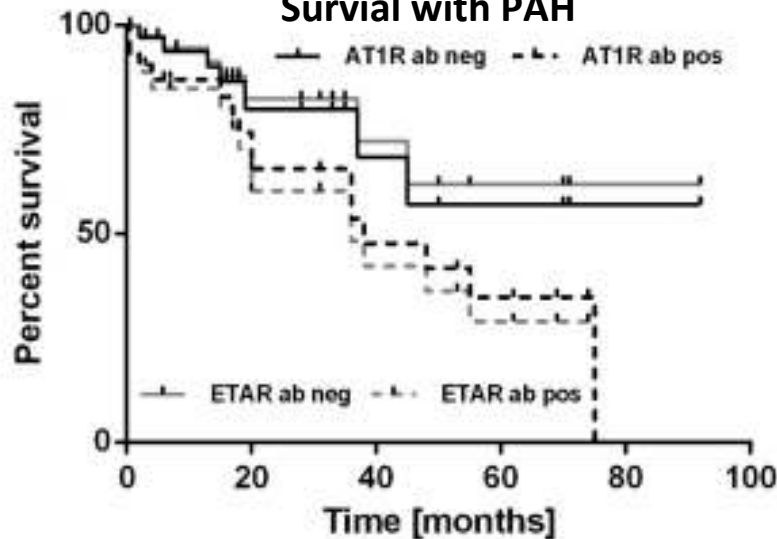
Overall survival



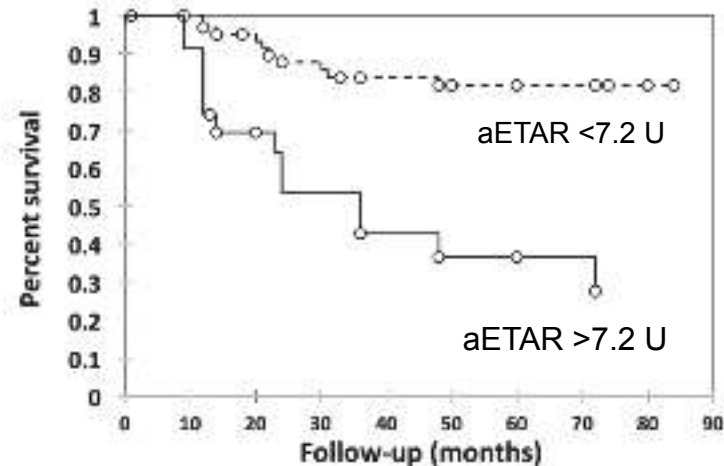
Impact of AT1R ab on PAH-free survival

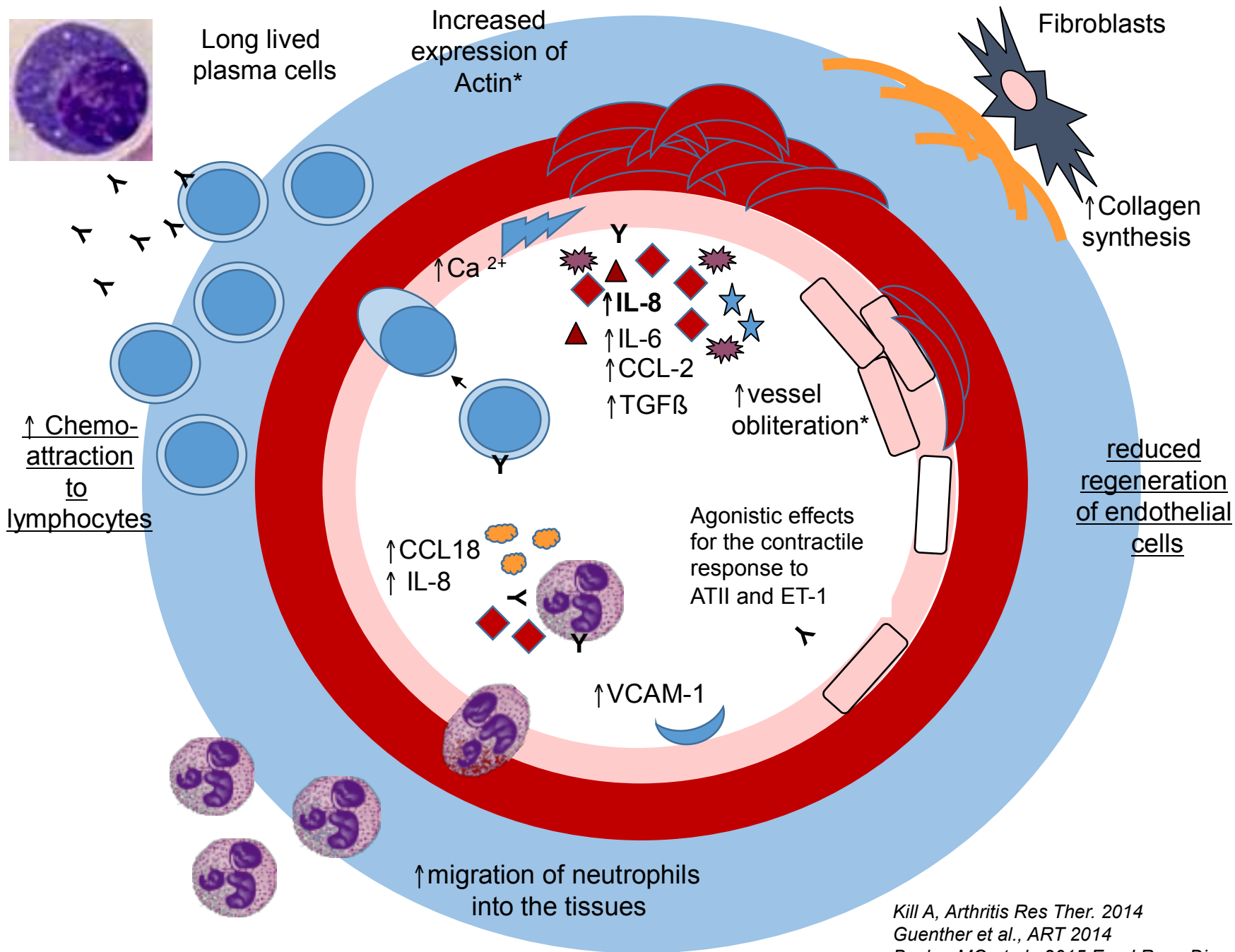


Survival with PAH



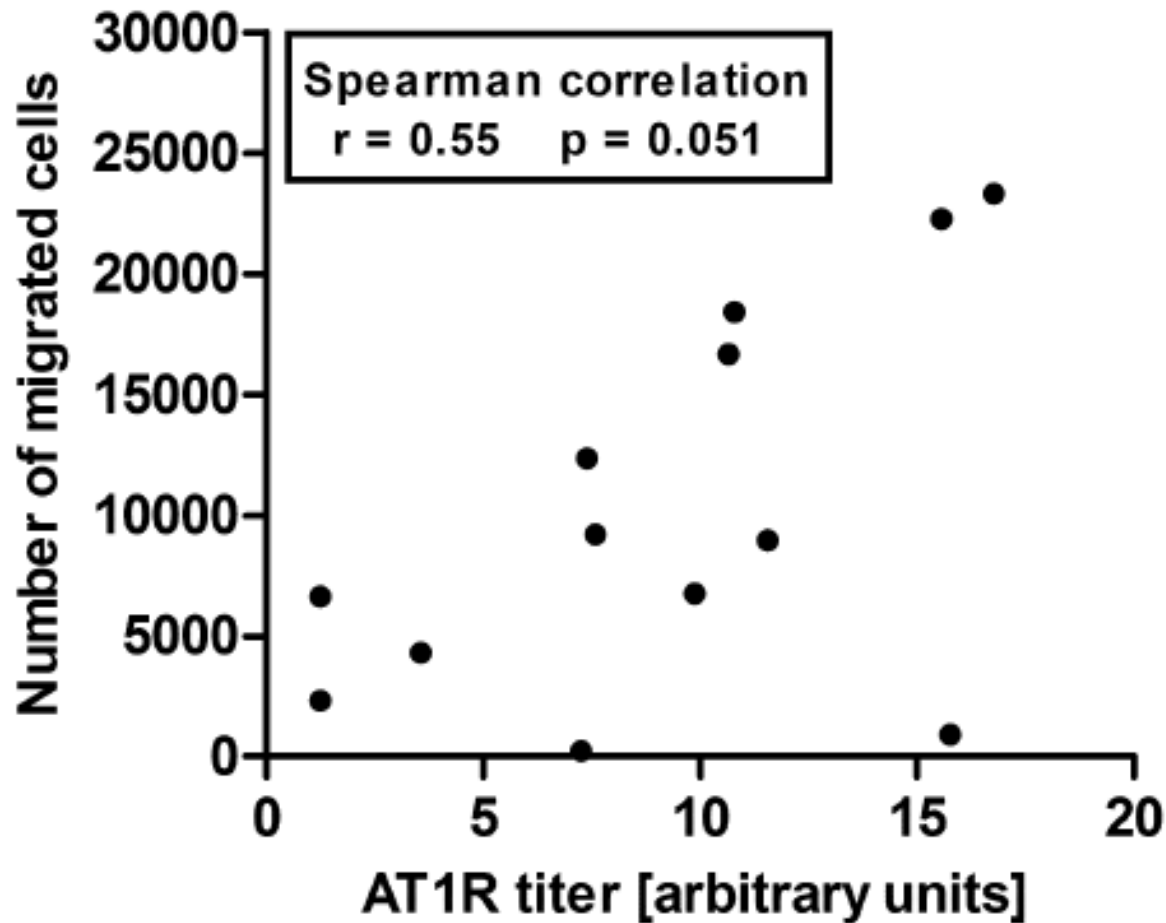
Digital ulcers





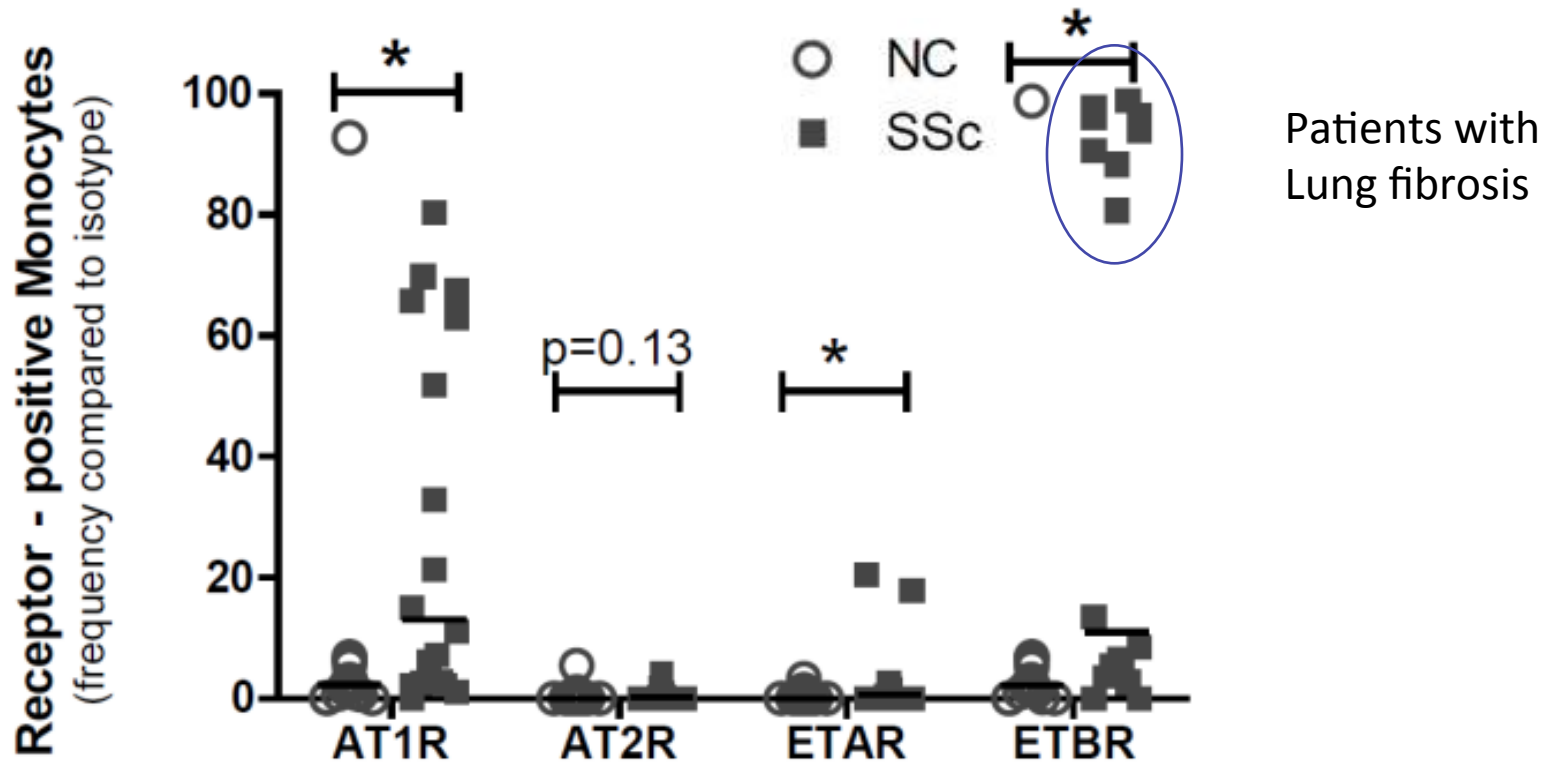
Kill A, *Arthritis Res Ther.* 2014
 Guenther et al., *ART* 2014
 Becker MO et al., 2015 *Eur J Resp.Dis*
 Guenther et al. *Seminar in Immunopathol.* 2015.

Anti-AT1R/ETAR antibodies mediate migration T cells dependent on their concentration



Receptor expression in PBMC is higher in SSc patients

Expression on monocytes



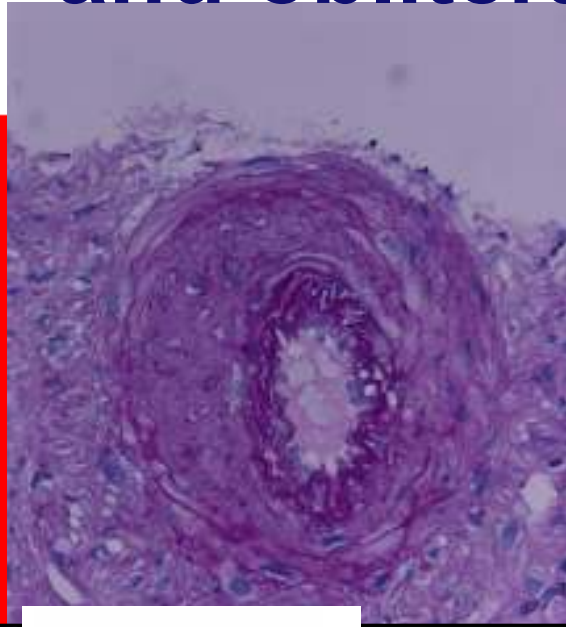
Highest expression in early disease

What doctors think about the therapy of SSc

1. Any therapy is successful as long as it is not used in systemic sclerosis
2. There is no causal therapy in systemic sclerosis
3. There is no treatment of fibrosis

All these statements are not true!

Vasculopathy in SSc; hyperreagibility and obliteration



Renal crisis



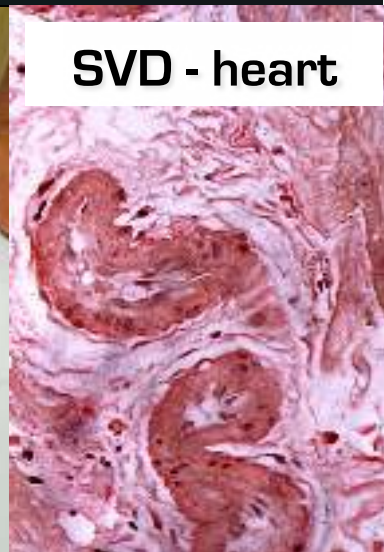
PAH



Raynaud



Digital ulcers



SVD - heart

Therapy of systemic Sclerosis: an approach to ask experts

Walker-KM, Sem Arthritis Rheum 2012, 42:42-55

Symptoms	1. choice (agreement)	2. Line
Mild Raynaud`s phenomenon	CCB, PDE-V inhibitors (35%), ATRB (32%), Prostanoids	
Severe RP	CCB plus PDE-V inhibitors (54%), prostanoids (32%)	
Prevention of digital ulcers	CCB (73%)	PDE-V inhibitors, ERA, prostanoids

Treatment of Raynaud's phenomenon

Related to the burden of RP, trophic skin changes, acroosteolyses

No therapy

Calcium Channel blockers
(20% responders)

Individual iloprost therapies depending on the severity of symptoms, benefit of the patient, personal situation, presence of digital ulcers, time of main problems (before winter period)

ASS?
MTX?

Add ATRB, if tolerated
Fluoxetine if depression

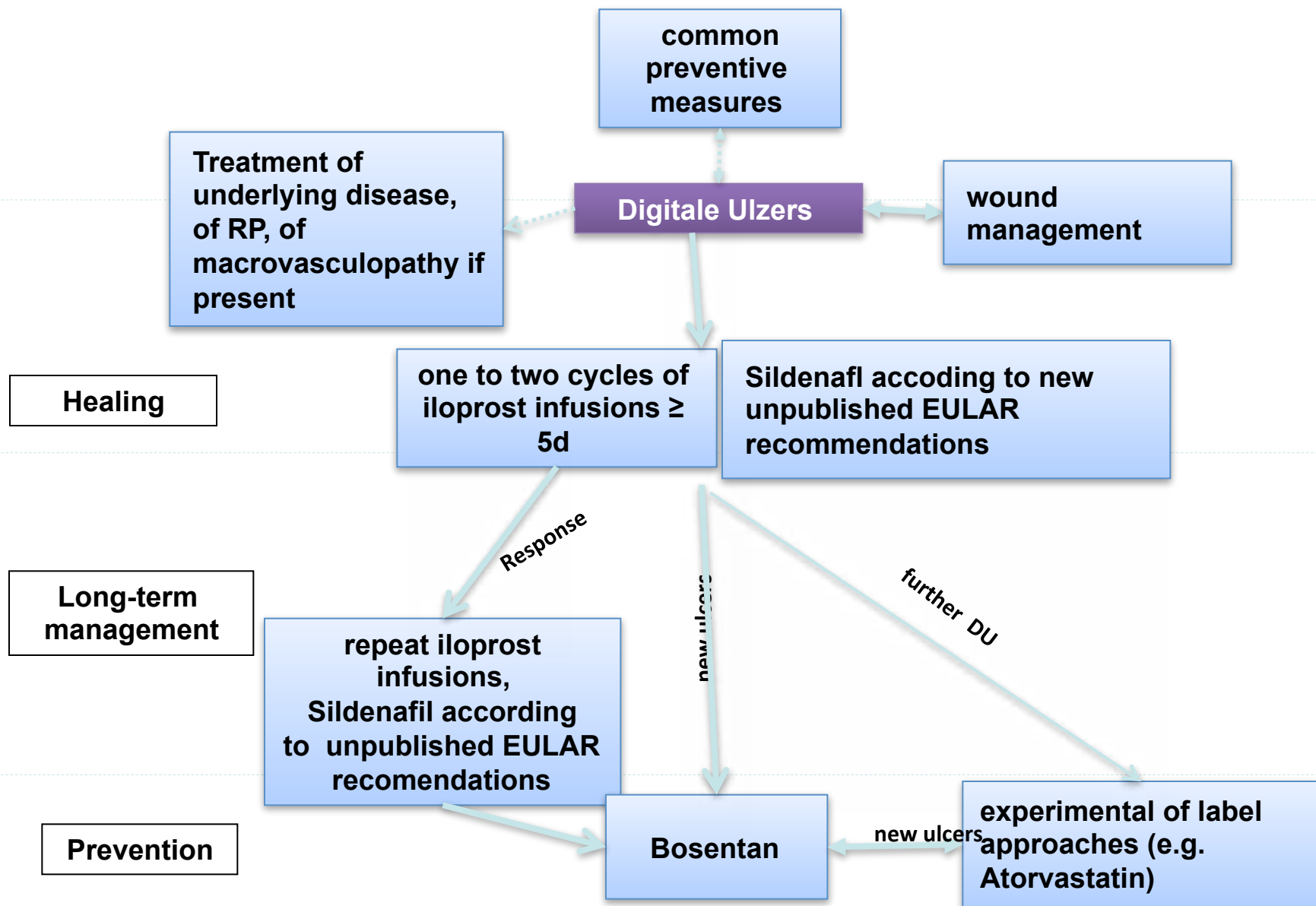
+ or alternatively?

Phosphodiesterase-V inhibitors

Off label ulse

New EULAR recommendation

Treatment of digital ulcers in systemic sclerosis



Pulmonary arterial hypertension as most severe complication of SSc

Can occur at each time point in the disease, better hemodynamic compared to IPAH, worse prognosis

**Diagnosis: Screening better as symptom-oriented
Assessment of functional class
Echocardiography (yearly)
Lung function with DLCO-SB (at least yearly)
NT-proBNP
in any doubt: right heart catheter**

If present: Lung scintigraphy to exclude CTEPH

PVOD: Deterioration by specific PAH therapy

State of the art in the therapy of pulmonary arterial hypertension

Ambition Study, Abstract ERS international congress 2014

AMBITION: A randomised, multicenter study of first-line ambrisentan and tadalafil combination therapy in subjects with pulmonary arterial hypertension (PAH)

Prof. Nazzareno Galie, MD¹; Prof. Joan Albert Barbera, MD²; Prof. Adaani Frost, MD³; Prof. Hossein Ardeschir Ghofrani, MD⁴ Prof. Marius Hoeper, MD⁵; Prof. Vallerie Mclaughlin, MD⁶; Prof. Andrew Peacock, MD⁷; Prof. Gerald Simonneau, MD⁸; Prof. Jean Luc Vachiery, MD⁹; Ms. Christiana Blair¹⁰; Dr. Hunter Gillies, MD¹⁰; Ms. Julia Harris¹¹; Mr. Jonathan Langley¹¹ and Prof. Lewis Rubin, MD¹²



Combination therapy is the most effective therapy together with trainings therapy

Immunosuppressants: in progressive inflammatory disease

MTX: moderate progressive skin fibrosis, myositis, arthritis,

Ciclosporin-A: few data, patients refractory to MTX,
skin fibrosis

Azathioprine: few data, maintenance therapy after
cyclophosphamide, before MMF therapy

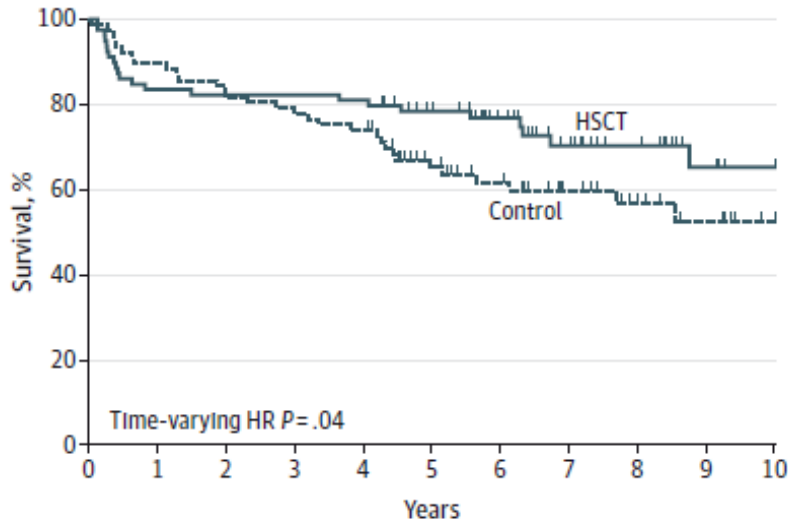
Not all patients need immunosuppressants, most need
vasoactive therapies

Autologous stem cell transplantation in early diffuse SSc: ASTIS trial

van Laar-JM et al., JAMA 2014; 311: 2490

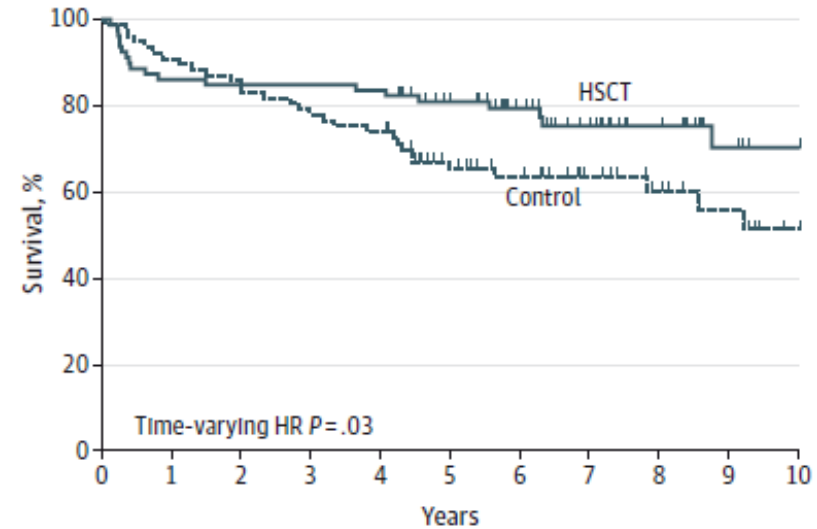
ASCT with ATG und Cyclo as previous therapy versus i.v. Cyclo 750mg/m²/Mo

A Event-free survival



No. at risk	0	1	2	3	4	5	6	7	8	9	10
HSCT	79	66	65	65	64	53	41	29	21	13	10
Control	77	69	63	60	57	40	33	23	17	11	6

B Overall survival



No. at risk	0	1	2	3	4	5	6	7	8	9	10
HSCT	79	68	67	67	66	55	43	32	23	14	11
Control	77	70	64	60	57	40	34	25	18	12	6

Decreased long-term mortality, but increased early mortality

Autologous stem cell transplantation in early diffuse SSc: ASTIS trial

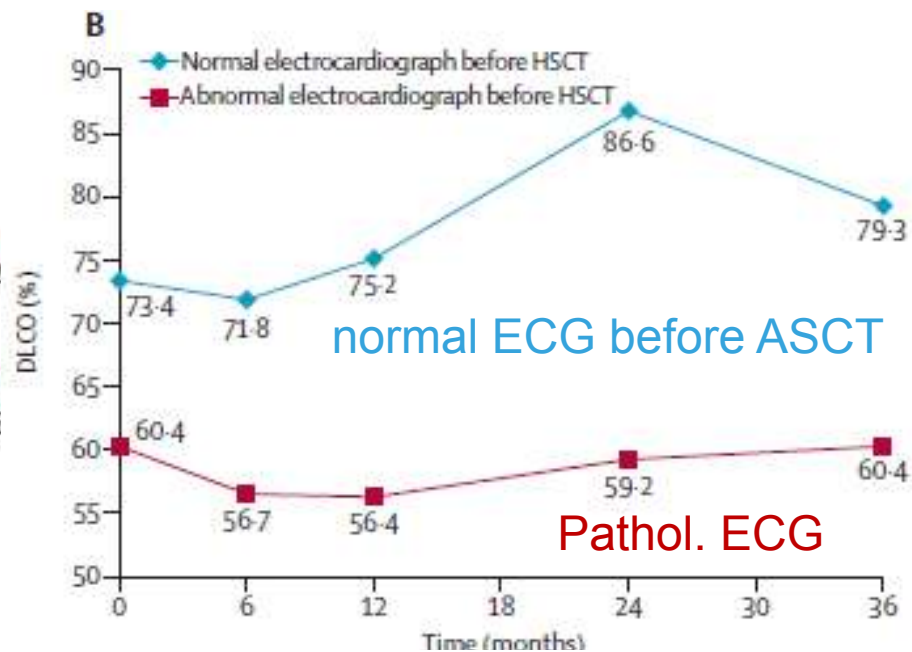
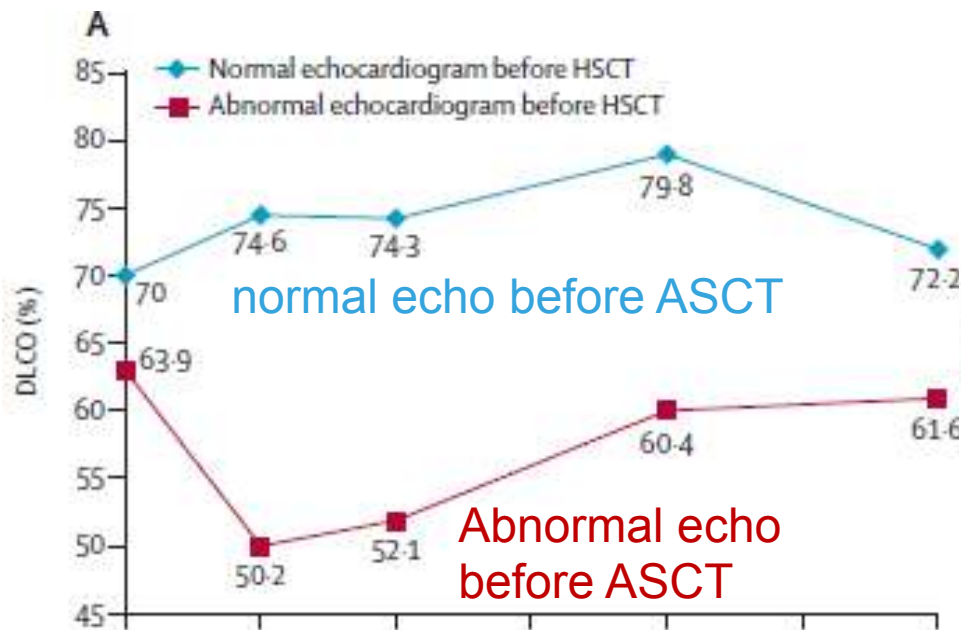
van Laar-JM et al., JAMA 2014; 311: 2490

Parameter	ASCT	Cyclo	P-Wert
MRSS	-19.9	.8.8	< 0.001
FVC (%)	+6.3	-2,8	0.004
HAQ-DI	-0.58	-0.19	0.2
SF36, physical component	10.1	4	0.01
Crea Clearance	-12.1	-1.2	0.02

Improvement of lung function and quality of life as proof of concept

Effects of ASCT depend on cardiac involvement

Burt-RK, Lancet 2013;381:1116

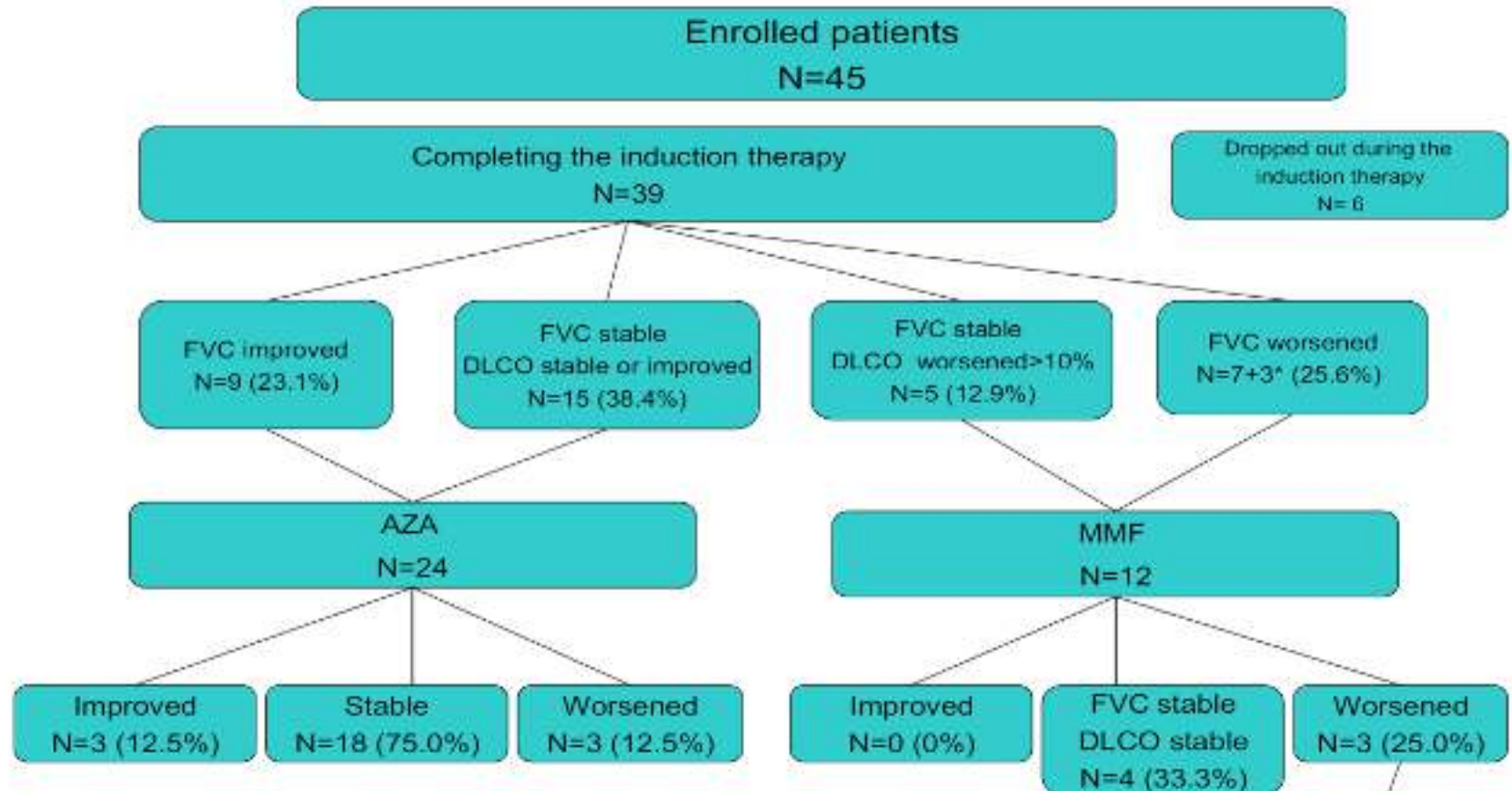


Patients without cardiac involvement profit best from ASCT

ACR 2015: VES \geq 1000/day 83% die with 100% specificity
cTnT $>$ 0,014 g/ml and RBB were predictive for \uparrow VES

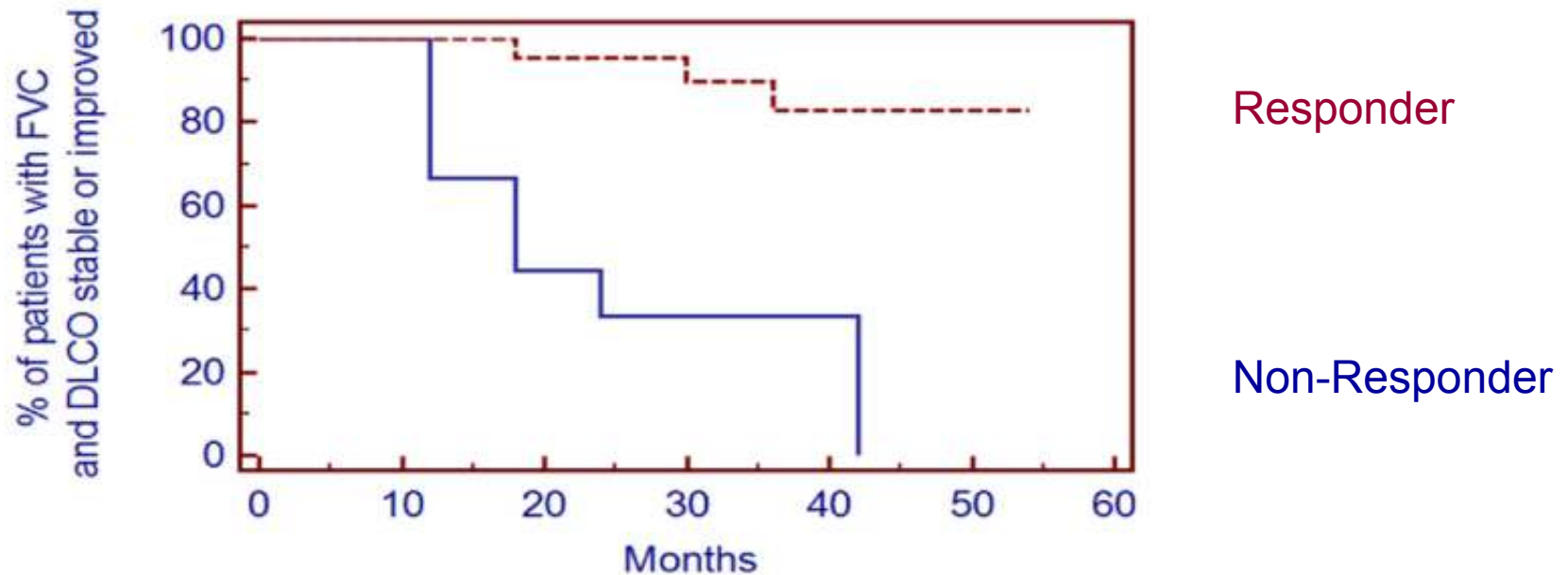
Cyclophosphamide in daily practice: a monocentric analysis

Iudici-M, Sem Arthritis Rheum 2014; S49



Cyclophosphamide in daily practice: a monocentric analysis

Iudici-M, Sem Arthritis Rheum 2014; S49



Cyclophosphamide is effective in the majority of patients.

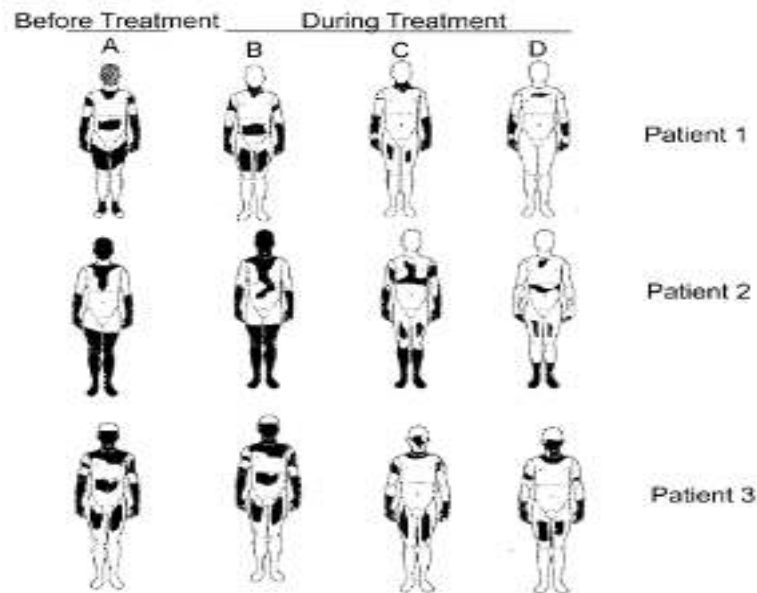
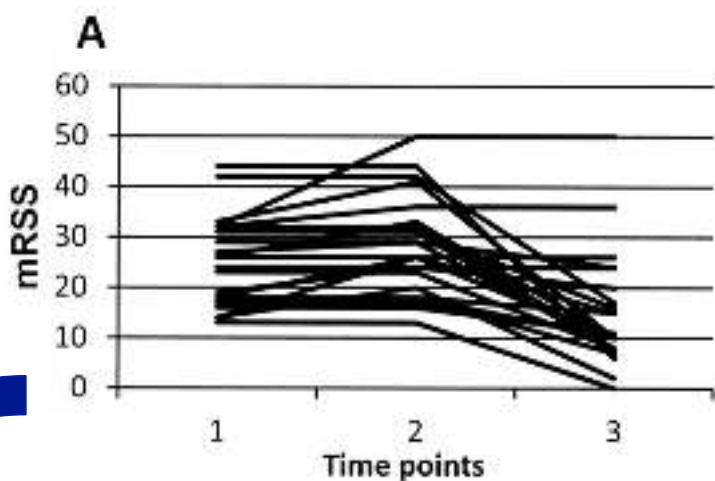
Azathioprine can be given as maintenance therapy.

MMF seems not to be superior to cyclophosphamide in the majority of patients, but 33% refr. patients remained stable in refractory patients
Cyclophosphamide failure was predictive for further deterioration (HR 9.1)

Effect of MMF on skin sclerosis: a prospective study

Mendoza-FA, J. Rheumatol. 2012

Prospective observational study on 25 consecutive Patients with early diffuse SSc

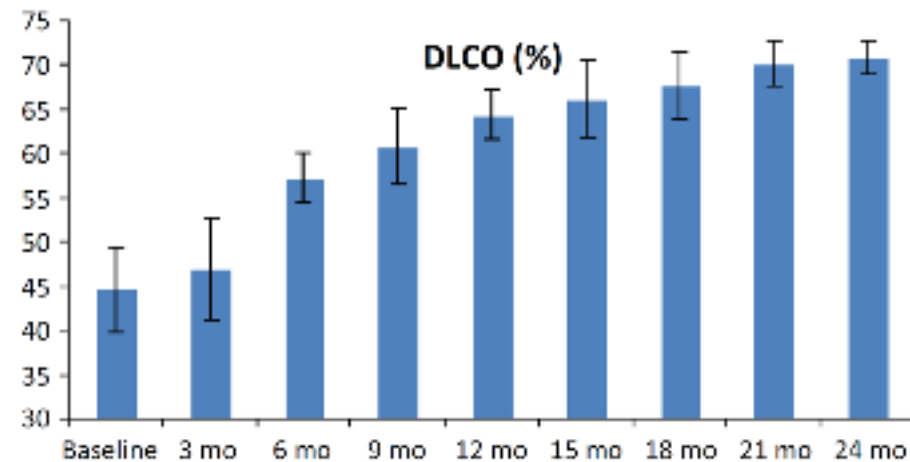
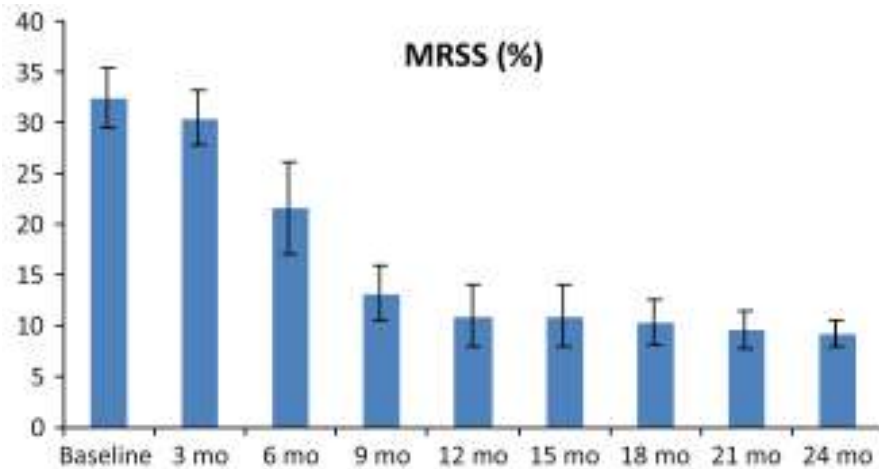


Scleroderma lung study show similar efficacy of 2 years MMF versus 1 year oral cyclophosphamide with fewer side effects

Rituximab as option in SSc without data from controlled studies

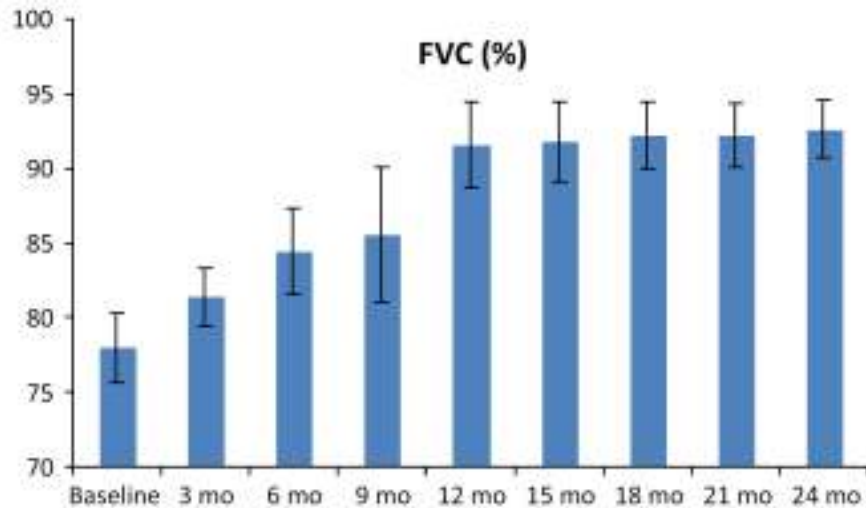
Moazedi-Fuerst- FC et al., Scand J. Rheumatol. 2014; 43: 257

5 SSc patients receiving two injections of 500 mg Rituximab (day 1 and 14) every three months



Rituximab as option in SSc without data from controlled studies

Moazedi-Fuerst- FC et al., Scand J. Rheumatol. 2014; 43: 257

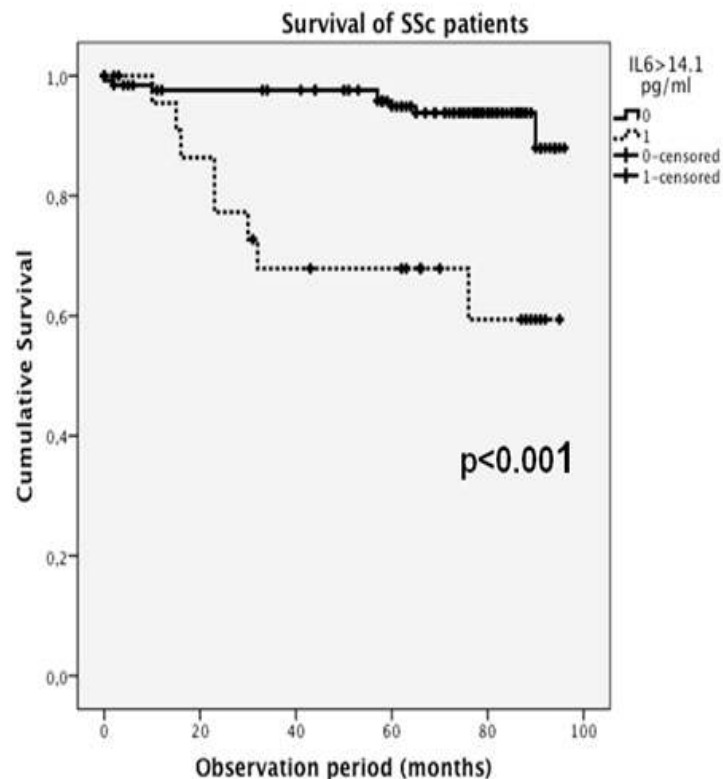
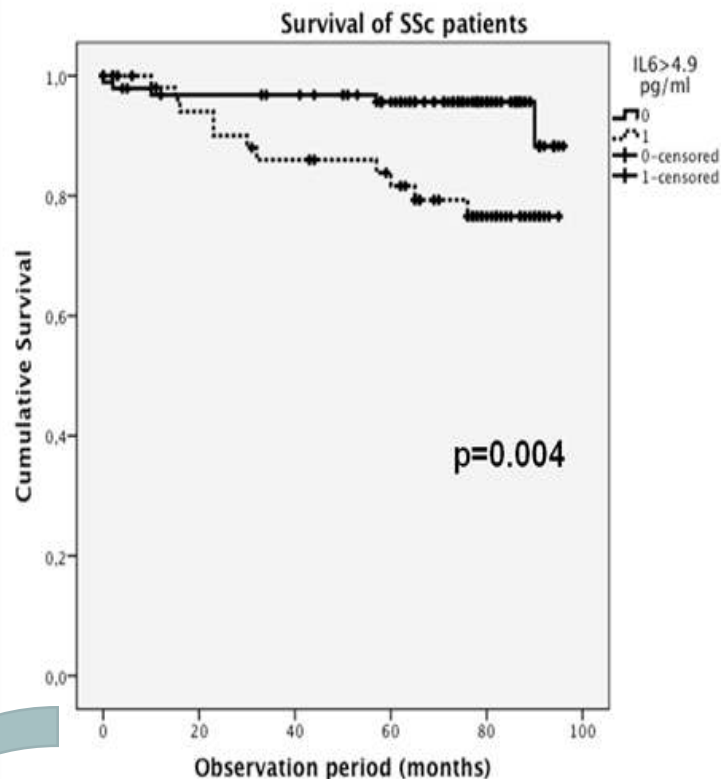


Facit: interesting option, unfortunately patients are not well characterized

Off label use

IL-6 levels predict mortality in patients with systemic sclerosis

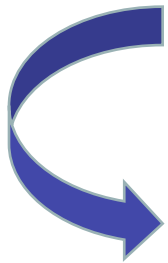
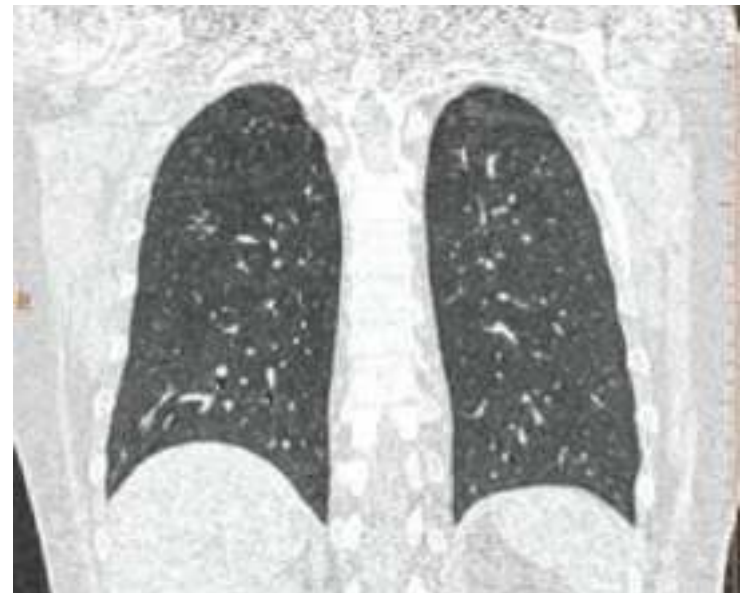
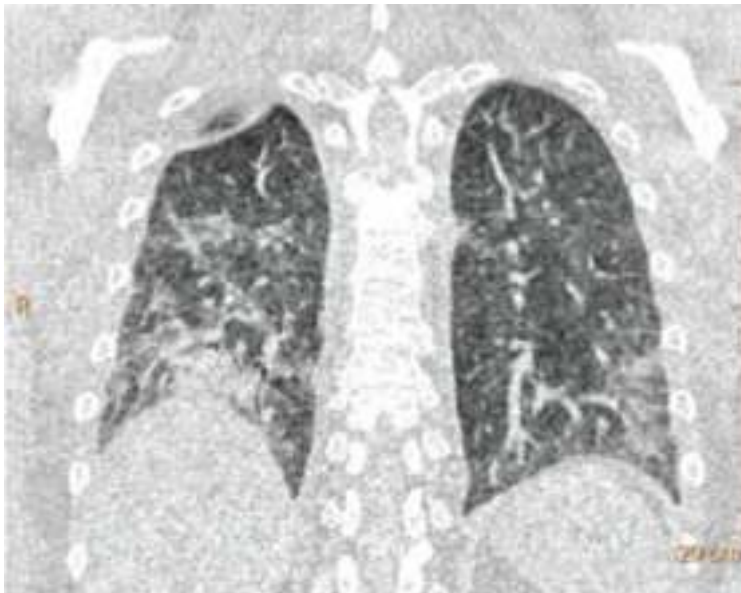
Radic, G. Riemekasten, EULAR-Poster



IL-6 has shown to affect lung fibrosis in SSc in One Placebo-controlled study

Abatacept plus cyclophosphamide as possible option in patients with SSc

de Paoli-FV et al., Scand J. Rheumatol 2014; 43: 342



Interesting option for the future, which probably states for combination therapies



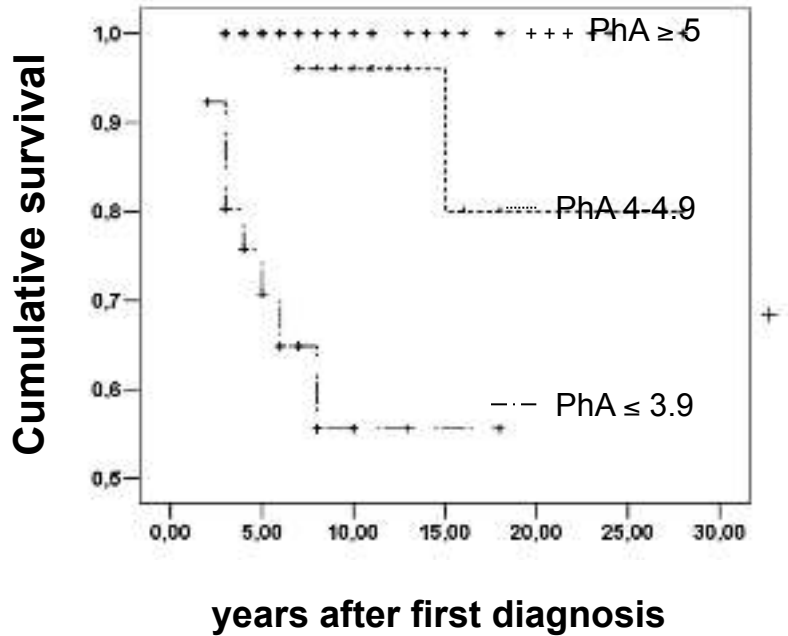
Supportive and symptomatic therapies in systemic sclerosis

Further problems that need to be addressed in patients with SSc

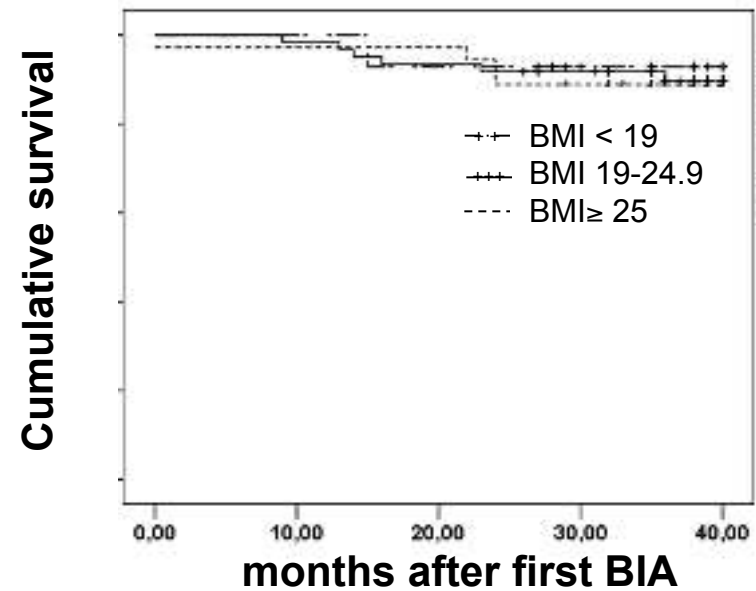
- Depressions (Fluoxetin, probably also effects on RP)
- Incontinence: biofeedback, no sacral innervation
- Calcinosis: local removal
- Increased risk for cancer: be aware of this
- 2-4-fold increased risk for thromboembolic events
- 2-4-fold risk of atherosclerosis
- Vitamine D deficiency
- 30% osteoporosis
- 50% of patients are malnourished, 20% have energy uptake lower than their basal metabolism

Identificaiton of malnutrition is best by BIA or DEXA

PhA



BMI



BMI and clinical impression not very indicative for malabsorption

Small intestinal bacterial overgrowth in systemic sclerosis

Marie I et al., Rheumatology 2009; 48:1314-1319

Eradication with rotating antibiotics, 7 days/months, e.g. with 2 x 400 mg Norfloxacin/d, followed by 3 x 250 mg Metronidazol /d

Parameter	Tx +	Tx -	P-Wert
Abdominal Pain	27,2 %	90 %	0.008
Bloating	18,1 %	70 %	0.03
Diarrhoea	0 %	60 %	0.004
abdominal tenderness	9,1 %	50 %	0.06

Malabsorption of Fructose (fruit sugar) in patients with SSc

I. Marie et al. , Medicine 2015

2,4% of the general population have intolerance. 80 SSc patients were analysed by breath test. GI symptoms were asked by questionnaires.

40% showed malabsorption, which suffered more from GI symptoms, 32 patients received FODMAP diet

Symptom	Before diet	After diet	P value
Nausea	47%	0 %	< 0.001
Vomiting	19%	0 %	0.024
Abdominal pain	81%	9%	< 0.001
Bloating	72%	28%	< 0.001
Diarrhea	31%	6%	0.00
Constipation	12%	6 %	Ns
GSS score	4	1	<0.001

Summary of current approaches in systemic sclerosis

There are effective and causal therapies in SSc, but we have many factors like in other diseases.

There is evidence that fibrosis is treatable by immunosuppressants.

We have to improve our treatments and the level of evidences.